NeuroImage: Clinical 9 (2015) 83–94

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

Mapping causal functional contributions derived from the clinical assessment of brain damage after stroke

Melissa Zavaglia[a,b,*], Nils D. Forkert[a,c], Bastian Cheng[d], Christian Gerloff[d], Götz Thomalla[d], Claus C. Hilgetag[a,e]

[a]Department of Computational Neuroscience, University Medical Center Eppendorf, Hamburg University, Martinistraße 52, Hamburg 20246, Germany
[b]School of Engineering and Science, Jacobs University Bremen, Campus Ring 1, Bremen 28759, Germany
[c]Department of Radiology, Hotchkiss Brain Institute, University of Calgary, 3330 Hospital Drive NW, Calgary, AB T2N 4N1, Canada
[d]Department of Neurology, University Medical Center Eppendorf, Hamburg University, Martinistraße 52, Hamburg 20246, Germany
[e]Department of Health Sciences, Boston University, 635 Commonwealth Ave., Boston, MA 02215, USA

ARTICLE INFO

Article history:
Received 7 April 2015
Received in revised form 3 July 2015
Accepted 15 July 2015
Available online 1 August 2015

Keywords:
NIHSS
Lesion inference
Multi-perturbation Shapley value Analysis (MSA)
Game-theory

ABSTRACT

Lesion analysis reveals causal contributions of brain regions to mental functions, aiding the understanding of normal brain function as well as rehabilitation of brain-damaged patients. We applied a novel lesion inference technique based on game theory, Multi-perturbation Shapley value Analysis (MSA), to a large clinical lesion dataset. We used MSA to analyze the lesion patterns of 148 acute stroke patients together with their neurological deficits, as assessed by the National Institutes of Health Stroke Scale (NIHSS). The results revealed regional functional contributions to essential behavioral and cognitive functions as reflected in the NIHSS, particularly by subcortical structures. There were also side specific differences of functional contributions between the right and left hemispheric brain regions which may reflect the dominance of the left hemispheric syndrome aphasia in the NIHSS. Comparison of MSA to established lesion inference methods demonstrated the feasibility of the approach for analyzing clinical data and indicated its capability for objectively inferring functional contributions from multiple injured, potentially interacting sites, at the cost of having to predict the outcome of unknown lesion configurations. The analysis of regional functional contributions to neurological symptoms measured by the NIHSS contributes to the interpretation of this widely used standardized stroke scale in clinical practice as well as clinical trials and provides a first approximation of a 'map of stroke'.

1. Introduction

Ischemic stroke is a common cause of brain injury that may lead to severe deficits in brain function, requiring substantial efforts in treatment and rehabilitation. Understanding the functional anatomy of acute stroke is an important prerequisite for clinical decision making, as well as for the guidance of stroke treatment in routine clinical practice and in the context of clinical trials (Saver et al., 1999). Moreover, the diverse behavioral and cognitive deficits resulting from strokes may be used for systematic inferences on the neural substrate of fundamental brain functions (De Freitas et al., 2009).

Today, a broad range of techniques exists to investigate the functions of the living brain through the correlation of behavior and cognition with brain activity, as revealed by functional imaging. However, inferences drawn from the behavioral impact of lesions remain a fundamental source of information about causal functional contributions of different brain territories; see Rorden and Karnath (2004) for a detailed review of traditional concepts as well as current approaches for lesion inference. Diverse statistical strategies for deriving lesion inferences by lesion behavior mapping have been described (Rorden et al., 2009), such as Voxel-based Lesion Symptom Mapping (VLSM) (Bates et al., 2003), Voxel-based analysis of lesions (VAL) (Rorden and Brett, 2000), or Multi-Variate Pattern Analysis (MVPA) (Smith et al., 2013).

Specifically, in VLSM and VAL, lesions are manually or automatically identified for each patient and used to derive patterns of damage through statistical map comparisons. The VLSM method, introduced by Bates et al. (2003), uses similar voxel-based procedures as employed in the analysis of functional neuroimaging data, by comparing patients with or without lesions in a given voxel with respect to differences in behavioral measures, yielding a t-statistic for each voxel. The method can be modified

Abbreviations: CT, computer tomography; DWI, diffusion weighted imaging; MCA, middle cerebral artery; MRI, magnetic resonance imaging; MAPP, Multi-Area Pattern Prediction; MSA, Multi-perturbation Shapley value Analysis; MVPA, Multi-Variate Pattern Analysis; NIHSS, National Institutes of Health Stroke Scale; SVM, support vector machine; VAL, voxel-based analysis of lesions; VLSC, VOI-based Lesion Symptom Correlation; VLSM, Volume-based Lesion Symptom Mapping; VBM, voxel-based morphometry; VOI, volume of interest.

* Corresponding author at: Department of Computational Neuroscience, University Medical Center Eppendorf, Hamburg University, Martinistraße 52, Hamburg 20246, Germany. Tel.: +49 40 7410 52938; fax: +49 40 7410 54882.
E-mail addresses: m.zavaglia@uke.de (M. Zavaglia), n.forkert@uke.de (N.D. Forkert), b.cheng@uke.de (B. Cheng), gerloff@uke.de (C. Gerloff), thomalla@uke.de (G. Thomalla), c.hilgetag@uke.de (C.C. Hilgetag).

http://dx.doi.org/10.1016/j.nicl.2015.07.009

into a Voxel-based Lesion Symptom Correlation (VLSC) approach, by relating lesion patterns to behavioral measures through correlations, rather than through statistical group comparisons. VAL is also similar to VLSM, but compares lesion locations between a group of patients with behavioral deficit and a group of patients with brain damage, but without deficit. Finally, Smith et al. (2013) introduced an inference approach based on machine learning, called Multi-Variate Pattern Analysis (MVPA), to predict the presence or absence of spatial neglect based on brain injury maps using linear and nonlinear support vector machines (SVMs).

As a further alternative, an inference approach based on game theory has been proposed for the analysis of behavioral effects resulting from multi-lesion patterns. This approach, Multi-perturbation Shapley value Analysis (MSA) (Keinan et al., 2004a) is a rigorous mathematical method to assess functional localization from perturbation data. It defines and calculates the contributions of network elements, specifically brain regions, from a dataset of multiple lesions (or perturbation experiments) and their associated performance scores. The regions are considered as 'players' in a game who interact to achieve a behavioral outcome. The approach can also be used to quantify the interactions of the network elements. The MSA approach has found a wide range of applications in neuroscience, such as the analysis of reversible deactivation experiments (Keinan et al., 2004b) and computational models of neurocontrollers (Keinan et al., 2006), as well as applications in biochemistry and genetics, for instance, the localization of function in gene-regulatory networks from gene knockouts (Kaufman et al., 2005). In a proof-of-concept study for clinical applications, Kaufman et al. (2009) applied MSA to lesion data and line bisection test scores of 23 right-hemisphere stroke patients.

Lesion inference methods have been frequently applied to study specific neurological symptoms, such as neglect (Smith et al., 2013; Karnath et al., 2001) or aphasia (Kümmerer et al., 2013). However, there is still only a limited understanding of the clinical consequences of acute stroke lesions in specific brain regions with respect to the whole picture of neurological symptoms. Moreover, while standardized clinical rating scales, such as the National Institutes of Health Stroke Scale (NIHSS, Brott et al., 1989), are widely used to characterize the functional abilities of patients and guide treatment decisions, only little is known about how scores in these scales relate to the involvement of specific brain lesions in acute brain ischemia (Menezes et al., 2007).

In the present study, we applied MSA systematically to a large and representative sample of patients with acute stroke, to derive contributions of bilateral cortical and subcortical regions to a broad range of neurological symptoms as captured by the NIHSS, which quantifies basic behavioral and cognitive capabilities through a test battery of simple sensory, motor, language, and attention tasks. We also compared the regional functional contributions indicated by MSA with those computed by other methods that relate stroke lesion patterns to behavior, such as VLSM, VLSC (Saver et al., 1999) and multi-variate pattern prediction. Our principal goals in this study were, first, to understand the functional contributions of different brain regions to the broad spectrum of neurological symptoms as reflected by the NIHSS, representing the most widely used standardized stroke symptom rating scale. Second, we wanted to assess the suitability of the MSA approach for processing clinical lesion data and use MSA to study the functional contribution of large-scale brain regions to basic behavioral functions, based on functional deficits after lesion damage. Third, our study compared the inferences provided by MSA with those of alternative approaches and investigate potential biases in the inferences due to a restricted sample of available lesion configurations.

2. Methods and data

2.1. Behavioral and lesion image data

In the present study, we used a large multi-center set of stroke patient data to investigate functional contributions of eight bilateral volumes of interest (VOIs), defined by the MNI structural atlas (Collins et al., 1995): caudate (CAU), insula (IN), frontal (FR), occipital (OCC), parietal (PAR) and temporal lobes (TEM), as well as putamen (PUT) and thalamus (TH). The MRI and clinical data used in this study (N = 148) constitute a subset of the patient data included in the *PRE-FLAIR* study, which is a multi-center observational study designed to analyze the combined use of FLAIR (fluid attenuated inversion recovery MR imaging) and DWI (diffusion-weighted MR imaging) for identifying patients with acute ischemic stroke within 4.5 h of symptom onset (Thomalla et al., 2011). All patients in this study were studied within 12 h of witnessed stroke onset, and severity of neurological deficit on admission was assessed using the global NIHSS. The DWI sequences, which were used as the basis for lesion segmentation, were acquired by applying diffusion gradients in three directions with strong diffusion weighting (b-value = 1000 s/mm^2). Detailed information about the imaging parameters can be found in Thomalla et al. (2011).

The NIHSS is a rating scale resulting from a standardized neurological examination quantifying symptom severity in acute stroke (Brott et al., 1989). The NIHSS comprises 11 items scoring specific abilities with values ranging between 0 (no symptoms, correct performance of task) and 2–4 (maximum symptom severity for corresponding item): Level of Consciousness, Horizontal Eye Movement, Visual field, Facial Palsy, Motor Arm, Motor Leg, Limb Ataxia, Sensory, Language (Aphasia), Dysarthria, Extinction and Inattention. Higher scores indicate more severe impairment. A sum score is calculated from the individual score values and ranges from 0 to 42. The NIHSS is widely used for standardized clinical assessment of stroke patients in routine clinical practice as well as in stroke research and is also frequently used to include or exclude patients in acute stroke trials.

2.2. Lesion image processing

For the purpose of a quantitative lesion analysis, the infarct lesions were semi-automatically segmented by an experienced neurologist (B.C.) for each DWI image sequence acquired with strong diffusion weighting in a standardized fashion (Cheng et al., 2013). More precisely, the visible lesions were manually surrounded in each axial slice including a safety margin by interactively placing points at the border of the visible stroke lesion. These points were automatically connected using a cubic spline interpolation and points were manually adjusted if required. After contour definition in each affected slice, a binary volume was generated using all spline-based contours. A second healthy volume of interest was then placed in the contralateral unaffected hemisphere in the corresponding brain tissue in the same manner. The resulting healthy volume of interest was defined in a way that it represents an approximation of the mirrored lesion volume. This healthy volume of interest was then employed for calculating the corresponding mean μ and standard deviation σ of the DWI signal intensities. These values were used for refining the defined coarse DWI lesion volume of interest by rejecting voxels with a DWI signal intensity $< \mu + 2\sigma$, such that only the actual lesion was covered by the resulting segmentation.

Due to different positions of the acute stroke patients within the MR scanner, different inter-subject head anatomies and variations regarding the spatial resolution of the DWI image sequences, a registration of the datasets into a reference space was necessary to quantify the number of lesioned voxels in different brain regions of interest that are defined in the reference space. Therefore, the 1 mm^3 MNI ICBM152 brain atlas, which has been designated as the standard template by the International Consortium for Brain Mapping, was used for definition of the reference space (Collins et al., 1995). To overcome the problem of differences regarding the signal intensities and visible tissues in the MNI brain atlas, which was constructed based on T1-weighted image sequences from 148 healthy subjects, and in the T2-weighted DWI image sequences, an iterative closest point (ICP) registration approach (Besl and McKay, 1992) was used in this work, which is illustrated in Fig. 1. Particularly, an