Predicting Stroke Recovery with Nonlinear Low-Dimensional Embeddings of Behavioral Profiles

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Abstract

Stroke is a leading cause of disability worldwide. Predicting functional outcomes is challenging due to heterogeneity in post-stroke deficits and recovery profiles. We assessed prediction accuracies of 101 chronic outcomes from 78 acute behavioral measures and (hypothesizing redundancy in the predictors) from low-dimensional embeddings thereof. Nonlinear 2D UMAP embeddings yielded predictions comparable to those from all predictors. We identified brain damage patterns associated with specific behavioral profiles (extrema of the patient distribution in UMAP embeddings). We show that predictions based on only four acute tests—chosen as best linear approximations to UMAP embeddings—matched prediction accuracies from all 78 tests, suggesting nonlinear dimensionality reduction offers novel and interpretable tools for understanding behavioral outcomes of brain lesions and clinical assessment.

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Keywords: brain lesion, stroke, prediction, nonlinear embeddings

Introduction

Stroke (if survived) impacts independence and quality of life. Predicting long-term effects immediately after the stroke is challenging, as deficits can change dramatically from the first weeks post-stroke (acute) to several months later (chronic). Moreover, large variations are seen across patients in both initial deficits and recovery profiles. Prior work has identified low-dimensional latent structures in post-stroke deficit patterns (Corbetta et al., 2015). Here, we assessed the ability of embeddings to *predict* chronic outcomes in stroke patients.

We leveraged a unique dataset (Corbetta et al., 2015) with extensive behavioral testing in both the acute (7–14 days post-stroke) and chronic (3 months) recovery epochs. 78 cognitive and motor measures were used to predict 101 functional outcomes (i.e., quality of life measures that assess independence and ability to perform daily life tasks) with data from 96 adult patients (45 female, mean age=53.8 ± 11.1 years). We compared the predictive accuracy of low-dimensional embeddings from several dimensionality reduction techniques to assess the most predictive patterns and measures within the acute data.

Predicting Chronic Outcomes

We used ridge regressions to predict chronic functional outcomes as measured by commonly utilized measures (Hall et al., 1993; Wood-Dauphinee et al., 1988; Ware et al., 1992; Bergner et al., 1976; Brott et al., 1989). The acute behavioral measures (i.e., predictors) evaluated visuospatial attention, language, memory, and motor function.

Prediction accuracies (i.e., correlation R^2 between predicted and measured outcomes across patients) were cross-validated over 50 repeats using randomly selected 80/20% train/test splits (Fig. 1). To safeguard against overfitting, the same was applied to scrambled-data yielding poor predictions.

We extend prior work investigating latent structures in post-stroke behavioral data with Principal Component Analysis (PCA) (Bisogno et al., 2021) and Factor Analysis (FA) (Bowren et al., 2020) by comparing the prediction accuracy obtained from several linear and nonlinear latent embeddings of acute behaviors. Embeddings were derived with 2, 4, 8, and 16 dimensions using several dimensionality reduction tools: PCA, FA, K-Means clustering, hierarchical agglomerative clustering, and Uniform Manifold Approximation (UMAP). UMAP, uniquely among the tools we tested, identifies a *nonlinear* n-dimensional manifold within the original space, upon which the data is distributed (McInnes et al., 2018). The prediction accuracy obtained from each embedding was compared to those obtained from all tests using a Wilcoxon signed-rank test (Fig. 1).

Predictions obtained from the UMAP embedding dimensions were as accurate as those from all tests, regardless of the number of embedding dimensions (Fig. 1). These results were replicated using different random seeds for the UMAP embedding (not shown).

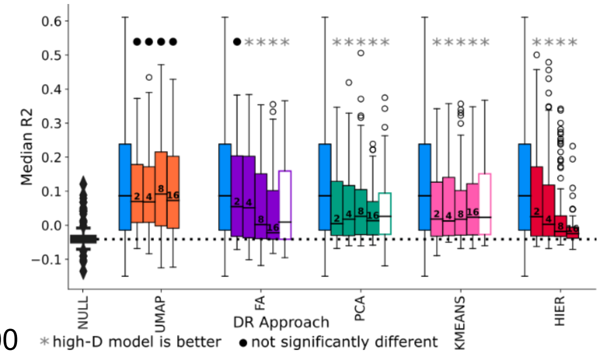

Figure 1: Prediction accuracies (distribution across all 101 outcomes) obtained from acute measures before (blues) and after compression with various tools and when using scrambled data (black). Hollow boxes denote embeddings with “optimal” number of dimensions, where standard methods allow. (α =.05; Bonferroni-corrected; dots show prediction accuracy was statistically indistinguishable from those derived from all data)

Exploring the UMAP Embedding

As UMAP embeddings of behavior robustly predicted outcomes, we examined their relationship to neural and behavioral data. We focused on 4D embeddings, which also predicted chronic neuropsychological test performance (not shown). In an exploratory lesion-symptom mapping analysis, we replaced traditional “symptoms” (i.e., test scores) with patient “location” in UMAP space, defined as distance from eight extremal reference points arbitrarily chosen at the edges of the patient distribution (Fig. 2). We applied sparse canonical correlation analysis for neuroimaging (Pustina et al., 2018), which identifies and cross-validates multivariate correlations between lesion anatomy (i.e., a binary lesion mask) and behavior.

We identified statistically significant correlations between lesion location and patient distance from 4 of the 8 reference points (labeled ‘A’—‘D’; each an extremal edge of the patient distribution in the 4D UMAP embedding). Proximity to ‘A’ and ‘B’ localized to partially overlapping brain regions in the left hemisphere; to ‘C’ and ‘D’ localized to partially overlapping regions in the right hemisphere, across subcortical (e.g., thalamus, putamen), insular cortex, and white matter regions.

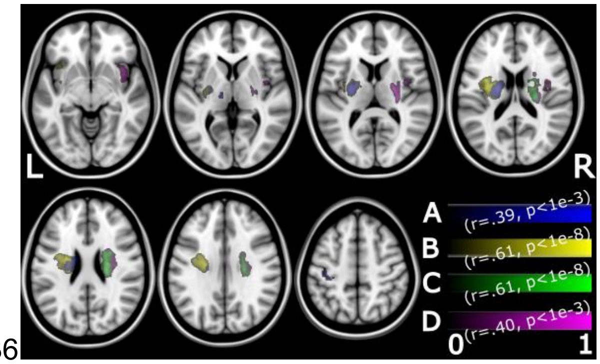

Figure 2: Voxels significantly associated with patient proximity to 4 reference points (‘A’–‘D’) in the 4D UMAP embedding of behavior profiles.

Robust prediction of chronic outcomes from a 4D embedding suggests substantial redundancy in the original 78 tests. We identified four acute tests that most strongly correlated with the UMAP 4D embedding dimensions: right (r=.69) and left (r=.78) Action Research Arm Test (ARAT; whole arm function from shoulder to fingers), left 9-hole pegboard (left finger dexterity; r=.71), and total spatial span score (visuospatial working memory; r=.80). Predictions from these four tests performed as well as those using all predictors (U=7637, p=.76).

Conclusion

This study shows that chronic functional outcomes of stroke recovery can be predicted from acute post-stroke behaviors. Moreover, they can be predicted from latent UMAP embeddings (though not from linear embeddings). This suggests that the original tests contain redundancy, which nonlinear embeddings are well-suited to reveal.

Lesion-symptom mapping revealed distinct anatomical substrates associated with patient “location” within a 4D UMAP embedding (i.e., a distinct behavioral profile) suggesting potential for clinical phenotyping. Moreover, predictions from only four acute measures (ARAT, left hand 9-hole pegboard, and Spatial Span total score; which comprise a best linear approximation to the UMAP embedding) yielded recovery predictions as accurate as those using all data, suggesting potential clinical applications of such approaches.

References

Bergner, M., Bobbitt, R. A., Pollard, W. E., Martin, D. P., & Gilson, B. S. (1976). The Sickness Impact Profile: Validation of a health status measure. *Medical Care*, 14(1).

Bisogno, AL., Favaretto, C., Zangrossi, A., Monai, E., Faccini, S., De Pellegrin, S., Pini, L., Castellaro, M., Basile, AM., Baraccini, C., & Corbetta, M. (2021). A low-dimensional structure of neurological impairment in stroke. *Brain Communications*. 3(2). https://10.1093/braincomms/fcab119.

Bowren, M., Jr., Adolphs, R., Bruss, J., Manzel, K., Corbetta, M., Tranel, D., & Boes, AD. (2020). *Journal of Neuroscience*, 40(46). https://doi.org/10.1523/JNEUROSCI.1415-20.2020

Brott, T., Adams, HP., Jr., Olinger, CP., Marle, JR., Barsan, WG., Biller, J., Spilker, J., Holleran, R., Eberle, R., Hertzberg, V., Rorick, M., Moomaw, CJ., & Walker, M. (1989). Measurements of acute cerebral infarction: A clinical examination scale. *Stroke*. 20(1). https://doi.org/10.1161/01.STR.20.7.864

Corbetta, M., Ramsey, L., Callejas, A., Baldassarre, A., Hacker, CD., Siegel, J.S., Astafiev, SV., Rengachary, J., Zinn, K., Lang, CE., Tabor Connor, L., Fucetola, R., Strube, M., Carter, AR., & Shulman, GL. (2015) Common Behavioral Clusters and Subcortical Anatomy in Stroke. *Neuron*, 85(5). https://doi.org/10.1016/j.neuron.2015.02.027

Hall, K. M., Hamilton, B. B., Gordon, W. A., & Zasler, N. D. (1993). Characteristics and comparisons of functional assessment indices: Disability rating scale, Functional Independence Measure, and Functional Assessment Measure. *Journal of Head Trauma Rehabilitation*, 8(4). https://doi.org/10.1097/00001199-99308020-00008

McInnes, L., Healy, J., Saul, N., & Großberger, L. (2018). UMAP: Uniform Manifold Approximation and Projection. *Journal of Open Source Software*, 3(29). https://doi.org/10.21105/joss.00861

van Straten, A., de Haan, R. J., Limburg, M., Schuling, J., Bossuyt, P. M., & van den Bos, G. A. (1997). A stroke-adapted 30-item version of the Sickness Impact Profile to assess quality of life (SA-SIP30). *Stroke*, 28(11). https://doi.org/10.1161/01.STR.28.11.2155

Ware, J. E., & Sherbourne, C. D. (1992). The MOS 36-Item Short-Form Health Survey (SF-36): Conceptual framework and item selection. *Medical Care*, 30(6). https://doi.org/10.1097/00005650-199206000-00002

Wood-Dauphinee, S. L., Opzoomer, M. A., Williams, J. I., Marchand, B., & Spitzer, W. O. (1988). Assessment of global function: The Reintegration to Normal Living Index. *Archives of Physical Medicine and Rehabilitation*, 69(8). https://doi.org/10.1016/0003-9993(88)90076-3