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Brain Network Theory Can Predict Whether Neuropsychological Outcomes Will Differ from Clinical Expectations

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Abstract

Objective: Theories of brain-network organization based on neuroimaging data have burgeoned in recent years, but the predictive power of such theories for cognition and behavior has only rarely been examined. Here, predictions from clinical neuropsychologists about the cognitive profiles of patients with focal brain lesions were used to evaluate a brain-network theory (Warren et al., 2014).

Method: Neuropsychologists made predictions regarding the neuropsychological profiles of a neurological patient sample ($N = 30$) based on lesion location. The neuropsychologists then rated the congruence of their predictions with observed neuropsychological outcomes, in regard to the "severity" of neuropsychological deficits and the "focality" of neuropsychological deficits. Based on the network theory, two types of lesion locations were identified: "target" locations (putative hubs in a brain-wide network) and "control" locations (hypothesized to play limited roles in network function).

Results: We found that patients with lesions of target locations ($N = 19$) had deficits of greater than expected severity that were more widespread than expected, whereas patients with lesions of control locations ($N = 11$) showed milder, circumscribed deficits that were more congruent with expectations.

Conclusions: The findings for the target brain locations suggest that prevailing views of brain–behavior relationships may be sharpened and refined by integrating recently proposed network-oriented perspectives.

Keywords: Profile agreement; Lesion; Neuropsychology; Brain; Cognition; Network

Introduction

The brain is widely believed to operate as a complex network, and in the last 10 years neuroimaging investigations have begun to demonstrate convincingly that specific cognitive functions are supported by multiple brain regions that comprise functional, networked systems (Buckner et al., 2009; Gratton, Nomura, Pérez, & D'Esposito, 2012; Power, Schlaggar, Lessov-Schlaggar, & Petersen, 2013; Woolgar et al., 2010; Yeo et al., 2011). However, the cognitive and behavioral consequences of physically disrupting hypothesized functional networks have only begun to be investigated (Carter et al., 2010; Corbetta et al., 2015; He et al., 2007; Nomura et al., 2010; Seeley et al., 2007; Sestieri, Corbetta, Romani, & Shulman, 2011). If theories of brain-network organization are to translate into clinical practice, their predictions that changes in network organization will influence brain function, cognition, and behavior in specific ways must be validated empirically.

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Neuropsychological evaluation of cognitive and behavioral functions in individuals with focal brain injuries to putative functional systems could help validate neuroimaging-derived theories. Specifically, a converging methods approach combining neuroimaging-based predictions with neuropsychological findings might serve to test and refine novel theories of brain networks. The approach we adopted in the current study used the expertize of clinical neuropsychologists to evaluate whether a patient's neuropsychological outcome matched conventional expectations based on the locale of that patient's brain lesion.

A particular focus of recent brain-network research has been the identification of network components that might have special importance to overall network function. Such regions have often been referred to as "hubs," and putative hubs have been defined according to a variety of criteria (Power et al., 2013; Warren et al., 2014). One definition suggests that hubs should link multiple brain systems (Power et al., 2013), and a corollary of this definition is that damage to hub regions may simultaneously affect cognitive functioning across multiple domains and thereby cause widespread neuropsychological deficits. A set of putative hub brain regions meeting the system-connection definition ("target locations") was recently proposed (Power et al., 2013) and was contrasted with an alternative set of putative hubs identified instead by the number of functional connections to other brain regions ("control locations," Fig. 1; additional details Materials and Methods). We evaluated this proposal in a previous study (Warren et al., 2014), in which we compared two groups of neurological patients with focal brain lesions affecting one of the two potential types of hub locations. One group had lesions in target locations and the other group had lesions in control locations. We found that the cognitive and behavioral deficits of patients with damage to target locations were much greater and more extensive than those of patients with damage to control locations.

While the findings of Warren and colleagues (2014) were consistent with the proposal that target locations are critically important for a wide range of complex functions, the study did not test whether the results could have been predicted by conventional neuropsychological expectations based on lesion location. The distinction is important: if the predictions of the network proposal were truly novel and not already incorporated into consensus understanding of brain–behavior relationships, then the difference in neuropsychological outcomes associated with lesion location may not have been predicted by conventional neuropsychological expectations.

Predictions of certain cognitive and behavioral impairments following brain injuries are the result of substantial progress in neuropsychology over the past decades (Lezak, Howieson, Bigler, & Tranel, 2012). Of course, these predictions are necessarily imperfect due to variability in injury extent, brain organization, and other individual-difference factors (Markowitsch & Calabrese, 1996; Ojemann, 1979), but major and systematic deviations from clinical expectations should be the exception rather than the rule. For example, a neuropsychologist whose new patient is a right-handed person who suffered from an ischemic stroke in the territory of the left middle cerebral artery would reasonably predict that the patient will have deficits in language functions but not in visuospatial functions (Lezak et al., 2012). Following this logic, in the current study we used the congruence between clinical neuropsychologists' predictions and patients' observed neuropsychological profiles as an operational measure of whether lesion location was a determining factor in the accuracy of anatomy-based neuropsychological predictions. If lesion location affected prediction accuracy, then brain-network organization theory has the potential to provide novel insights into brain–behavior relationships (Power et al., 2013; Warren et al., 2014). Thus, the current methodology is an important gauge of a theory's translational potential, and it provides a demonstration of how neuroimaging-derived theories may improve predictions regarding neuropsychological outcome following focal brain injury.

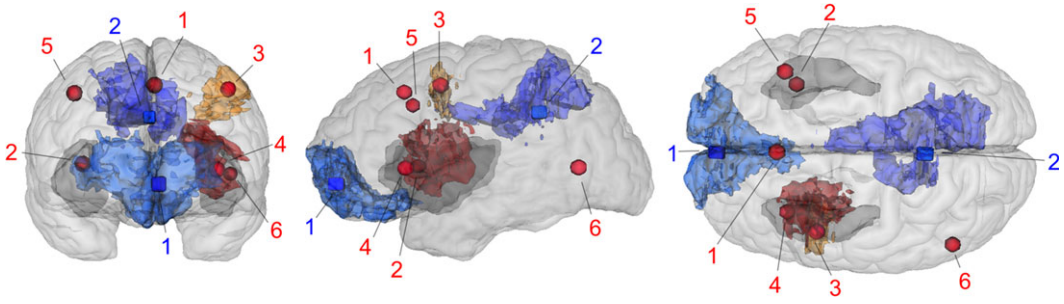

Fig. 1. Locations of putative brain-network hubs. Two sets of potential brain-network hubs were identified: "target" locations participated in many brain systems, whereas "control" locations were functionally connected to many brain areas (Warren et al., 2014). Here, target and control locations (spheres and boxes, respectively) are superimposed on the lesion-mapping template brain (in glass brain format) viewed from several perspectives (left to right: frontal, left lateral, and dorsal). Target locations were (1) dorsomedial prefrontal cortex (dmPFC), (2) right anterior insula (R aIns), (3) left posterior middle frontal gyrus (L pMFG), (4) left anterior insula (L aIns), (5) right posterior middle frontal gyrus (R pMFG), and (6) left posterior middle temporal gyrus (L pMTG). Control locations were (1) anterior medial prefrontal cortex (amPFC) and (2) posterior cingulate cortex (pCC). Other shaded portions of the figures indicate lesion overlap of the two target and two control ROIs that were sampled most often. Adapted from figure 3 of Warren and colleagues (2014).

We tested the congruence between predicted and observed cognitive and behavioral outcomes, or what we term "profile agreement," that was associated with unique patterns of focal brain injury that were hypothesized to play different roles in networks of brain systems. Using only neuroanatomical data, we identified patients with focal lesions to target locations or control locations (cases from Warren et al., 2014). We then tested: whether the expectations of clinical neuropsychologists regarding cognitive and behavioral outcomes (based solely on neuroanatomical information regarding lesion locale) were comparable to actual neuropsychological deficits; and whether there were differences in extent of prediction-observation agreement between the target and control groups. Specifically, clinical neuropsychologists evaluated whether a patient's "severity" of deficits was less than, equal to, or greater than clinically expected, and whether the "focality" of deficits across domains was more limited than, equal to, or more widespread than clinically expected.

Based on the network theory described earlier (Power et al., 2013; Warren et al., 2014), we hypothesized that target locations would participate in more functional systems than control locations, and that target locations would be important to more cognitive and behavioral processes than control locations. Furthermore, we predicted that conventional neuropsychological expectations might not accurately predict neuropsychological deficits after lesions to target locations, following the logic that damage to the target locations would impair communication between functional systems more than damage to control locations. If true, then patients with lesions of target locations would have deficits of greater than expected severity in a more widespread pattern than expected (i.e., severity > 0, focality > 0), whereas patients with lesions of control locations would have deficits of expected severity in predictable patterns (i.e., severity $= 0$, focality $= 0$). Additionally, we predicted a difference between the groups with the target group having more severe deficits in a more widely distributed pattern (i.e., $\Delta_{severity} > 0$, $\Delta_{focality} > 0$ where Δ represents between-group differences). Importantly, the outcome of this study was independent of the findings reported by Warren and colleagues (2014) because the greater cognitive and behavioral impairment in the target group observed by Warren and colleagues could have been attributable to lesion location but not be clinically surprising, whereas here, we explicitly tested the difference between predicted and observed neuropsychological outcomes.

Materials and Methods

Network Measures

Analysis of network measures used to identify target locations based on neuroimaging of healthy young adults (Power et al., 2013) was previously described by Warren and colleagues (2014), but is summarized briefly in the following section.

In order to identify locations in the brain that might serve important integrative functions in brain networks, three network analyses were performed using resting-state functional MRI data from 120 healthy young adults. The data set and first two analyses were previously reported (Power et al., 2013). Analysis 1 identified voxel-level communities in brain-wide networks, and then calculated at each voxel how many unique communities (or systems) were proximal to that voxel and thereby providing a measure of "system density." Analysis 2 identified communities in a brain-wide network of 264 nodes, and then summarized how evenly a node's edges were distributed among all communities using the measure of "participation coefficient." Nodes with high participation coefficient displayed signals highly correlated with many communities and could potentially facilitate communication or integration of multiple types of information (Power et al., 2013). Analysis 3 used exactly the same matrices used in the participation coefficient analyses to form link matrices (Ahn, Bagrow, & Lehmann, 2010), to which the Infomap algorithm was applied (Rosvall & Bergstrom, 2008), yielding a set of link communities. Link communities provide community assignments to edges instead of nodes. For a given analysis, for a given node, we defined "link community membership" as the number of link communities to which the node belonged divided by the total number of link communities present in that analysis. Thus, link community membership indexed the diversity of a node's correlations. An alternative analysis reported by Power and colleagues relied on voxel-level data rather than the 264-node parcellation, and the brain-wide map of network measures derived from voxel-level data was generally congruent with the map from the 264-node parcellation.

Sites with high system density, participation coefficient, and link community membership were hypothesized to be especially important for integrative brain functions. Locations meeting these criteria were identified as follows: volumetric peaks in community density were found; then at all 264 nodes, the summary values from each of the 3 analyses were averaged across analyses; finally, "target locations" were identified as locations where volumetric peaks fell near nodes that had high scores on all three integrative measures. "Control locations" were identified using an alternative set of criteria and were located in brain regions with different network properties (e.g., high degree centrality). The target locations and control locations were selected in order to contrast the cognitive correlates of two distinct sets of network measures: target location selection was driven by measures of participation in many functional networks; and control location selection was driven by

measures of number of connections within one or few networks. Control and target locations are illustrated in Fig. 1; note that all locations fell in association cortex rather than primary sensory or motor regions.

Participants

Participant selection and demographics were described in Warren and colleagues (2014), and are briefly summarized here.

Consent. All patients granted informed consent at the time of their enrollment in the Iowa Neurological Patient Registry ("the Registry"), and all experimental procedures were conducted in accord with the Declaration of Helsinki.

Selection procedure. Participants were selected from the Registry based solely on neuroanatomical criteria by authors DEW and JB, who were blind to the neuropsychological status of the participants. Lesion mapping was conducted using the MAP-3 method so that all lesions were represented in a common template space (Damasio & Frank, 1992). The MAP-3 method was designed to accommodate neuroanatomical information from any common structural neuroimaging modality such as computerized tomography or magnetic resonance imaging, and the lesion maps used in this study were generated based on a variety of neuroimaging modalities. Participants were eligible to be included in the current study if their mapped lesion intersected with a target or control region of interest (ROI; operationalized as an 8-mm sphere around the location in template space), but not if their mapped lesion intersected with both types of ROIs (nb. the distance between the target and control locations made this very unlikely a priori). The inclusion criterion required that more than 50% of the ROI volume be lesioned, with relaxation of this criterion to include any percentage of damage for one of the control nodes (the posterior cingulate). Overall, the selection process yielded $N = 30$ patients: 19 with damage to a target location; and 11 with lesions to a control location (nb. no selected case had damage to both types of location).

Demographics. Demographic information for the target and control groups is presented in Table 1. All patients incurred the onset of their brain lesion in adulthood (≥21 years old), and all had contemporaneous structural neuroanatomical and neuropsychological studies (both obtained more than 3 months after lesion onset). Patients had no history of intellectual limitation, learning disability, psychiatric disease, or dementia, and lesions were focal and stable. Among resection patients, several had tumors, but all were benign and non-invasive. Raw years of education were marginally greater in the control group. The target group was statistically older than the control group, and stroke was a more frequent etiology in the target group (16 of 19 vs. 4 of 11 cases). Follow-up analyses included in our previous report did not find evidence that between-group demographic or lesion differences accounted for the observed differences in neuropsychological impairment, and similar follow-up analyses were performed for the current study as well (see Analysis and Results section).

Procedure

Neuropsychologist Raters. Two neuropsychologist raters provided rating data for the current study as well as the previous study (Warren et al., 2014): authors NLD (Rater 1) and EJW (Rater 2). Critically, both raters were blind to the study hypotheses and objectives a priori and throughout all rating procedures. All ratings were completed before analysis of the data that were later published by Warren and colleagues (2014). The contribution of the raters was central to the study, and we provide additional information about their training and experience here. Both raters were trained in the methods of the Iowa-Benton School of Neuropsychology (Tranel, 2009). Regarding qualifications and experience, both raters were licensed psychologists. Both were members of the faculty in the Department of Neurology at the University of Iowa. Rater 1 had 15 years of clinical experience, and Rater 2 had 4 years of clinical experience. Additionally, both raters had extensive experience with the assessment of patients with focal neurological injuries, having evaluated many hundreds of such patients during their careers.

Neuropsychological Ratings from Previous Study. The neuropsychological ratings reported previously (Warren et al., 2014) were an important supporting component of the current study, and so we here describe the manner in which the ratings were generated. Patients who enrolled in the Registry received a comprehensive neuropsychological exam in the chronic epoch (>3 months post-injury) that included an interview with a board-certified clinical neuropsychologist and an extensive battery of neuropsychological tests (see Tables 2 and 3). Tests were administered by psychometrists who also recorded behavioral observations. At the time of testing, scores and behavioral observations were synthesized into detailed summary reports by neuropsychologists. Based on those tests, standardized quantitative indices were available for major aspects of cognition and behavior, including intellectual abilities, memory, speech and language, perception and attention, visuoconstructional ability, psychomotor and psychosensory functions, executive functions, personality and affect, and adjustment and functional status.

To quantify the cognitive and behavioral data, neuropsychological reports, test data, and accompanying notes describing test–time behavioral observations, the two neuropsychologist raters reviewed all available information order to rate each patient's degree of impairment across cognitive and behavioral domains. Each patient was rated in nine domains: Orientation/Attention; Perception; Memory; Verbal Functions/Language Skills; Construction/Motor Skills; Concept Formation/Reasoning; Executive Functions; Personal Adjustment/Emotional Functions; and Adaptive Functions. For each domain, a rating scale was employed as follows: 0 = no impairment, meaning no significant impairment; 1 = moderate impairment, meaning neuropsychological performance 1.5–2 *SD* below normative expectations and some adverse effect on activities of daily life; 2 = severe impairment, meaning neuropsychological performance 2 or more *SD* below normative expectations that substantially affected activities of daily living. Each patient was independently rated by the two neuropsychologist raters described earlier. The raters

Table 1. Demographic and lesion information for participants

Group	ROI	ID	Sex	Age (lesion)	Age (test)	Chron.	Etiology	Hand.	Edu. (Cat.)	Occup.
Control	amPFC	1	F	33	38	67	Stroke (H)	+100	13 (2)	3
	amPFC	2	F	54	55	5	Resection (T)	+100	13 (2)	1
	amPFC	3	M	46	48	19	Resection (T)	+100	12 (2)	4
	amPFC	4	M	22	26	38	Resection (T)	+100	14 (2)	3
	amPFC	5	F	63	66	37	Resection (T)	−60	13 (2)	3
	amPFC	6	M	52	56	40	Resection (T)	+100	18 (3)	1
	pCC	7	F	38	40	28	Resection (A)	+100	19 (3)	1
	pCC	8	F	38	43	59	Stroke (H)	−100	12 (2)	2
	pCC	9	F	33	34	10	Resection (A)	+100	16 (3)	1
	pCC	10	F	46	47	11	Stroke (I)	+100	12 (2)	2
	pCC	11	F	34	35	12	Stroke (H)	−100	12 (2)	3
Mean				41.727	44.364	29.636			14.000	
SD				11.723	11.535	20.631			2.530	
Target	L pMFG	12	F	56	71	179	Stroke (I)	+100	12 (2)	3
	L pMFG	13	M	30	35	63	Stroke (I)	+100	12 (2)	2
	L pMFG	14	F	55	62	76	Stroke (I)	+100	12 (2)	2
	L pMFG	15	F	47	47	4	Stroke (I)	+100	12 (2)	2
	L pMFG	16	F	54	56	14	Stroke (I)	+100	12 (2)	5
	L pMFG	17	M	67	68	16	Stroke (I)	+85	12 (2)	4
	L aIns	18	M	73	75	25	Stroke (I)	+100	12 (2)	4
	L aIns	19	M	27	27	5	Stroke (I)	+100	12 (2)	4
	L aIns	20	M	56	58	23	Stroke (H)	+100	12 (2)	3
	L aIns	21	M	57	57	6	Stroke (I)	+100	11 (1)	5
	L aIns	22	M	52	53	15	Stroke (I)	+100	12 (2)	5
	L aIns	23	M	47	49	24	Stroke (I)	+100	16 (3)	1
	dmPFC	24	F	24	32	94	Resection (A)	+100	16 (3)	1
	dmPFC	25	M	50	50	11	Resection (T)	+100	11 (1)	5
	R aIns	26	M	49	64	171	Stroke (I)	+60	16 (3)	1
	R aIns	27	M	76	77	5	Stroke (I)	+100	12 (2)	2
	R pMFG	28	F	52	53	11	Resection (T)	+100	14 (2)	2
	L pMTG	29	F	66	67	9	Stroke (H)	+100	12 (2)	3
	L pMTG	30	F	59	65	77	Stroke (H)	+100	9 (1)	5
Mean				52.474	56.105	43.579			12.474	
SD				13.962	13.984	54.027			1.806	
Statistical diff			n.s.	*	*	n.s.			∼	n.s.
Statistic value			Fish.	2.148	2.355	.817			1.924	Fish.
p value			.1	.041	.026	.421			.065	.264

Note: Group means and standard deviations are presented at the bottom of each group's section, and between-group tests are presented at the bottom of each column of numerical data. ROI, region of interest; these ROI abbreviations are defined in the Figure 1 caption as well; ID, patient ID number; Age (lesion), age of patient at time of brain injury, in years; Age (test), age of patient at time of research neuroimaging used for lesion tracing, years; Chron., chronicity, time between lesion onset and neuroimaging study, in months; Fish., Fisher's exact test (which yields only a *p* value); Stroke (H), hemorrhagic stroke; Stroke (I), ischemic stroke; Resection (T), resection of benign tumor; Resection (A), resection of arteriovenous malformation; Hand., handedness ranging from fully right handed (+100) to fully left handed (−100); Edu., education in years; Cat., educational attainment category (1, less than high school diploma; 2, high school diploma with some additional education; 3, college degree and beyond); Occup., pre-injury occupation categorized as US Bureau of Labor Statistics high-level aggregated Standard Occupational Classification (SOC) code (smaller values reflect higher professional attainment); *, $p < .05$; ∼, $.1 > p \geq .05$; n.s., $p \geq .1$.

Table 2. The Iowa-Benton Core Battery

Order	Activity or instrument
1	Interview
2	Orientation to time, personal information, and place
3	Wide Range Achievement Test-4, Reading Subtest (or Wechsler Test of Adult Reading)
4	Recall of recent presidents
5	Information subtest (WAIS-IV)
6	Complex Figure Test (copy and delayed recall)
7	Auditory Verbal Learning Test (with delayed recall) (or California Verbal Learning Test)
8	Draw a clock
9	Arithmetic subtest (WAIS-IV)
10	Block Design subtest (WAIS-IV)
11	Digit Span subtest (WAIS-IV)
12	Similarities subtest (WAIS-IV)
13	Trail-Making Test
14	Coding subtest (WAIS-IV)
15	Controlled Oral Word Association Test
16	Benton Visual Retention Test
17	Benton Facial Discrimination Test
18	Boston Naming Test
19	Picture Arrangement subtest (WAIS-III)
20	Geschwind-Oldfield Handedness Questionnaire
21	Beck Depression Inventory-II
22	State-Trait Anxiety Inventory

Note: The core battery required approximately 3 h to complete. Patients reported in this study typically completed the tests listed in the table in addition to specialized follow-up neuropsychological tests determined by performance on this battery (see Table 3). Adapted from table 4-1 in Tranel (2009). WAIS, Wechsler Adult Intelligence Scale III or IV as indicated.

evaluated each patient's history, clinical notes, and neuropsychological data set, and they rendered ratings for each of the nine domains. Raters were blind to the lesion details of all participating patients in this rating phase. After the independent ratings were completed, an average of the two raters' scores was taken for each patient for each domain.

These neuropsychological ratings were summarized and analyzed in our previous report (Warren et al., 2014). Importantly, while the target group was found to have greater impairment in more domains, we did not empirically address whether that finding would have been expected based on the neuroanatomical locale and extent of each group's brain damage. The "profile agreement" rating procedure described in the next section was explicitly designed to address the degree of agreement between expectations and outcome.

Profile Agreement Rating Procedure. Based on experience, training, and conventional principles of brain–behavior relationships (Lezak et al., 2012), the two clinical neuropsychologists rated for each patient the congruence between neuropsychological expectations based on lesion locale and neuropsychological outcomes based on test results, which we refer to as "profile agreement." Neuropsychological outcome was summarized using the impairment ratings reported by Warren and colleagues (2014), which were generated as described in the preceding section. During the preceding impairment-rating phase, neuropsychologist raters were blind to the neuroanatomical details of the cases. In the current phase, structural neuroimaging data illustrating each patient's lesion were (for the first time) presented to the rater along with the impairment ratings. A 5-point scale was used to rate two characteristics of profile agreement for each patient. First, the "severity" of the patient's impairments was rated as: much less than expected (−2), as expected (0), or much more than expected (+2) (ratings of −1 and +1 were intermediate). Second, the "focality" of the patient's impairments across cognitive domains was rated as: much more focal than expected (−2), as expected (0), or much more wide-ranging than expected (+2) (ratings of −1 and +1 were intermediate). The ratings of severity and focality were domain general, that is, only one pair of profile agreement ratings was generated for each patient by each neuropsychologist rater. To illustrate how the profile agreement scales were used, we provide an example in Fig. 2A.

Analysis

Profile agreement scores were used to evaluate whether the two groups differed from expected severity and focality of impairment, and whether the two groups differed from each other on these measures. We first qualitatively summarized the

Table 3. Follow-up neuropsychological tests

Domain	Instrument(s) or activity
Intellectual abilities	Wechsler Adult Intelligence Scale-IV
Memory	Wechsler Memory Scale-III
	Recognition Memory Test
	Iowa Autobiographical Memory Questionnaire
	Iowa Famous Faces Test
	Brief Visuospatial Memory Test—Revised
Language	Multilingual Aphasia Examination
	Boston Diagnostic Aphasia Examination
	Boston Naming Test
	Benton Laboratory Assessment of Writing
	Iowa-Chapman Reading Test
	Category Fluency Test
Academic achievement skills	Wide Range Achievement Test-4
	Subtests: reading, spelling, arithmetic, and sentence comprehension
Perception and attention	Judgment of Line Orientation
	Hooper Visual Organization Test
	Agnosia Screening Evaluation
	Screening evaluation for visual, auditory, and tactile neglect
	Rosenbaum Visual Acuity Screen
	Pelli-Robson Contrast Sensitivity Chart
Visuoconstruction	Drawing of a house, bicycle, flower
	Three-Dimensional Block Construction
Psychomotor and psychosensory functions	Grooved Pegboard Test
	Right–Left Discrimination
	Finger Localization/Recognition
	Dichotic Listening
	Line Cancellation Test
Executive functions	Wisconsin Card Sorting Test
	Stroop Color and Word Test
	Visual Image (Nonverbal) Fluency
	Category Test
	Tower of London Test or Tower of Hanoi Test
	Iowa Gambling Task
	Delis–Kaplan Executive Function System
Personality and affect	Beck Anxiety Inventory
	Minnesota Multiphasic Personality Inventory-2 (MMPI-2)
	Iowa Scales of Personality Change
	Geriatric Depression Scale
Miscellaneous Instruments	Dementia Rating Scale
	Smell Identification Test
	Useful Field of View Test
	Repeatable Battery for the Assessment of Neuropsychological Status

Note: These tests (or contemporary equivalents) were used to further inform results from the core battery described in Table 2. Adapted from table 4-2 in Tranel (2009).

ratings and the agreement between the two raters. These qualitative summaries were congruent with the preliminary nature of our rating scale and procedure. We also subjected the rating data to a standard statistical analysis (in the interest of methodological rigor, and while acknowledging limitations of our method and sample; see Discussion). Inter-rater reliability was evaluated using a weighted variant of Cohen's κ to account for the ordered nature of the ratings, and the p values provided for κ test whether the observed value was significantly greater than 0. Next, we analyzed a data set containing the per-case scores (averaged across raters) using inferential statistics as follows. Per-domain and overall impairment ratings were analyzed by testing for main effects of group membership (levels: target and control) and measure (levels: severity and focality) using a parametric repeated-measures ANOVA test. ANOVA effect sizes are described with a variant of η^2 (Bakeman, 2005). Supplemental ANOVA analyses evaluated the effects of potential covariates such as patient age at lesion onset, age at time of testing, time between lesion and testing (i.e., chronicity), and years of education. Planned comparisons between groups on each measure used parametric t tests. For both measures of profile agreement, a rating of 0 indicated congruence of expectations with observations. Therefore, planned tests of group deviation from expectations (i.e., ratings of 0) were carried out

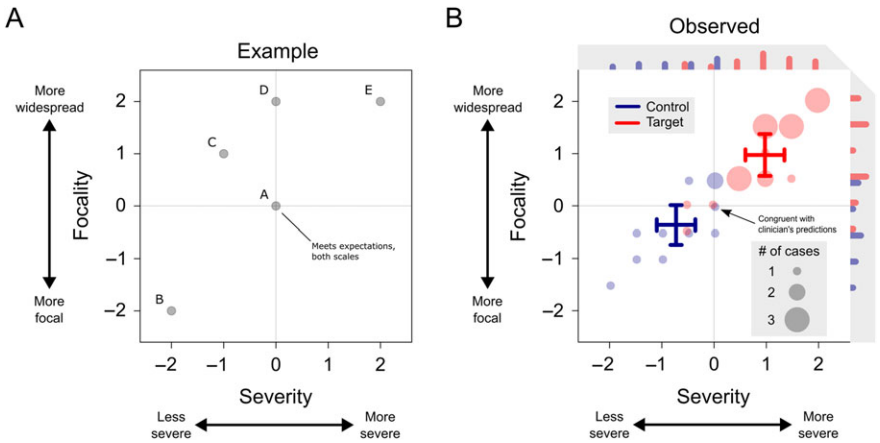

Fig. 2. Example of profile agreement rating (**A**) and observed profile agreement data for target and control groups (**B**). (A) In this example, we consider a hypothetical case with a left-hemisphere lesion in the territory of Broca's area, which might predict a language production deficit and no other cognitive or behavioral deficits. Ratings for various outcomes might include: A, the neuropsychological outcome matched the prediction; B, the outcome involved no deficits of any kind; C, the outcome was a moderate deficit the language domain combined with a moderate deficit in executive function; D, the outcome was a severe language deficit combined with a moderate deficit across several other cognitive domains; E, the outcome involved severe impairment across most cognitive domains that were much greater than predicted. (B) In the observed data, the exaggerated deficits of the target group (light) relative to expectations and to the control group (dark) are evident in both the group-level summaries (crosshairs) and individual data (circles). Circles indicate per-case ratings of profile agreement based on correspondence between expectations of neuropsychological impairment based on neuroanatomy and observed neuropsychological profile; circle size indicates the number of cases represented at each location. Crosses indicate mean and one-sample 95% confidence intervals of scores for the two groups on profile agreement components "focality" (ordinate, vertical) and "severity" (abscissa, horizontal). Shaded regions at top and right show marginal distributions of scores for focality (right) and severity (top). For display purposes only, circles were shifted slightly from observed values (which were always whole numbers or halves) in a regular manner for both groups to avoid completely overlapping values (e.g., see points at [0,0]). Notably, the correlation between the two profile agreement components across all cases was strong, $\tau = 0.846$, $Z = 5.909$, $p < .001$.

using parametric one-sample *t* tests. Sample effect sizes are described using Cohen's *d*. Correlations between profile agreement components of severity and focality were tested using Kendall's rank method (τ). We also examined the effects of potentially confounding demographic or neuropsychological variables in supplemental analyses by censoring the main data set to control for potential contributions of sex, handedness, etiology, damage to Broca's area, and language impairments. All tests used $\alpha = 0.05$.

Results

We first examined how the two raters used the scoring system as well as whether they agreed with one another. Both raters used the entire range of the severity and focality scales (i.e., −2 through +2). Examination of median scores per rater on each scale showed that, across all participants, Rater 1 tended to assign higher scores (median severity = 1.0, median focality = 2.0) than Rater 2 (median severity = 0.0, median focality = −0.5). Inter-rater reliability on both measures was significantly greater than chance ($p_s = .017$, $p_f = .037$), but the magnitude of inter-rater reliability was relatively low ($\kappa_s = 0.362$, $\kappa_f = 0.199$). The contingency tables provided in Fig. 3 illustrate the distribution of scores between raters across the two scales.

Qualitative assessment of the severity and focality scores showed that both raters assigned the target group higher mean scores than the control group on both scales (Fig. 4, top row). Across raters, this between-group difference presented in distinct patterns. Rater 1 scored the target group as having deficits much more severe and widespread than expected, whereas the control group was scored as having deficits less severe than expected and within the expected domains. Meanwhile, Rater 2 scored the target group as having impairments as severe as expected and distributed across domains as expected, but scored the control group as having impairments less severe and more circumscribed than expected. Thus, the relative difference between the target and control groups was qualitatively similar for the two raters (i.e., target group > control group on both scales), although the distribution of scores differed.

Applying inferential statistical methods to the average scores for each patient across raters supported the conclusion that patients with lesions to target locations had deficits that were more severe than expected and that involved more cognitive domains than expected. In contrast, the control group exhibited deficits that were circumscribed and conformed to conventional expectations (Fig. 2B). Specifically, ANOVA revealed a main effect of group membership, $F(1, 28) = 32.238$, $p < .001$, $\eta^2 = 0.516$, but not a main effect of measure, $F(1, 28) = 3.285$, $p = .081$, $\eta^2 = 0.009$. The target group scored significantly

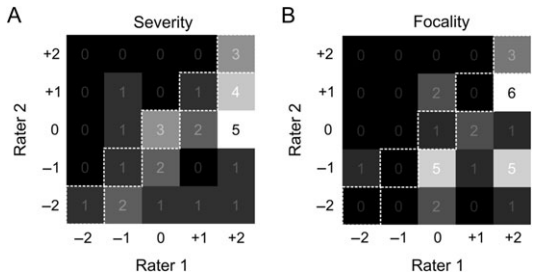

Fig. 3. Contingency tables showing inter-rater scoring summaries. Contingency tables showing the distribution of scoring and inter-rater agreement on the scales for severity (**A**) and focality (**B**). Counts are presented as numerical values in each cell, and cells are color-coded to reflect count magnitude (lighter colors indicating greater magnitude). The dashed lines surrounding cells on the diagonal highlight locations that would indicate perfect agreement between Raters 1 and 2. The distribution of counts indicates that Rater 1 tended to score cases higher than Rater 2 on both scales.

higher on severity and focality than the control group, each $T(28) > 4.8$, each $p < .001$, each $d > 1.8$, indicating a greater degree of impairment than expected and more widespread impairment than expected in the target group than in the control group (Fig. 2B). Supplemental ANOVA tests indicated that this quantitative outcome was not altered by the addition of potential covariates (i.e., age at lesion onset, age at test, chronicity, and years of education) (Table 4). Further examination of several other potentially confounding variables (i.e., sex, handedness, etiology, damage to Broca's area, and language impairments) in conditionally censored data sets indicated that the same qualitative pattern (i.e., target > control for severity and focality) was observed in the averaged data set irrespective of which variable was controlled (Fig. 4, left column). The directionality and statistical significance of the target > control group difference in each averaged censored data set was confirmed by supplemental ANOVA analysis (max. $p = .014$) (Table 4). Finally, the same qualitative pattern was also observed in the data of the individual raters (Fig. 4, center and right columns) in all cases except one: when controlling for language deficits, there was essentially no numerical difference between groups in the evaluations of Rater 2.

In planned contrasts testing whether the neuropsychological profiles of the target or control groups differed from conventional expectations (i.e., scores $\neq 0$), the target group had cognitive deficits that were more severe (severity: $M = 0.974$; $SEM = 0.190$; $T(18) = 5.628$, $p < .001$, $d = 1.291$) and widespread (focality: $M = 0.974$; $SEM = 0.205$; $T(18) = 5.628$, $p < .001$, $d = 1.291$) than what was clinically expected based solely on neuroanatomical location. In contrast, the control group showed impairments slightly less severe than expected (severity: $M = -0.727$; $SEM = 0.188$; $T(10) = 3.351$, $p = .007$, $d = 1.010$) and of a relatively focal nature that was congruent with clinical expectations (focality: $M = -0.364$; $SEM = 0.192$; $T(10) = 1.789$, $p = .104$, $d = 0.539$).

Discussion

We tested a theory of brain-network function using congruence of outcome with neuropsychological expectations to operationalize the degree to which theory-based predictions were (or were not) incorporated into prevailing clinical perspectives. Specifically, we reasoned that conventional neuropsychological expectations for brain–behavior relationships (Lezak et al., 2012) may not be sufficient to predict the consequences of damage to brain regions that have been identified as putatively important to network organization of the brain (Power et al., 2013; Warren et al., 2014). Our findings were consistent with this proposition. The neuropsychological deficits of patients with lesions to target locations were significantly greater and more widespread than expected, whereas the neuropsychological deficits of patients with lesions to control locations were generally congruent with expectations. This pattern was frequently observed within the data of both raters individually and on aggregate. These findings are consistent with a recently proposed model of the network organization of the brain (Power et al., 2013; Warren et al., 2014) and add empirical support to the potential importance of particular brain regions for many cognitive and behavioral processes. More specifically, these findings and those of Warren and colleagues (2014) suggest that brain regions which participate in many functional brain networks (i.e., target locations) may be more important to normal cognitive and behavioral performance in many domains than brain regions which are functionally connected to many brain regions but participate in relatively few functional brain networks (i.e., control locations). This perspective is potentially important for theories of brain-network function and for clinical evaluation of patients with brain injury.

The translational potential of the perspective expressed in this line of research (Power et al., 2013; Warren et al., 2014) is demonstrated by our finding that clinical expectations of cognitive impairment in brain-injured patients varied systematically according to lesion location and location-specific functional network properties derived from neuroimaging of healthy individuals. These neuroimaging-derived network properties have begun to be recognized during the last decade as the field converges

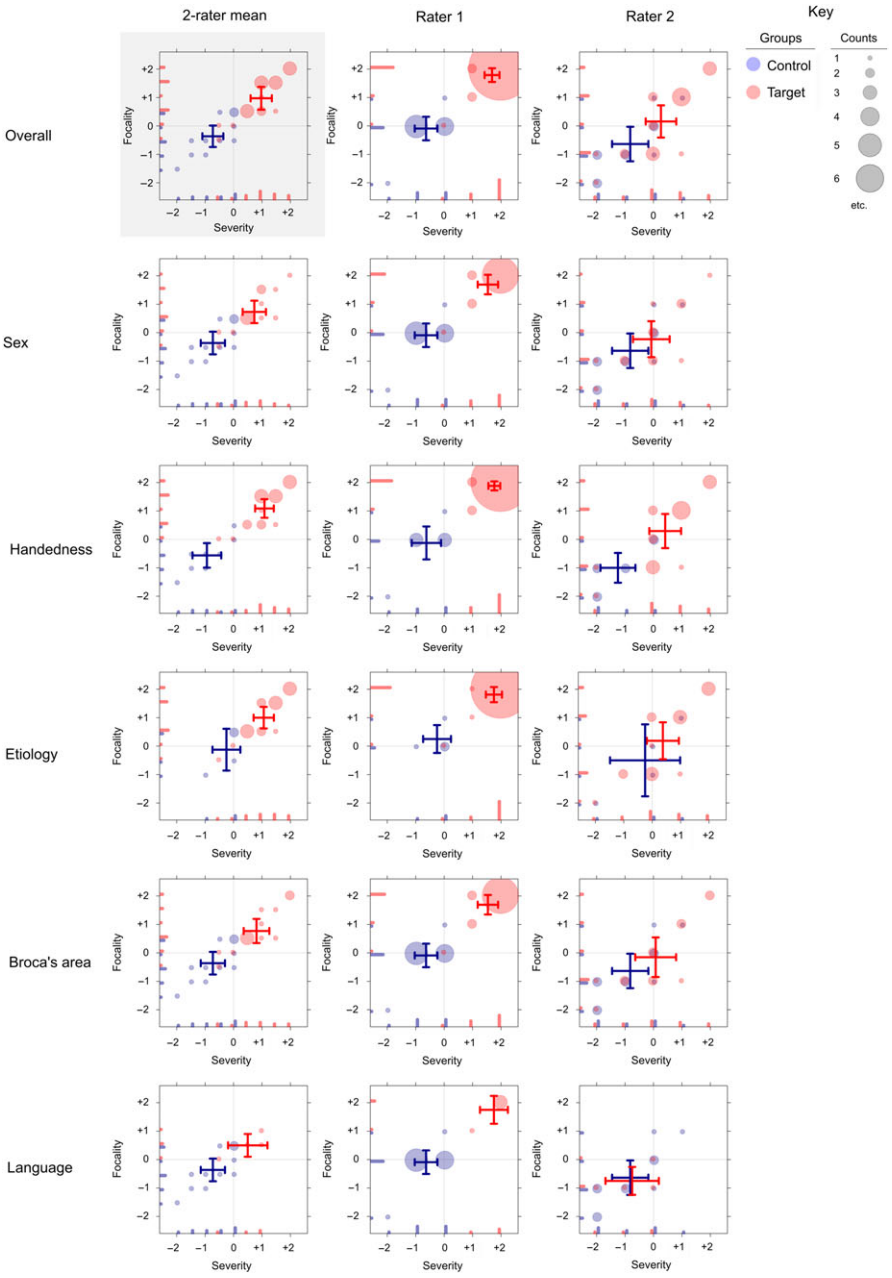

Fig. 4. Expanded profile agreement data for target and control groups. This figure presents an expanded consideration of the profile agreement data summarized in a manner similar to Fig. 2B. In the left column, the averaged 2-rater data are presented; in the center column, data from Rater 1 are presented; and in the right column, data from Rater 2 are presented. At upper right, the key indicates the colors assigned to groups (light for target cases, dark for control cases) and the correspondence between dot size and cases in the bivariate plots. The top row displays the entire data set; the highlighted plot at upper left reproduces the data of Fig. 2B for reference. Note the pattern present in the averaged data and in the data of the two raters, that is, the group means of severity and focality ratings (indicated by the light and dark crosses) differ in that the target group has higher ratings on both measures and is therefore higher and to the right of the control group. The presence or absence of this pattern of group differences in each individual plot provides a test of our hypothesis. Additional rows display censored data sets intended to address potentially confounding variables. Row 2 was censored to address a potential confound of sex by excluding data from one all-male target subgroup. Row 3 was censored to address a potential confound of handedness by including only right-handed patients. Row 4 was censored to address a potential confound of etiology by excluding any patients who had an etiology that was not stroke. Row 5 was censored to address a potential confound of damage to Broca's area by excluding patients who had any damage to a neuroanatomically defined region of interest corresponding to Broca's area. Row 6 (bottom) was censored to exclude patients with any language deficits indicated by the ratings reported by Warren and colleagues (2014). Note that the key qualitative pattern (i.e., target group > control group on ratings of severity and focality) is observed in all but one case (Rater 2, language-deficit control analysis; bottom row, right column).

Table 4. Group factor statistical significance in supplemental ANOVA tests using several conditioning variables

Type	Variable	*N*	*df*	*F*	*p*
Covariate	Age, Lesion	30	1,26	30.031	<.001
	Age, Test	30	1,26	30.523	<.001
	Chronicity	30	1,26	30.955	<.001
	Edu.	30	1,26	37.284	<.001
Censoring	Sex	24	1,22	20.509	.002
	Hand.	25	1,23	42.311	<.001
	Etiology	20	1,18	9.473	.007
	Broca's	24	1,22	19.921	<.001
	Language impairment	15	1,13	7.973	.014

Note: Using covariates or censoring variables did not affect the statistical significance of the group factor in ANOVA tests. *N*, number of participants included (nb. varies only for censored data sets); df, numerator and denominator degrees of freedom for group difference factor test; *F*, *F* value for main effect of group factor; *p*, *p* value for *F* test.

on common methods and definitions (Buckner et al., 2009; Gratton et al., 2012; Power et al., 2013; Woolgar et al., 2010; Yeo et al., 2011). Critically, because the topography of normal brain-network organization is obtained from large samples of healthy individuals, commonly available structural neuroimaging data of a neurological patient (e.g., CT or T1-weighted magnetic resonance imaging) may now provide improved predictive validity for normative network changes based on lesion location. This speculation should not be interpreted to mean that the cognitive and behavioral consequences of a particular person's brain injury will ever be perfectly predicted, but rather that normative predictions regarding those consequences can be substantially refined and improved through network-based analysis of neuroimaging data. Our findings to date are currently limited to a small number of specific brain locations (Fig. 1), and we are currently conducting further empirical tests to extend and refine our understanding of the relationship between the brain's network topology and neuropsychological outcomes.

In recent years, a number of theories of brain organization based primarily on neuroimaging data have been developed (Buckner et al., 2009; Gratton et al., 2012; Power et al., 2013; Woolgar et al., 2010; Yeo et al., 2011). While these theories are providing new insights into the functional organization of the brain, the current study shows that neuropsychological measures provide an important test of their predictive power and translational potential by evaluating the necessity of specific brain regions for cognitive or behavioral functions (Caramazza, 1992). A converging methods approach incorporating predictions from neuroimaging and evaluation via neuropsychology may eventually yield more robust conclusions than either method alone (Gratton et al., 2012; Warren et al., 2014) especially when complex theories of whole-brain networks are being tested.

The application of neuropsychological predictions to evaluate theories of brain-network organization may be novel, but discrepancies between neuropsychological and neuroanatomical findings have been described previously. Typically, reports using this approach have the immediate goal of identifying and reducing such discrepancies rather than evaluating specific theories of brain function. However, prior work provides useful examples of gaps in understanding brain–behavior relationships. Markowitsch and Calabrese (1996) described a variety of situations, both empirical and schematic, in which neuropsychological and neuroimaging results might disagree. So-called "silent" pathology is one example, referring to the scenario in which relatively normal neuropsychological presentations are accompanied by significant neuroanatomical findings via neuroimaging or post-mortem examinations. Conditions such as stroke (Chodosh et al., 1988), multiple sclerosis (Phadke & Best, 1983), hydrocephalus (Feuillet, Dufour, & Pelletier, 2007), and pathology associated with Alzheimer's disease (Crystal et al., 1988; Snowdon, 1997) have all been shown to present without clinically significant symptoms in some individuals. Conversely, conditions such as traumatic brain injury (Bigler, 2001) and psychiatric disorders (Andreasen, 1985), to name but a few, can produce neuropsychological deficits without gross neuroanatomical abnormalities or changes. Both false-positive predictions associated with silent pathology and false-negative predictions associated with deficits unaccompanied by obvious pathology demonstrate that our understanding of brain–behavior relationships is incomplete. We expect that some of these gaps will be filled by the results of research on brain-network organization, which will reduce mismatch between lesion-based expectations and neuropsychological outcome.

One avenue of research that could reveal new examples of mismatching expectations would involve a more comprehensive operationalization of expectation-outcome congruence. In the current study, the selection of potentially interesting brain regions was driven by analysis of functional neuroimaging data from healthy young adults (Power et al., 2013; Warren et al., 2014) followed by neuropsychological evaluation of select neurological cases. An intriguing approach in future studies would be to reverse the process. Given a sufficiently large sample of neuropsychological patients with focal brain lesions, profile agreement ratings by neuropsychologists could potentially uncover other brain regions that play unexpected roles in cognition

and behavior. In such an investigation, profile agreement ratings describing patients with lesions of many different brain regions would be compiled and the degree of congruence with expectations could be mapped to individual brain regions in the manner of voxelwise lesion-symptom analysis (Bates et al., 2003). The strictly empirical, atheoretical nature of this approach could identify brain regions showing greater or lesser deviation from expectations without appeal to *a priori* explanatory factors, and the findings might reveal new, previously unappreciated roles for some brain regions. In turn, these roles might also be reflected in network properties derived from functional neuroimaging data. Such mutually informative interactions between neuropsychology and neuroimaging will take time but could be profitable avenues for advancing both disciplines.

Our study had limitations. As in many neuropsychological investigations our sample sizes were not large. Another limitation was that ratings were provided by two neuropsychologists from the same institution. Although each had significant clinical expertize and a unique, diverse training history from their graduate and internship experience, it is possible that different neuropsychologists might rate the same patients somewhat differently. We plan to explore this issue in future work by polling larger groups of neuropsychologists to gain a broader perspective. We would note, though, that we have every reason to believe that the views of the neuropsychologists who participated in this study would be fairly typical of the field. Regardless, polling of additional neuropsychologists will also provide a further test of whether profile agreement is well characterized by two components, given that severity and focality were correlated in our sample (Fig. 2B). Another limitation was that the clinical neuropsychologists who provided profile agreement ratings here previously rated the neuropsychological profiles of the same patients (as reported by Warren et al., 2014). However, we reiterate that the neuropsychologists were blinded to the aims and hypotheses of the study until after all ratings were collected, which would make systematic biases unlikely to support our hypotheses. Also, we note that despite the shared institutional affiliation of both raters, we observed inter-rater differences. While the same qualitative pattern (target > control) was evident in their individual ratings for the main analysis and most control analyses (Fig. 4), one exception was found in the language-deficit control analysis (see Results). Uniquely in this condition, Rater 2's profile agreement ratings did not reflect the general pattern of target > control, and the groups were instead rated similarly. It is therefore possible that language deficits may underlie some of the differences in profile agreement between the groups, and this potential confound should be carefully controlled in future studies by including target-group patients without language deficits. A further limitation was variation in the ecological validity of the neuropsychological tests used to generate patient profiles (Chaytor & Schmitter-Edgecombe, 2003). This limitation is relevant to many neuropsychological studies, and we addressed it by including ratings of adaptive function and outcome in the patient profiles based on information from neuropsychological reports (Warren et al., 2014). Finally, our theory of brain-network organization was tested using a limited number of target and control locations. Additional target and control locations are currently under investigation. We also plan to collect functional neuroimaging data from neurological patients with the related goal of evaluating how brain damage affects the organization of brain networks.

In conclusion, our findings demonstrate that the accuracy of clinical expectations based on neuroanatomy alone can vary with lesion locale. These findings are consistent with the predictions of a novel theory of brain-network organization (Power et al., 2013; Warren et al., 2014) that has the potential to enhance clinical care by improving predictions of neuropsychological impairment. More specifically, our findings indicate that brain regions such as the selected target locations are potentially critically important for complex cognition, and that resting-state functional neuroimaging data from healthy individuals may be sufficient to identify such regions at the population level. We believe that future refinements of this model will allow clinicians to develop more accurate predictions regarding neuropsychological outcomes for individuals with brain injury, potentially augmented by functional neuroimaging analysis of brain networks post-injury. Finally, our study underscores the continuing importance of neuropsychological evaluation despite the increasing availability of neuroimaging data. While neuroimaging and conventional expectations may inform diagnosis, neuropsychological testing remains essential for the evaluation of cognitive impairment in every unique individual with a brain injury.

Author contributions

DEW, JDP, JB, HS, SEP, and DT designed the research; NLD and EJW performed neuropsychological ratings; DEW conducted analysis; all authors wrote the paper.

Conflict of Interest

None declared.

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