Multiperturbation Analysis of Distributed Neural Networks: The Case of Spatial Neglect

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Abstract: This study assesses the feasibility of using a multiperturbation analysis (MPA) approach for lesion-symptom mapping. We analyze the relative contribution of damage in different brain regions to the expression of spatial neglect, as revealed in line-bisection performance. The data set comprised of normalized lesion information and bisection test results from 23 first-event right-hemisphere stroke patients. Obtaining quantitative measures of task relevance for different regions of interest (ROIs), the following ROIs were found to be the most contributing: the supramarginal and angular gyri of the inferior parietal lobule, the superior parietal lobule, the anterior part of the temporo-parietal junction connecting the superior temporal and supramarginal gyri, and the thalamus. MPA is likely to play an important role in elucidating the anatomical substrate of complex functions. *Hum Brain Mapp 00:000–000, 2009*.

Key words: lesion method; functional neuroanatomy; neuroimaging; unilateral spatial neglect; spatial attention; multiperturbation analysis; localization of function

INTRODUCTION

One of the fundamental challenges in neuroscience is to define what elements of the nervous system participate in the processing and execution of different functional tasks. In the case of complex behavioral or cognitive tasks, defining structure-function relationships poses a special difficulty. This is because complex functions are based on the integrated activity of separate brain structures, each supporting a unique subroutine necessary for the overall network function [Mesulam, 1998]. When using the lesion-effect paradigm, it is essential to define the relevance of each anatomical structure involved in the lesion process, while taking into consideration the relative importance of other regions found to be connected with the studied function. As pointed out originally by Luria [1973], success in this task depends on the quality of theoretical modeling of the studied function, the quality of symptom (manifested dysfunction) analysis, and finally, the quality of lesion analysis.

The aim of this study was to assess the value of a novel computational framework to lesion-based analyses of structure-function relationship. The method is of special appeal in cases of damage to complex operations relying on the integrity of distributed neural networks. Based on a predictive model which aims to avoid the individual-bias

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in the data, the method analyzes the contribution of multiple concomitantly affected and potentially interacting regions, using a multiperturbation analysis (MPA) approach [Kaufman et al., 2005]. It defines and computes the relevance of various structures to a behavioral task from a data set of multiregion involvement in a group of patients, and their corresponding task performance scores. The contribution of a region to a studied task denotes its importance, that is, the part it causally plays in the successful performance of that task. The suggested analysis method overcomes many of the lesion approach shortcomings reviewed recently by Rorden and Karnath [2004], mainly by acknowledging the high redundancy in the functional organization of the human brain and by considering the interactions between the different brain regions. The contributions of the brain regions are calculated while taking into account the cross region interactions, resulting in a rigorous quantitative representation which does not assume "localization" of different cognitive functions to discrete anatomical regions. MPA is based on the Shapley [1953] value theory and it relies on axiomatic foundations from game theory [Keinan et al., 2004]. MPA was previously utilized to analyze other biological systems, including protein signaling and regulatory networks, the chemosensory neural network in the *C. elegans* nematode, and spatial attention in cats [Kaufman et al., 2005; Keinan et al., 2004; Yosef et al., 2006]. In the latter study by Keinan et al. [2004], MPA has been utilized to rigorously quantify "paradoxical" effects concerning spatial attention in cats where the deactivation of some regions results in a better-than-normal performance (these effects have been previously discovered and reported in a study of human spatial attention by Hilgetag et al. [2001]).

To test the feasibility of MPA application in lesion studies, we performed a retrospective analysis of normalized lesion data and corresponding line-bisection performance, obtained from first-event stroke patients with unilateral spatial neglect (USN). The syndrome of spatial neglect is generally conceived in terms of disturbance to the proper functioning of a distributed network subserving spatial attention [Mesulam, 1999], and is known to result from damage to a large variety of cortical and subcortical structures [Karnath et al., 2001, 2004; Mort et al., 2003; Vallar and Perani, 1986]. The neuroanatomy of neglect became the subject of a heated debate in recent years, focusing on the question of which region is more important (for neglect as well as for spatial awareness)—the posterior parietal or superior temporal cortex. Lesion studies yielded conflicting results, with some studies supporting the primacy of the former [Mesulam, 1999; Mort et al., 2003; Vallar and Perani, 1986] and others of the latter region [Karnath et al., 2001, 2004]. To add to the complexity of the matter, a series of functional imaging studies in normal subjects engaged in spatial attention tasks revealed activation patterns that suggest a crucial role for some other structures as well [Corbetta and Shulman, 2002; Corbetta et al., 1995; Gitelman et al., 1999; Wojciulik and Kanwisher, 1999]. Lesion studies in USN were expected to point to the critical components of the spatial attention network and to shed light on their specific roles and patterns of interaction. This expectation was only partially fulfilled so far. From a clinical point of view, a large variety of documented double dissociations between different testing paradigms of USN raised questions on the utility of the term [e.g., Halligan and Marshall 1992, 1993]. Here again, better understanding of the role and the relative importance of the different regions where damage contributes to the formation of USN phenomena could help delineate different subtypes of the syndrome. Such knowledge is expected to facilitate the development of novel treatment modalities to this highly disabling condition [Katz et al., 1999], which take into account the specific needs of individual USN patients, based on the distinct pathophysiology related to different lesion configurations.

Given this background, our retrospective analysis of lesion data and correlative line-bisection performance in USN aims to demonstrate that MPA can contribute to the insights provided by lesion-effect studies. With the accumulation and analysis of larger datasets employing a variety of relevant behavioral tasks, the quantification of the regions' contribution will serve to provide a more comprehensive and rigorous description of the underlying brain network, replacing the rather simplistic previous efforts to identify the one or two most important regions.

MATERIALS AND METHODS

Lesion and Performance Data

We re-analyzed, for the purposes of this study, lesion data and line-bisection test results retrieved from the files of 23 USN patients, hospitalized in the past at the Loewenstein Hospital, for rehabilitation after stroke. Only files that met the following strict inclusion criteria were selected: (a) first occurrence of an ischemic or hemorrhagic stroke localized in the right cerebral hemisphere; (b) absence of marked mass effect (with possible unrecognizable distant effects) in the acute-stage CT scan; (c) negative neurologic or psychiatric past history; (d) absence of significant morphometric and densitometric markers of brain atrophy or small vessel disease with possible latent subcortical damage; (e) availability of multilength line-bisection test results undertaken 1–3 months after stroke onset (to minimize variance related to early medical and functional instability on one hand, and variance related to late plastic changes and functional reorganization on the other hand); (f) availability of normalized lesion data derived from high quality follow-up (6–8 weeks post onset) transaxial CT scans, with uniform slice width and interslice distance (10 mm both), where the scanning plane was aligned to the cantomeatal line as defined in the lateral scout film, thus closely paralleling to the plane traversing the anterior and posterior commissures; (g) right handedness (based on self description).

Appropriate files were retrieved from three earlier studies done in our department for other purposes [Serfaty et al., 1995; Soroker et al., 2005; Zaidel et al., 2002]. These studies were approved by the ethical committee of the Loewenstein Rehabilitation Hospital. The normalized lesion data and the corresponding line-bisection scores gathered in these studies were submitted to MPA for the purposes of this study.

The age range of the subjects (16 men, 7 women) whose files were used in this study was 37–78 years (mean and standard deviation: 59.4 ± 10.4). Stroke was ischemic in 21 and hemorrhagic in two cases. All but two patients suffered from severe left hemiparesis or hemiplegia, and 11 patients were defined as having hemianopsia, based on demonstrated inability to detect dynamic visual stimuli on the left visual field in confrontation testing. All but one patient scored much below the cut off for normality on the standardized Behavioral Inattention Test (BIT) battery [Wilson et al., 1987] (except for this patient, who scored 139 on the BIT but manifested clear USN in activities of daily living as well as in line bisection, the patients' scores ranged between 21 and 119; mean performance of the entire group was: 73.0 ± 31.2; the normality cut-off and maximal scores in this test are 130 and 146, respectively [Wilson et al., 1987]).

The normalization procedure employed in the original studies [Soroker et al., 2005; Zaidel et al., 2002] utilized lesion information derived from high quality follow-up CT scans. The lesion data was reconstructed, separately for each patient, on a set of standard templates, using a normalization procedure based on Talairach's proportional grid system [Talairach and Tournoux, 1988]. The fraction of each region of interest (ROI) of the standard templates, which was involved in the lesion process, entered into the analysis. Given the small sample size and the feasibility-testing purpose of this study, we have focused the MPA on a limited series of ROIs (11 in total) repeatedly reported as lesion areas in USN studies [Karnath et al., 2001, 2004; Mort et al., 2003; Vallar and Perani, 1986], or as areas of prominent activation in functional imaging studies of spatial-attention [Corbetta and Shulman, 2002; Corbetta et al., 1995; Gitelman et al., 1999; Wojciulik and Kanwisher, 1999], for which a minimum set of data points was available.

The cortical areas analyzed were the superior parietal lobule (PSL), the angular and supramarginal gyri of the inferior parietal lobule (PAG, PSG), the temporo-parietal junction divided into the junction area of middle temporal and angular gyri and the junction area of superior temporal and supramarginal gyri (TM-PAG, TS-PSG), the superior and middle gyri of the temporal lobe (TS, TM), and the middle frontal gyrus. The subcortical areas entered to the analysis were the thalamus (Th), the lentiform nucleus (LNu), and the intrahemispheric white matter (IHWM). Table I shows the involvement of these 11 ROIs in the lesion process (group's mean and standard deviation values of damaged voxels in each ROI, and distribution of subjects showing different levels of involvement in each ROI). As can be seen, superior and middle temporal, inferior parietal, and temporo-parietal junction areas were the most widely involved cortical regions. Large variance can be noted in lesion extent in each ROI.

Testing took place 8.3 ± 4.8 weeks after the onset of stroke. The patients bisected 144, 162, and 180 mm black lines printed on A4 size sheets, one line per page. Each line length was presented 10 times in random order. The

TABLE I. Damage characteristics in the 11 ROIs forming the MPA model

ROI	Percentage of voxels involved (mean ± STD (%))	<10% Involvement	10–50% Involvement	>50% Involvement
IHWM	31.6 ± 19.9	4	14	5
Th	2.6 ± 6.1	20	3	0
LNu	23.1 ± 24.1	11	9	3
PSL	8.7 ± 18.7	18	3	2
PAG	21.3 ± 29.7	13	6	4
PSG	33.5 ± 31.6	7	9	7
TM-PAG	21.3 ± 29.6	13	6	4
TS-PSG	53.4 ± 39.4	7	3	13
TM	29.3 ± 31.1	10	8	5
TS	50.4 ± 34.5	5	6	12
FM	8.5 ± 12.9	16	7	0

The table shows group ($n = 23$) mean and standard deviation of each ROI's involvement in the lesion process (% of voxels involved), and number of subjects showing <10% involvement (including no involvement), 10–50% involvement, and >50% involvement.
ROIs, regions of interest; IHWM, intrahemispheric white matter; Th, thalamus; LNu, lentiform nucleaus; PSL, superior parietal lobule; PAG, angular gyrus of the inferior parietal lobule; PSG, supramarginal gyrus of the inferior parietal lobule; TM-PAG, junction area of middle temporal and angular gyri; TS-PSG, junction area of superior temporal and supramarginal gyri; TM, middle temporal gyrus; TS, superior temporal gyrus; FM, middle frontal gyrus.

mean signed displacement of the subjective midpoint from the true midpoint was used as a measure of neglect. The group's mean signed displacement was 16.3 ± 14.3, 20.1 ± 15.4, and 22.8 ± 17.9 mm, right of the true midpoint, for the 144, 162, and 180 mm line lengths, respectively. The group's mean "relative error" (mean signed displacement divided by half line length) across different line lengths is 24.8%, denoting severe neglect on line bisection.

Multiperturbation Shapley Value Analysis

The starting point of MPA [Kaufman et al., 2005; Keinan et al., 2004] is a dataset of multiperturbation observations studying a system's performance in a certain function. In this study, a multiperturbation observation relates to a patient with a multi-ROI brain injury and the corresponding performance function is the patient's score in the line bisection task. In each patient, a different subset of the brain regions is typically injured (denoting a multiregion injury configuration, or more generally, a multiperturbation configuration), leading to a different score on the line bisection task. The data from the 23 patients comprises the 23 samples composing the multiperturbation data set. Given this dataset, the goal of MPA is to ascribe to each ROI its contribution (importance) in carrying out the studied line bisection function.

MPA, described in full detail in [Kaufman et al., 2005], is briefly outlined latter: The system investigated, line bisection in USN, can formally be described by a pair (N, v), where $N = \{1, \ldots, n\}$ is the set of all brain ROI and $v(S)$, for every subset of regions S ($S \subseteq N$), denotes the performance measure (score in the line bisection test) under the multiregion injury configuration in which all the regions in S are intact and the rest are damaged. The marginal importance of region i to the task studied is computed by comparing the performance under a given injury configuration S that does not include i with the performance when i is added to that configuration of system elements, that is,

$$\Delta_i(S) = v(S \cup \{i\}) - v(S). \quad (1)$$

To obtain the full contribution of region i to the task studied we compute γ_i, the Shapley [1953] value. The marginal importance of region i (1) is computed over all possible lesion configurations S, for all regions $i \in N$, obtaining

$$\gamma_i(N, v) = \frac{1}{n!} \sum_{R \in \Re} \Delta_i(S_i(R)) \quad (2)$$

where in accordance with the Shapley value theory the set of all lesion configurations is computed by enumerating all permutations of the N system elements, that is, $\Re$ is the set of all $n!$ orderings of N, and $S_i(R)$ is the set of regions preceding i in the ordering R. The Shapley value, representing the contribution of a region, thus attains a clear intuitive interpretation, denoting the average (marginal, additional) importance of region i to the studied function over all possible injury configurations. In essence, the contribution, γ_i, of a region is calculated taking into account the effects and interactions it has with all other regions. In a simple additive system (with no interactions between elements), the Shapley value contribution of an element computed by MPA in accordance with Eq. (2) is equal to its single-injury effect. Yet, the significance of the proposed contribution calculation emerges when complex interactions do occur in the system. Importantly, the Shapley value has an axiomatic foundation which is well suited for the analysis of biological data [Keinan et al., 2004].

Obviously, obtaining the large number of multiregion injury observations (2^N in a system with N regions) required for the computation of the Shapley value is most often intractable. In such cases, MPA involves training a predictor using a given subset of multiregion injury observations to predict the performance levels of the missing observations. Given the predicted outcomes of all multiregion injuries, the predicted Shapley value is calculated. The accuracy of the predicted Shapley value depends on the accuracy of the predicted outcomes [Kaufman et al., 2005], which is determined using standard cross validation techniques such as leave-one-out. For a more comprehensive and formal description of this issue and the MPA, see Keinan et al. [2004, 2006]. For a detailed discussion on the accuracy of MPA with partial and noisy data, see Kaufman et al., [2005]. The final outcome from the MPA analysis is a unique set of relative contributions for all ROI.

In complex tasks, as spatial attention, the contribution of a region may strongly depend on the state (damaged or intact) of other regions. A higher order description may be necessary to capture these interactions. Such high-dimensional analysis provides further insights into the network's functional organization. A formal explanation of the way the interactions are calculated is given in Kaufman et al., [2005]. Intuitively, the interaction between a set of regions quantifies how much the contribution of the two regions together is larger (or smaller) than the sum of the contributions of each of them when the other is perturbed. Thus, this definition quantifies the synergistic interaction between elements, denoting how much "the whole is greater than the sum of its parts." In cases where the whole is smaller than the sum of its parts, that is, when the two elements exhibit functional overlap or redundancy, the interaction is negative.

Constructing a Predictive Model

MPA requires all possible multiregion injury configurations. Focusing on the predefined 11 brain ROI requires line bisection performance measurements under all 2048 different multiregion injuries ($2^{11} = 2048$). As such, a requirement is not feasible, we utilize a predictor trained on the patient injury data in hand to predict the line

bisection performance on unseen injury configurations. The analysis presented throughout this paper is based on a standard *K*-nearest neighbor predictor (with $K = 5$) applied to the data after discretization. The *k*-nearest neighbor (*k*-NN) algorithm is a method for prediction based on the closest training examples in the feature space. *K*-NN is a rather simple machine learning algorithm, in which an object (in our case a lesion configuration) is assigned with a value (performance) based on the average values of its *k* nearest neighbors. For example, in this study, we used $k = 5$, i.e., for a given unseen lesion configuration, we predict its performance to be the average performance of the five closest "neighbors" for which we have evidence on their performance. Neighbors are defined in the distance space of the lesion configurations, where the latter distance is based on Hamming distance/similarity between the discretized lesion configurations. The accuracy of the predictor is estimated based on a crossvalidation leave-one-out procedure. The accuracy achieved in our bisection data shows that the predictor obtained explains 30–50% of the variance in the data, depending on the specific task (according to the line lengths). Statistical significance of the predictor's accuracy was computed against an empirical null hypothesis, constructed by repeating the prediction procedure with shuffling: in each such repetition the performance measures were shuffled amongst all subjects (randomly shuffling the line bisection performances of the patients). The outcome of the prediction stage is the predicted line bisection performance under each of the 2048 lesion configurations, as required for the computation of Eqs. (1) and (2).

Data Discretization

We applied a threshold to the lesion level in each ROI in the normalized CT scans to transform the continuous lesion levels to a discrete binary representation. The threshold for each region was determined by searching for the threshold which best divides the performance score into two distinct distributions based on a *t*-test score. That is, for each threshold tested the performance measure scores are divided into two parts (those of the subjects with lesions below and above the threshold)—to each division a *t*-test was applied and the threshold manifesting the best separation in terms of the associated line-bisection performance levels was chosen. The discretization procedure was performed within the leave-one-out procedure to avoid over-fitting, meaning on an iterative manner using in each iteration, only 22 subjects to find the threshold, and based on that threshold we construct a predictor and evaluate the performance of the 23rd (unseen) subject. Note that the discretization procedure can be done in various ways, and there is no specific way required by the method, as long as some discretization is employed.

RESULTS

An MPA analysis was applied to each of the three line bisection tasks ("task" is defined by the length of the bisected line—144, 162, and 180 mm). The outcome is a list of contributions for each of the 11 brain regions in each task. We first applied a discretization procedure to the initial data (brain injury and bisection performance of 23 subjects) and then constructed a predictive model to compute the expected line bisection performance for the missing injury configurations (see Methods section). The predictor's accuracy was measured by a leave-one-out cross validation procedure, calculating the percentage of variance in the raw data that is explained by the predictive model. This resulted in 50.7% explained variance for the 180 mm line bisection task, 30.8% for 162 mm task, and 50.1% for 144 mm task. All predictors provided a statistically significant signal when compared with predictions obtained on randomly shuffled data ($P < 0.01$, see Methods section).

Figure 1 presents the contribution of each brain region to the line bisection tasks. We present mean and standard error across the three line bisection tasks analyzed (we collapsed the data from the three tasks as the correlation between "relative error" (see Methods section) on 180 mm

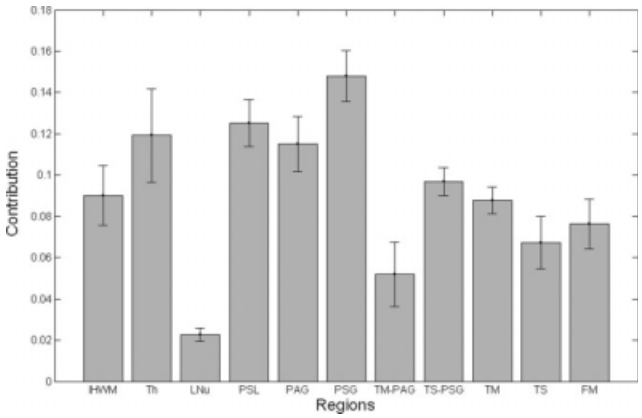

Figure 1.

MPA average contributions of different brain regions to line bisection performance. MPA contributions of the different brain regions to line bisection performance (normalized such that their sum equals one). The contributions presented are the average contributions obtained in the three line bisection tasks, the error bars show the standard deviation across the three tasks. Positive contribution means that the ROI's intactness is important for successful task performance. Regions (left to right): intrahemispheric white matter (IHWM), thalamus (Th), lentiform nucleaus (LNu), superior parietal lobule (PSL), angular gyrus of the inferior parietal lobule (PAG), supramarginal gyrus of the inferior parietal lobule (PSG), junction area of middle temporal and angular gyri (TMPAG), junction area of superior temporal and supramarginal gyri (TS-PSG), middle temporal gyrus (TM), superior temporal gyrus (TS), and middle frontal gyrus (FM).

lines and the other lengths was very high: 0.934 and 0.943 for 180 vs. 162 mm, and 180 vs. 144 mm, respectively). Positive contributions mean that the ROI's intactness is important for successful line bisection performance. Evidently, many regions play a significant role, the top five important regions are the supramarginal and angular gyri of the inferior parietal lobule (PSG, PAG), the PSL, the thalamus (Th), and the more anterior part of the temporo-parietal junction connecting the superior temporal and supramarginal gyri (TS-PSG). The contribution of the superior temporal region lags behind that of the posterior parietal and temporo-parietal junction regions. Note that one of the advantages of MPA is that the contributions are comparable. If two regions have the same contribution it means that they both contribute to the system equally. If a region contributes, averaged over all lesion configurations, twice as much as another region, its contribution will be double in magnitude. Table II describes the significance of the differences between the contributions of the different areas

Clearly, the results demonstrate that the spatial task performed by the patients is highly distributed across various brain regions. Applying a measure, suggested by Aharonov et al. [2003], to quantify the level of localization for a given task results in a localization index of 0.12. The localization index is computed over the set of contributions obtained across all ROIs. A fully localized function will be characterized by a single region carrying all the contribution. In contrast, in a fully distributed system, the contributions are equally divided across all regions. Formally, the measure L denotes the mean standard deviation of the contributions divided by the potential maximum standard deviation (with N regions).

$$L = \frac{\mathrm{std}(c)}{\sqrt{(N-1)/N^2}}$$

where L is in the range of [0,1], where $L = 0$ indicate full distribution and $L = 1$ indicates localization of the tasks to one region only. The high level of distribution, revealed in this study (0.12), implies on the processing complexity of the line bisection task and emphasizes the need for analysis methods that consider high orders of interactions between the various brain regions.

Table III describes the two-dimensional interactions between the ROIs in the study. Interestingly, all the significant interactions are positive/synergistic, that is, any two significantly interacting regions contribute more together than the sum of their individual contributions. This overall synergistic pattern reflects the general cooperative nature of the regions participating in line bisection performance.

DISCUSSION

The aim of this study was to test the feasibility of using MPA for the assessment of structure-function relationships in the human brain, based on the lesion method. Line bisection performance in USN was used as a test case. The idea of utilizing MPA for this purpose stems from earlier success demonstrated in other biological systems, where MPA served to describe, evaluate, and explain various workings of these systems [Kaufman et al., 2005; Keinan et al., 2004; Yosef et al., 2006]. The insights obtained from the earlier studies both reinforced previous knowledge in a rigorous quantitative manner and lead to novel insights and hypotheses, for example, a new suggestion concerning the localization of visual spatial attention in the cat's brain [Keinan et al., 2004], and the identification of putative novel genes and proteins that play a role in DNA postreplication repair [Kaufman et al., 2004].

In this study, MPA was able to generate a quantitative description of the relative contribution of damage in different brain structures to bisection errors in USN. All the structures entered to the analysis were found to contribute to the variance revealed in bisection performance by these

TABLE II. Significance of differences in contributions across ROIs

	IHWM	Th	LNu	PSL	PAG	PSG	TM-PAG	TS-PSG	TM	TS	FM
IHWM	1	0	0	0	0	0	0	0.0013	0.2529	0	0.0025
Th		1	0	0.3	0.96	0	0	0	0	0	0
LNu			1	0	0	0	0	0	0	0	0
PSL				1	0.2733	0	0	0	0	0	0
PAG					1	0	0	0	0	0	0
PSG						1	0	0	0	0	0
TM-PAG							1	0	0	0.0489	0.0018
TS-PSG								1	0	0	0
TM									1	0.0003	0.041
TS										1	0.071
FM											1

The table describes the statistical significance (P-values) of the difference in contribution values between pairs of regions (zero P-values indicate the P-value is below 0.0001). Gray cells are occasions of insignificant difference between the two regions forming the pair, using a standard two-sample t-test assay and correction for multiple hypotheses using FDR. Although in a few cases, the difference is not statistically significant (e.g., between PAG and PSL, or FM and TS), in most cases, it is significant.

TABLE III. Significant double interactions between ROIs

	HWW	DIEN	LNU	PSL	PAG	PSG	TM-PAG	TS-PSG	TM	TS	FM
HWW		0.065		0.038	0.011	0.031					0.039
DIEN				0.027							
LNU											
PSL					0.007						
PAG											
PSG							0.015				
TM-PAG									0.021		
TS-PSG									0.015		
TM											
TS											
FM											

The table describes the two-dimensional interactions between the ROIs in the study, presenting only significantly interacting regions (the interactions' significance was corrected for multiple hypotheses using the Bonferroni scheme, with significance level of 5%).

patients. The contribution of inferior parietal, superior parietal, temporo-parietal junction, and thalamic regions was more prominent than that of superior and middle temporal and middle frontal regions. One particular finding that points to the advantage of MPA and to the novel insights it can provide is the demonstration that regions with relatively lower involvement rate may have greater contribution to the explained variance in task performance, compared with regions with high-average involvement rate (e.g., the SPL and the thalamus contribute more than the superior temporal gyrus; Table I, Fig. 1). Other researchers [e.g., Karnath et al., 2004; Mort et al., 2003] studied the neuroanatomy of neglect using more traditional methods of lesion analysis, not taking into account the possibility that the contribution of damage in one region to the observed functional impairment depends on the concomitant damage in other regions. This fact may be responsible to the contradictory results of these studies.

As much as USN reflects a disturbance of spatial attention [Mesulam, 1999], and line bisection performance is related to the mechanisms underlying this heterogenous symptom complex, the results of this study seem to favor the primacy of posterior parietal [Mort et al., 2003; Vallar and Perani, 1986] over superior temporal [Karnath et al., 2001, 2004] role in spatial attention. This would be in accord with prominent theoretical notions and functional imaging studies of the neural basis of spatial attention [Corbetta et al., 1995, 2000; Wojciulik and Kanwisher, 1999] (see also Corbetta and Shulman, [2002]; Husain and Nachev, [2007] for review). It should be noted however that although bisection and cancellation tasks constitute the most widely used behavioral markers of USN, each of these tests reflects most probably only part of the entire syndrome (in this study, the correlation between bisection "relative error" [mean of the three line lengths, see Methods section] and the total score on the "star cancellation" subtest of the BIT was only 0.491). In fact, these two tests were shown to dissociate not only behaviorally [Binder et al., 1992] but also anatomically [Rorden et al., 2006], with impaired cancellation localizing probably more on the superior temporal and insular cortex [Committeri et al., 2007; Karnath et al., 2001, 2004], whereas impaired line bisection localizes more on the posterior parietal cortex (see Rorden et al., [2006] for discussion of this possibility and its implications).

As explained in the Introduction section, MPA assumes that the effect of damage in a given structure is related to what happens concomitantly in other structures of the functional network. In this respect, the current feasibility study deviates significantly from all earlier lesion-based studies of USN. This feature of the analysis may explain the success of MPA, based on a small ($n = 23$) sample showing significant anatomical variance, to predict the expected high relevance of network components with only minor average involvement in this sample (e.g., thalamus and superior parietal cortex). It also demonstrates that structures with high involvement rate are not necessarily the structures that contribute more to the variance revealed in task performance (e.g., the superior temporal gyrus; see Table I). Note that not always are such few samples sufficient for applying MPA to the data. For example, in this study, the analysis of the star cancellation task with the limited number of patients in this cohort was not possible, since a reliable predictor, which is an essential prerequisite for a robust MPA analysis, could not have been established. Since the analysis is based on the prediction capabilities of "unseen" lesion configurations, there may be cases where the predictor is biased. In general, however, MPA is relatively insensitive to specific missing configurations because the contributions are calculated by averaging the regions' marginal contribution over all possible lesion configurations [Kaufman et al., 2005]. Yet, this study lacks data from patients without neglect and hence the predictor may be moderately biased in some regions.

Thus, MPA approach overcomes current caveats in using lesion-based methods for understanding the neural organization of different behaviors. First, it overcomes the

controversial assumption of assigning different cognitive functions to discrete anatomical regions, this by describing an importance pattern across many regions. Second, the method is designed to address the typical scenario of patients with brain damage that occurs over several brain regions concomitantly, which markedly complicates previous suggested methods. Moreover, due to the redundancy in the functional organization of the human brain, damage to a given brain region might not lead to any obvious behavioral effect, and hence it is important to consider the interactions and crossregion effects between the different brain regions as incorporated by MPA (the contribution is computed by taking into account all possible lesion configurations). The crucial role of such interactions, both in the expression of USN and for recovery from it was convincingly shown recently in functional imaging studies [Corbetta et al., 2005; He et al., 2007].

The MPA framework can potentially aid in defining different subtypes of USN. Applying the MPA to several neglect related behavioral tasks, for example, traditional cancellation, bisection, copying, and drawing paper-and-pencil tasks, as well as to more theoretically driven computerized visual-search and spatial-cueing tasks [Deouell et al., 2005; Sacher et al., 2004] is likely to result in a specific and distinct contribution pattern for each such behavioral task. Based on these contributions one can further divide the tasks into behavioral modules based on similarity in the contribution patterns. Essentially, the outcome of such an analysis can dissociate between neglect behaviors based on different patterns of involvement of the spatial attention network.

In summary, we have presented a novel method, MPA, for treating the lesion-symptom mapping problem, and in a test case provided a rigorous comparison of relative contributions across a predefined set of brain regions responsible for impaired line bisection performance in USN. Specifically, the results of this study point to the posterior parietal cortex, its junction with the superior temporal cortex, and the thalamus as the most important regions. The conclusions from the study should be considered in the context of some obvious limitations: the relatively small sample, which enlarges the impact of the variance in imaging parameters, performance instability, time of testing after onset, rehabilitation effects, and so forth. Another limitation derives from the fact that only one USN task (line bisection) was analyzed. Applying the method to a larger dataset, using other diagnostic measures beside line bisection, will further refine and quantify the current understanding of the complex neural networks underlying USN, and potentially, other brain disorders.

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