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Research report

Reperfusion of specific cortical areas is associated with improvement in distinct forms of hemispatial neglect

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ABSTRACT

Objective: To test the hypothesis that restoring blood flow to specific right cortical regions in acute stroke results in improvement in distinct forms of hemispatial neglect distinguished by reference frame: viewer-centered versus stimulus-centered neglect.
Methods: Twenty five patients with acute right stroke were evaluated at Day 1 and Day 3–5 with a battery of neglect tests and Diffusion- and Perfusion-Weighted MR Imaging. Multivariate linear regression analysis revealed Brodmann areas (BAs) where reperfusion predicted degree of improvement in scores on each type of neglect, independently of reperfusion of other areas, total change in the volume of infarct or hypoperfusion, and age.
Results: Reperfusion of dorsal frontoparietal cortex (including BAs 40, 46, and 4) independently predicted improvement in viewer-centered neglect, such as detecting stimuli on left in line cancellation and scene copying ($r = .951$; $p < .0001$). Reperfusion of a more ventral temporo-occipital cortex, including right BAs 37, 38, 21 and 18, independently contributed to improvement in stimulus-centered neglect, such as detecting left gaps in circles ($r = .926$; $p < .0001$). Reperfusion of right midfusiform gyrus (temporal occipital cortex), change in total volume of ischemia, change in volume of hypoperfusion and age predicted degree of improvement in reading (reduction in "neglect dyslexic" errors; $r = .915$; $p < .0001$). Results demonstrate that reperfusing specific cortical regions yields improvement in different types of neglect.

1. Introduction

Unilateral spatial neglect (USN) is a failure to report, respond, or orient to a novel or meaningful stimulus on the side of space contralateral to a brain lesion that cannot be attributed to malfunction in primary sensory or motor systems (Heilman et al., 1993). Studies investigating the neural loci of USN have found evidence that USN can arise from damage to a number of different brain regions.

It is widely agreed that USN is a heterogeneous disorder (Heilman et al., 1993; Na et al., 1998; Vallar et al., 2003, 2010; Verdon, et al., 2010; Hillis, 2006). One important criterion for distinguishing different types of USN is the spatial reference frame with which the neglect is defined (Chatterjee, 1994; Ota et al., 2001; Hillis and Caramazza, 1995). *Viewer-centered* USN results in a tendency to neglect stimuli on the contralesional side of the viewer, irrespective of the orientation of the viewer or of the stimulus (Chatterjee, 1994; Hillis et al., 1998).

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Stimulus-centered USN results in errors that increase further toward the contralesional side of the stimulus, regardless of the position of the stimulus relative to the viewer (Medina et al., 2009; Hillis and Caramazza, 1991, 1995). For example, someone with left stimulus-centered USN would not neglect the entire stimulus, but only the left half of the stimulus, whether the stimulus was presented on the right or the left side of his body. Finally, *object-centered* USN results in a failure to process one side of the canonical representation of objects with inherent left and right sides (e.g., words, letters, maps, certain flags) regardless of the orientation of the object at presentation (Baxter and Warrington, 1983; Hillis et al., 2005; Barbut and Gazzaniga, 1987). One can differentiate between viewer-centered and stimulus-centered USN by investigating the error pattern that results from the administration of certain behavioral tasks involving stimuli that are designed to indicate explicitly the presence of intact viewer-centered versus stimulus-centered spatial processing. For example, in a gap detection task (see Ota et al., 2001) subjects are instructed to indicate whether stimulus targets on a sheet of paper are complete circles or whether they contain a gap on either side. The presence of a viewer-centered neglect manifests itself in this task as a tendency to completely ignore stimulus targets on the neglected half of the sheet regardless of their stimulus class. In contrast, stimulus-centered neglect often results not omission of targets on the left side of the viewer, but instead in a high frequency of errors involving misclassification of circles with left gaps as complete circles (see Fig. 1 for an example of this task).

Neglect can also differ based on the nature of the underlying bias, with a "perceptual-attentional" bias resulting in a failure to detect stimuli on the contralesional side, versus a "motor-intentional" bias that results in a reduction of movements toward the contralesional side (Coslett et al., 1990). Using a novel video apparatus described by Nico (1996), some investigators have isolated the effects of these biases by having subjects perform line bisection and target cancellation in a setup that decoupled visual feedback from the physical workspace (Na et al., 1998). Some patients showed mostly perceptual-attentional bias, some showed mostly motor-intentional bias, and others showed a combination of the two.

Given the heterogeneity of the neglect disorder, it is not surprising that multiple studies have found evidence for different neural substrates. Most studies of lesion location have implicated the right posterior parietal lobe as the likely cortical candidate for USN. In a computed tomography (CT)-scan study with 47 neglect patients, Vallar and Perani (1986) found that lesions to the right inferior parietal lobule (IPL) are most frequently correlated with neglect. Other lesion correlation studies (Heilman et al., 1983; Maguire and Ogden, 2002) and single case studies also support this relationship. Correlational studies have also implicated the right temporoparietal–occipital junction in USN (Heilman et al., 1983; Leibovitch et al., 1999).

In addition to this variability within the parietal region, other studies have even implicated areas outside the parietal lobe in the neglect syndrome. One study found lesions to the right middle temporal gyrus (MTG) to be most highly correlated with USN, with 12 out of 18 neglect patients presenting with damage to this area (Samuelsson et al., 1997). Finally, the frontal lobes have also been implicated in USN (Heilman et al., 1983; Damasio et al., 1980; Husain and Kennard, 1996).

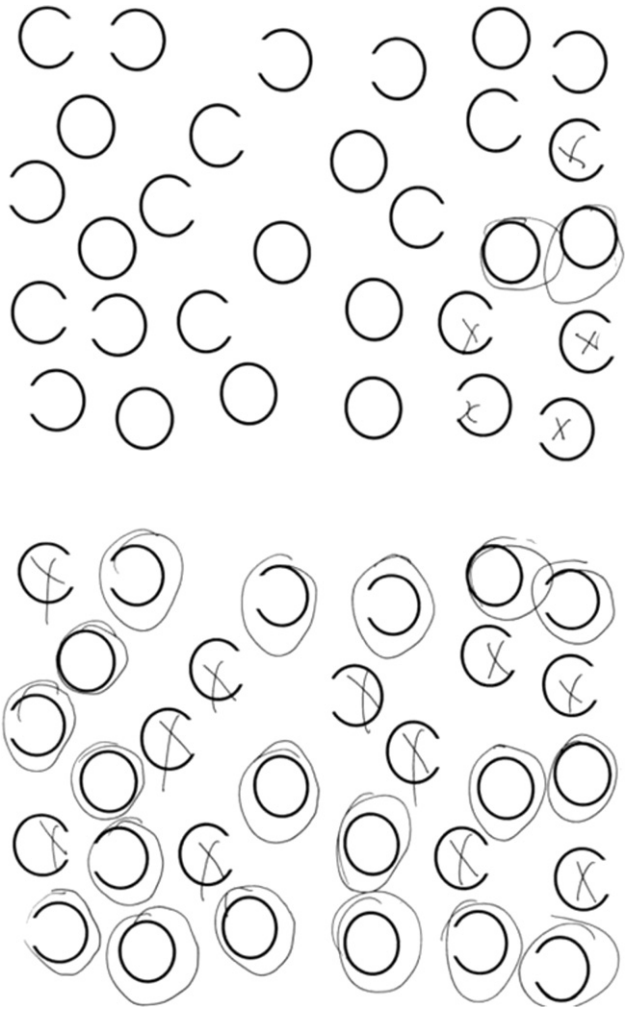

Fig. 1 – Examples of the task described by Ota et al. (2001). Top panel shows a performance of a patient with viewer-centered USN who failed to mark lines on the left side of the view. The lower panel shows performance of a patient with stimulus- or object-centered neglect who incorrectly marked stimuli with left gaps as complete by circling them, whether they were on the left or the right side of the view.

Neuroimaging methods that allow an investigator to correlate recovery of localized damaged brain tissue with improvements in task performance can be used along with behavioral tasks designed to differentiate between different forms of USN in order to elucidate structure–function relationships. Acutely, Diffusion-Weighted Imaging (DWI) identifies areas of permanent structural damage (Fisher, 1995). In contrast to marking irreversibly damaged tissue, Perfusion-Weighted Imaging (PWI) reveals the total region of brain tissue affected by insufficient blood flow; although these areas of tissue are dysfunctional due to their lack of perfusion, they are potentially salvageable if blood flow can be restored (Beaulieu et al., 1999). It follows that any mismatch between the DWI and PWI (the "diffusion–perfusion mismatch") represents areas of brain tissue that are dysfunctional but can be recovered with the restoration

of blood flow; this potentially recoverable tissue is often referred to as the ischemic penumbra.

Because the diffusion–perfusion mismatch provides a measure of potentially recoverable brain tissue, comparison of mismatch over a 2–3 day period indicates areas of brain tissue that have become reperfused. At the same time, changes in behavioral task performance between Days 1 and 3 provide a measure of which cognitive abilities have improved over time. By correlating the area of tissue that has been recovered via reperfusion with any improvement in task performance one can then construct a structure/function relationship between the recovered area and the concomitant improvement in behavioral performance.

In this study, we apply this method of investigation to the neglect syndrome to test the hypothesis that reperfusing specific brain regions results in recovery of specific types of neglect. Because spatial neglect is a heterogeneous disorder that manifests itself in distinct ways in behavioral testing, improvement from impaired performance can be isolated to a specific form of spatial processing. For example, omission of stimuli on the left of the viewer in the gap detection task is indicative of a *viewer-centered* USN – indicating a deficit in egocentric spatial processing. A reduction in omission errors on follow-up testing might reflect that certain brain region(s) involved in constructing, maintaining, or processing an egocentric representation of space had been successfully recovered through reperfusion. In contrast, omission of left-sided gaps on both sides of the viewer in the gap detection task is indicative of a *stimulus-centered* USN – indicating a deficit in allocentric spatial processing. Reduced errors in left gap detection in follow-up testing might reflect that different brain region(s) – those involved in constructing, maintaining, or processing an allocentric representation of space had been successfully recovered through reperfusion. Analyzing changes in the DWI/PWI abnormalities in this same period would test these hypotheses.

2. Methods

2.1. Subjects

Twenty five patients diagnosed with acute right hemisphere stroke participated in the study. Inclusion criteria were: 21 years or older; admittance into the hospital within 24 h after onset of symptoms of acute ischemic right hemispheric stroke; and the ability to provide informed consent or have a relative/caregiver provide informed consent. Exclusion criteria included: previous stroke or neurological disease; premorbid lack of proficiency or literacy in English; premorbid uncorrected visual loss; hemorrhage on initial magnetic resonance imaging (MRI) or CT scan; brainstem or cerebellar stroke; allergic reaction to Gadolinium; diminished level of consciousness; need for intubation or ongoing IV sedation; and contraindication for MRI (e.g., claustrophobia, pregnancy, metallic implants, cardiac pacemaker). Although the presence of USN was not required for enrollment in the study, there was a bias for patients with USN to be referred for enrollment because these patients clinically were assumed to have hemispheric rather than brainstem strokes even before imaging.

2.2. Neglect testing

A battery of tests was administered to each patient in order to determine both (a) severity of neglect, and (b) the frame(s) of reference by which the neglect was defined. Although other tests were administered, we only analyzed performance for the purpose of this study on three tests that (1) were administered to the majority of patients, and (2) helped distinguish between neglect in different reference frames. Tests were first administered on Day 1 after admission into the hospital. The same battery was again given on Day 3–5 in order to determine the degree and character of any persistent neglect and any neglect amelioration during the intervening period. Each administration of the test was coupled with both DWI and PWI in order to assess the total area of brain dysfunction associated with the observed behavioral performance and to localize areas that may have reperfused.

(i) Line cancellation – Subjects were given a standard line cancellation task in which they were asked to cross out a series of lines approximately evenly distributed across a sheet of paper. This task was presented to the left (Left Body Field – LBF), middle (Center Body Field – CBF), and right (Right Body Field – RBF) of midline of the subject's body. Deteriorating performance on line cancellation when the test is administered left of the patient midline is indicative of viewer-centered neglect.

(ii) Gap detection task – In this task, the patient was given a sheet of paper filled with whole circles and circles with gaps on either the right or the left side (see Ota et al., 2001). The patient was then instructed to cancel out (with an X) the circles with gaps while circling the full circles. This test was administered at the midline of the patient's body. Omission of targets on the left side of the sheet is a pattern characteristic of viewer-centered neglect, as those targets are on the left side of the patient's midline. In contrast, stimulus-centered neglect is manifested in this task as a tendency to make errors involving failure to note the left gap circles on both sides of the viewer (incorrectly circling the circles with left gaps).

(iii) Reading task – Subjects were asked to read aloud from a list of words ($n = 30$) divided into two columns. Subjects were also presented with a passage consisting of 34 words. Both tests were presented at the patient's midline. Errors on the left side of individual words on both sides of the paper ("neglect dyslexic" errors, such as cable read as "able" or "cable" or "wobble") were taken as evidence for stimulus/object-centered neglect. Omission of the words on the left half of the paper or the left column was taken as evidence of viewer-centered neglect.

(iv) Scene copy – Participants were asked to copy a scene of a house, a fence, and two trees. Omission of left parts of stimuli on both sides of the scene was taken as evidence of stimulus-centered neglect; omission of stimuli on the left side of the scene was taken as evidence of viewer-centered neglect. This test was administered at the midline of the patient's body.

2.3. Imaging

MRI sequences included T2, Fluid Attenuated Inversion Recovery (FLAIR) to rule out old strokes, Diffusion-Weighted Images (Trace Images) and Apparent Diffusion Coefficient Maps (to identify the acute infarct), Susceptibility Weighted Images (to rule out hemorrhage) and Perfusion-Weighted Images (PWI). Scans were obtained on a 3 T Philips magnet (in a few cases scans were obtained on a 1.5 T GE or Siemens magnet). For PWI, 20 cc GdDTPA contrast was power-injected at 5 cc/sec. Voxel volume for PWI and DWI was 4.4 mm^3. Slices were 5 mm thick; whole brain coverage was obtained parallel to the anterior commissure to posterior commissure line (AC–PC line). Images were analyzed by technicians blinded to the cognitive data. Hypoperfused tissue was defined as tissue with >4 sec delay in time to peak (TTP) arrival of contrast relative to homologous voxels in the unaffected hemisphere.

2.4. Reperfusion

This was an observational study; there was no attempt to influence treatment. There were 15 patients who showed a diffusion–perfusion mismatch such that the perfusion abnormality was twice the volume of the ischemic tissue on DWI. All patients who showed such a diffusion–perfusion mismatch had some intervention designed to improve or restore blood flow to the cortex. Ten patients received medications and/or intravenous fluids to increase mean arterial blood pressure to improve collateral circulation; two patients received urgent carotid endarterectomy; two patients had urgent stents placed in the carotid artery on the left; two patients received intra-arterial thrombolysis.

2.5. Statistical analysis

Multivariate regression analyses were carried out with severity of viewer-centered neglect and severity of stimulus-centered neglect as the dependent variables, and the following variables as independent variables: extent of reperfusion of each of the following Brodmann areas (BAs) in the right hemisphere: 10, 18, 19, 21, 22, 37, 38, 39, 40, 44, 45, 46, age, total change in volume of reperfusion on PWI, and total change in volume of dense ischemia on DWI as independent variables.

Hypoperfused tissue was defined as tissue with >4 sec delay in TTP arrival of contrast relative to homologous voxels in the unaffected hemisphere, based on earlier studies showing that this degree of delay results in dysfunction (Hillis et al., 2001a, 2001b). Reperfusion was defined as change from >4 mean sec delay in TTP arrival of Gadolinium to <2 sec delay in TTP in that BA compared to the same BA in the left hemisphere. Technicians masked to the cognitive performance examined each of 12 BAs in the frontal, parietal, temporal, and occipital cortices for partial, complete, or no reperfusion. Partial reperfusion was identified when only part of the BA was reperfused. The BAs that were selected (10, 18, 19, 21, 22, 37, 38, 39, 40, 44, 45, 46) were based on previous studies showing a relationship between these cortical regions and neglect (Heilman et al., 1993; Vallar et al., 1999; Sameulsson et al., 1997; Verdon et al., 2010). We did not examine subcortical white matter tracts because we did not expect to be able to show reperfusion of these structures, and this was a study of the role of reperfusion in recovery.

Change in viewer-centered USN was defined by the change in mean omission across the following scores: lines omitted in line cancellation on the left side of the viewer in line cancellation, words omitted on the left side of the viewer in reading, stimuli omitted on the left side of the viewer in the gap detection test, and segments omitted on the left side of the viewer in the scene copying task. The left side of the viewer was defined in these tasks as beginning with the part of the view/page most to the left where the patient responds; so if the patient only copied the far right stimulus in the scene, all parts of stimuli to the left of that copied stimulus are counted as omitted. We considered sheets presented on the patient's left and at center in scoring change in viewer-centered neglect.

Change in stimulus-centered USN was defined by the change in mean errors on left parts of stimuli across the following scores: "neglect dyslexic errors" (words misread on the left side; e.g., *chair* read as "fair") in reading, failure to detect left gaps in the gap detection test, and left segments of individual stimuli omitted on both sides of the viewer in the scene copying task. The mean percent error at Day 3 was subtracted from the mean percent error at Day 1, so that a reduction in error rate (improvement) resulted in a positive value.

The alpha level to include a variable was $p < .05$; the alpha level to exclude a variable was $p > .1$. We evaluated for collinearity by checking the variance inflation factor (VIF) for included and excluded factors. We then carried out multivariable regression to identify which variables independently contributed to severity of each type of neglect, by entering together change in perfusion status in all of the BAs (for all patients), total change in volume of hypoperfusion, and age.

3. Results

Mean age of stroke patients was 65.5 (±SD 16.1). There were 14 women and 11 men. On Day 1, 8 (30%) had some degree of viewer-centered neglect; 6 (22%) had some degree of stimulus-centered neglect as well as viewer-centered neglect.

The mean volume of dense ischemia on DWI at Day 1 was 23.1 (±27.2) cc. The mean volume of hypoperfusion (>4 sec delay in TTP relative to the left homologous voxels) on PWI was 94.6 (±85.5) cc. The mean change in volume of ischemia on DWI was 3.2 (±18.5) cc increase (growth in infarct); the mean change in volume of hypoperfusion on PWI was 35.1 (±55.0) cc decrease, or improvement.

Multivariate linear regression analysis revealed BAs where reperfusion was associated with improvement in each type of neglect independently of reperfusion of other regions and independently of age and change in volume of infarct and hypoperfusion.

3.1. Viewer-centered neglect

The degree of improvement in viewer-centered neglect was based on the improvement in the number of stimuli detected on the left side in the gap detection test, improvement in accuracy in line cancellation, and improvement in accuracy of detecting stimuli on the left side of the scene in scene copying.

Improvement of viewer-centered neglect (ΔVCN) was accurately predicted by the following model, where BA = reperfusion in a given Brodmann area:

$$\Delta VCN = (1.6)BA\ 40 + (1.4)BA\ 46 + (.91)BA\ 4 - (.51)BA\ 10 - (.58)BA\ 44 + .19(r = .951;\ p < .0001)$$

In this formula, the integer in parentheses, the beta value, provides the weight of the association between the improvement in viewer-centered neglect and reperfusion of the Brodmann area.

In other words, improvement in viewer-centered neglect was associated with reperfusion of right BA 40 (supramarginal gyrus in the IPL) and BA 46 (dorsolateral prefrontal cortex – DLPFC) and BA 4 (motor cortex) and negatively associated with reperfusion of BA 10 (orbitofrontal cortex) and BA 44 (right pars opercularis).

3.2. *Stimulus-centered neglect*

Improvement of stimulus-centered neglect (ΔSCN) was accurately predicted by the following model, where BA = reperfusion in a given Brodmann area:

$$\Delta SCN = (1.4)BA\ 37 + (1.3)BA\ 18 + (.73)BA\ 38 - (.83)BA21\ (r = .926;\ p < .0001)$$

In other words, improvement in stimulus-centered neglect was associated with reperfusion of right BA 37 (fusiform gyrus in the inferior temporo-occipital cortex) and BA 18 (anterior occipital cortex) and BA 38 (anterior temporal cortex) and negatively associated with reperfusion of BA 21 (inferior temporal cortex).

The only single task where accuracy was significantly predicted by location of reperfusion was reading. Improvement of reading was predicted by the following model:

$$\Delta Reading = (26.5)BA\ 37 + (.49)age + (.0001)\ \text{total reduction in volume of ischemia on DWI} + (.0001)\text{total volume of reperfusion on PWI} - 46(r = .915;\ p < .0001)$$

In other words, improvement in reading, manifest primarily by a reduction in "neglect dyslexic" errors (e.g., clock read as "rock") was very strongly associated with reperfusion of fusiform cortex in posterior temporo-occipital temporal cortex, an area strongly activated in reading in normal subjects (McCandliss, et al., 2003; Hillis and Rapp, 2004) and homologous to an area associated with impaired reading in left hemisphere stroke (Binder and Mohr, 1992; McCandliss, et al., 2003). It was minimally influenced by age and change in total volumes of dense ischemia and hypoperfusion as well.

In the above analyses, collinearity was acceptable, with a VIF of 1.037 to 2.255 for variables included in the models.

3.3. *Illustrative cases*

We now present some case studies, both to illustrate our experimental paradigm of successive behavioral testing with concomitant DWI/PWI scanning, and to emphasize the effects of reperfusion on specific types of neglect.

3.3.1. *Case studies*

Case 1: Improvement in stimulus-centered neglect with reperfusion of temporal cortex

Case 1 is a 62-year-old man who had both viewer-centered and stimulus-centered neglect as well as left hemiplegia on Day 1 associated with a watershed infarct on DWI and hypoperfusion of the entire right middle cerebral artery (MCA) territory (Fig. 2). Magnetic resonance angiogram (MRA) showed occlusion at the middle cerebral artery stem. On line cancellation, he canceled only 11% of lines even when the paper was place on his right (good side). He could not find the paper when it was placed on his left side or at midline. His copy of a scene showed both viewer-centered neglect and stimulus-centered neglect. He omitted the left two items in the scene (viewer-centered neglect) as well as the left parts of the right-sided items (stimulus-centered neglect). In reading words he showed both viewer-centered and stimulus-centered neglect as well. He failed to read the left column of words. He read none of the words in the right column correctly, but made "neglect dyslexic" errors on all of them. His errors included *speaking* read as "king", *swallow* read as "allow", and *known* read as "crown". His mean arterial pressure (MAP) was increased with fluids and medications to

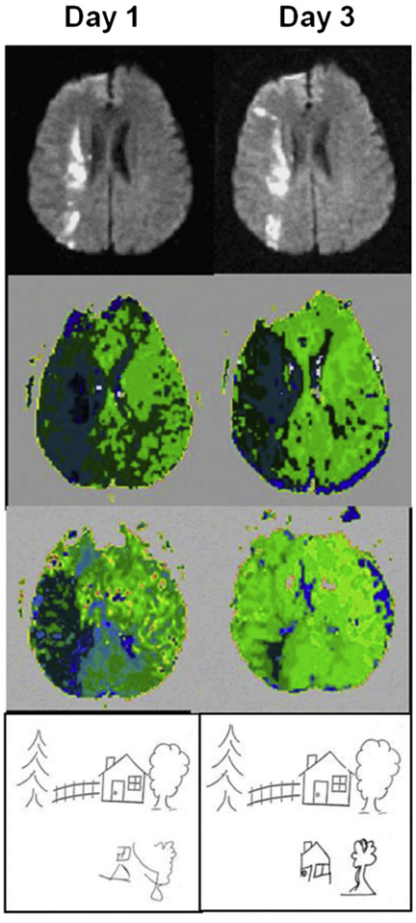

Fig. 2 – Top panel: DWI scans at Day 1 (left) and Day 3 (right) of Case 1. Middle 2 panels: PWI scans at Day 1 (left) and Day 3 (right) of Case 1. Lowest panel: Copy of the scene at Day 1 (left) and Day 3 (right) by Case 1.

slightly above average in attempt to improve collateral circulation and reperfuse the ischemic tissue.

On Day 3, he showed no improvement in viewer-centered neglect (11% correct to 8% correct on line cancellation on the right, still with 0% on the left side of his body and at midline), but did show improvement in stimulus-centered neglect, improving from 0% to 33% correct reading words on both sides of the page ($\chi^2 = 27$; $p < .0001$). His copy of the scene also showed improvement in stimulus-centered neglect; he now copied the left sides of the right items, although he still showed viewer-centered neglect by omitting the left items in the scene. Perfusion images from the same day show reperfusion of the right temporal cortex including BA 37 and 38 but persistent hypoperfusion of the frontoparietal cortex including BA 40, 46, and 4 (Fig. 2). He also remained left hemiplegic.

Case 2: Improvement in viewer-centered neglect with reperfusion of frontoparietal cortex

Case 2, whose scans are shown in Fig. 3 at Day 1 had a MAP that was slightly below normal of 90. He had viewer-centered neglect manifest by canceling 69% of lines in line cancellation when the page was presented on the left side of his body versus 96% of lines when the page was presented on the right side of his body ($\chi^2 = 12.1$; df = 1; $p < .0004$) (he canceled 90% of lines when the page was presented at the body midline). At that time, MRI showed a subcortical infarct on DWI and hypoperfusion of the right parietal cortex including supramarginal gyrus as well as posterior frontal cortex (Fig. 3, left). Although he had mild delay of perfusion in BA 38 (anterior temporal lobe), the perfusion was not sufficiently abnormal within this area to meet our criteria for hypoperfusion. His blood pressure was elevated with a combination of intravenous fluids and medications, titrated to improvement in hemispatial neglect. On Day 3, his MAP was 119 and he made no errors in line cancellation on the left or right side of his body (i.e., he was 100% correct at all locations). Repeat MRI showed reperfusion of the entire frontoparietal cortex, including right BA 40, 46, and 4.

Case 3: Partial improvement in viewer- and stimulus-centered neglect with partial reperfusion of parietal and temporal cortex

Case 3, whose scans are shown in Fig. 4 at Day 1 had a normal MAP of 103. She had both viewer-centered neglect and stimulus-centered neglect as illustrated by omission of both a left-sided figure in copying a scene and the left side parts of the figures in the scene at Day 1. Her blood pressure was elevated with a combination of intravenous fluids and medications, titrated to improvement in hemispatial neglect. On Day 4, she showed partial reperfusion of both the left temporal cortex (including BA 37) and left parietal cortex including supramarginal gyrus (BA 40). Her copy of the scene at Day 4 showed improvement of both viewer-centered neglect, with inclusion of the left-most item now, and stimulus-centered neglect, with better inclusion of left sides of several stimuli.

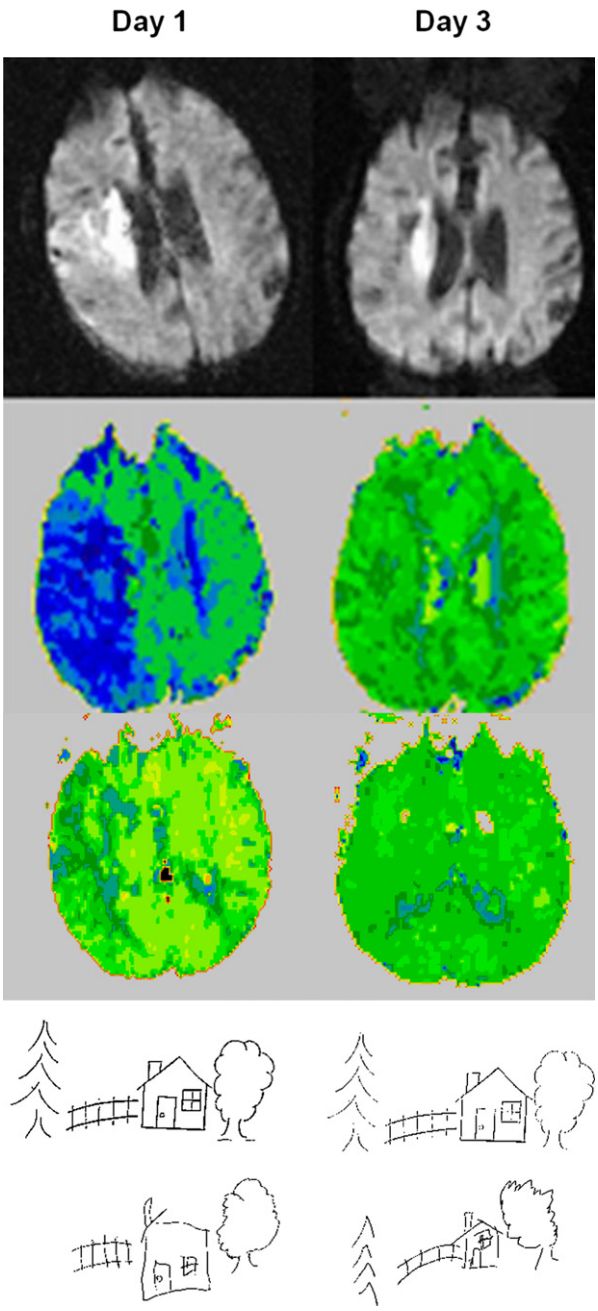

Fig. 3 – Top panel: DWI scans at Day 1 (left) and Day 3 (right) of Case 2. Middle 2 panels: PWI scans at Day 1 (left) and Day 3 (right) of Case 2. Lowest panel: Copy of the scene at Day 1 (left) and Day 3 (right) by Case 2.

4. Discussion

Our findings support the hypothesis that specific areas of the brain contribute to the construction and processing of specific forms of spatial representation (e.g., egocentric or allocentric), such that dysfunction of these specialized areas can independently lead to particular variants of USN with different reference frames and restoration of function can lead to recovery from these forms of USN. Individual cases showed recovery of distinct forms of USN, with reperfusion of dorsal frontoparietal cortex leading to improvement in viewer-centered USN and reperfusion of more ventral, temporal cortex leading to improvement in stimulus-centered USN.

The fact that reperfusion of the supramarginal gyrus (SMG) led to amelioration of viewer-centered neglect is consistent with the previous finding that damage or dysfunction of the SMG leads to viewer-centered neglect (Hillis et al., 2005). Many

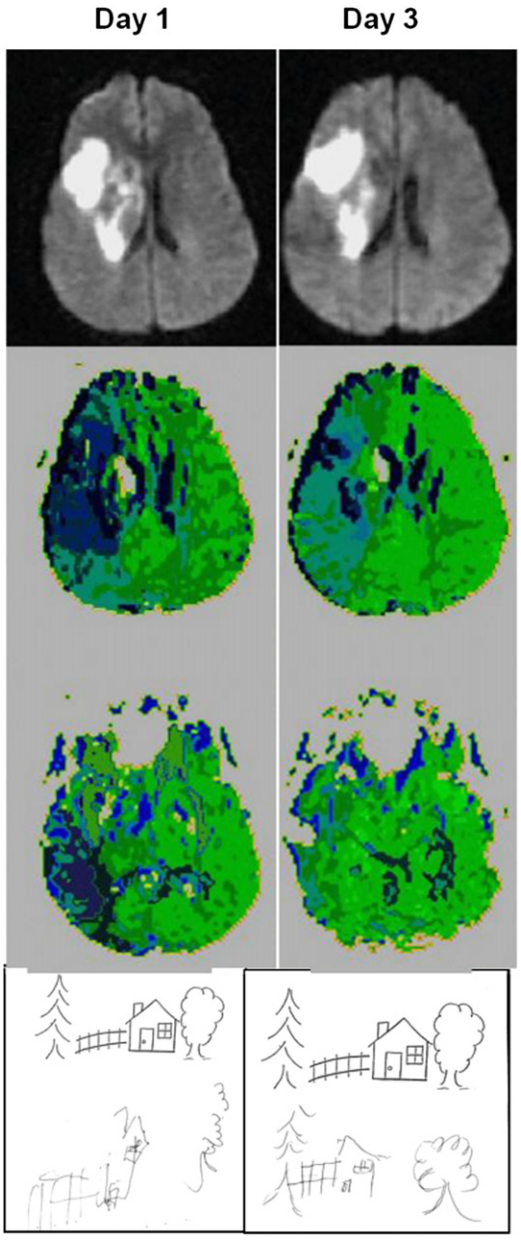

Fig. 4 – Top panel: DWI scans at Day 1 (left) and Day 3 (right) of Case 3. Middle 2 panels: PWI scans at Day 1 (left) and Day 4 (right) of Case 3. Lowest panel: Copy of the scene at Day 1 (left) and Day 4 (right) by Case 3.

others have reported lesions of the IPL, including the SMG, associated with USN (Heilman et al., 1983, 1993).

Right frontal cortex has been implicated in "motor-intentional" neglect, as it has been reported that damage to this region leads to reduced movements toward the left side of space (Mesulam, 1981; Coslett et al., 1990). With this perspective, it is not surprising that damage or dysfunction to the right DLPFC (BA 46) leads to viewer-centered USN, and restoring function to this area improves viewer-centered USN. Overall, these findings are consistent with earlier ideas suggesting that areas posterior frontal cortex would be heavily involved in computing egocentric spatial representations to guide self-movement. Functional imaging studies have also corroborated this idea, showing that dorsal parietal and associated frontal cortices are involved in egocentric spatial coding (Galati et al., 2000; Committeri et al., 2004).

The finding that reperfusion of BA 18 leads to improvement in stimulus-centered neglect (detecting left gaps in circles and word reading errors) indicates that this area is partially responsible for processing of visuospatial information integral to the construction of allocentric spatial representations. This finding is not surprising, as there is prior evidence that this cortical area is involved in computing intermediate visual information that conceivably feeds into upper-level regions responsible for computing allocentric spatial representations and recognizing objects.

BA 18 is part of the Lateral Occipital Complex (LOC), a functionally-defined visual area found to show a selective response for objects (Malach et al., 1995). Although the LOC response was heightened to the "Lincoln" illusion, in which blurring of objects digitized into large blocks paradoxically increases their recognizability; the LOC did not modulate its response to objects that varied in their recognizability. Given this combination of selectivity for objects in the context of blindness to specific object identities, it seems that this area is an intermediate in a processing stream required for the perception and recognition of objects. It then follows that damage to this region may result in impaired early visuospatial processing for recognition, resulting in stimulus-centered neglect. Damage to this area can also cause visual field deficits (Horton and Hoyt, 1991), but we think that a visual field deficit is unlikely to explain stimulus-centered USN, which is in invariant with respect to where the stimulus is presented in the visual field.

BA 37 is also thought to be involved in high-level object recognition (Kanwisher and Yovel, 2006). BA 37 is located in the "ventral stream" of visual processing – a serial network believed to be responsible for producing orientation-invariant representations of objects for recognition and perception (Goodale and Milner, 1992; see also Haxby et al., 1991). This process is likely to require the computation of allocentric spatial representations such that the orientation of the object relative to the viewer is no longer necessary for recognition, as objects are often recognized in a variety of viewer-relative orientations. If more neurons in right BA 37 are devoted to processing the left sides of allocentric spatial representations of objects, and more neurons in left BA 37 are devoted to computing the right sides of objects, then hypoperfusion in this region on either side would lead to a spatially selective deficit involving allocentric spatial representations (and bilateral hypoperfusion or infarct would cause visual agnosia) – precisely what is observed.

Functional imaging studies have also supported this role for the temporal lobe, as ventral occipitotemporal cortex has been shown to be involved in object-centered attention (Arrington et al., 2002; Committeri et al., 2004). Given past findings that damage to the temporal cortex results in stimulus-centered USN, along with our finding that its reperfusion results in the amelioration of stimulus-centered USN, it appears that the temporal cortex is a central site for the construction and/or manipulation of allocentric spatial representations.

Although Karnath et al. (2001) in a study of 25 patients with right hemisphere stroke found that the right superior temporal gyrus (STG) was the region most correlated with spatial neglect

(when patients were not examined for different types of USN), we have found that this region is only associated with stimulus-centered or allocentric USN (Hillis et al., 2005; Medina et al., 2009).

Also consistent with our results is a recent study of 80 patients 6–23 days after right hemisphere stroke with severe neglect (16 patients) to absent neglect (25 patients) who were assessed with a variety of tests of hemispatial neglect, in which a factorial analysis of voxel-based lesion-symptom mapping (VLSM) was used to identify the neural correlates of each component of neglect (Verdon et al., 2010). The authors identified two components that would be considered viewer-centered using our criteria: a perceptive/visual-spatial component associated with the right IPL and an exploratory visuomotor component associated with right DLPFC. Furthermore, they also identified an allocentric/object-centered component associated with right deep temporal lobe. Our results are broadly consistent with their findings, supporting associations between dysfunction in frontoparietal brain regions and viewer-centered deficits, and temporal regions with stimulus-centered (allocentric) deficits.

In this study we found only a single dissociation between viewer-centered and stimulus-centered USN, although in previous (larger) studies we have found a double dissociation. No patient in this study had stimulus-centered USN only. After *left* hemisphere stroke, we found that stimulus-centered USN is more common than viewer-centered USN, and that no patient had only viewer-centered USN (but some had both viewer- and stimulus-centered USN) (Kleinman et al., 2007), indicating that the right hemisphere may be more specialized for more viewer-centered processes such as navigating in space, and the left hemisphere may be more specialized for processes that require computation of stimulus-centered representations such as reading and writing.

We also found a few areas where there was a marginally significant negative correlation between reperfusion and improvement in neglect (BA 10, 44). It is difficult to explain these results, unless other areas (where reperfusion was associated with improvement in neglect) were reperfused by "stealing" collateral circulation from these areas, such that improvement was temporally associated with worsening perfusion of BA 44 and 10.

In this study the patients had subcortical lesions often involving the basal ganglia, or corona radiata, occasionally extending to the cortex as in cases 1 and 3. We did not specifically study the relationship between neglect and the site of lesion on DWI because: (1) our previous larger study of subcortical stroke with cortical hypoperfusion revealed no association between the site of subcortical lesion and either allocentric or egocentric neglect (Hillis et al., 2005), (2) reperfusion of the cortex resulted in recovery of neglect in these patients even in the presence of persisting subcortical lesions, indicating that it was the hypoperfusion of the cortex, not the subcortical lesions that caused the neglect; and (3) we did not have diffusion tensor imaging (DTI) in these patients to map the affected white matter tracts to determine disconnections that might have explained some of the neglect performance observed. We are currently obtaining both functional connectivity studies and anatomical connectivity (DTI) studies on our stroke patients, and believe that these studies may shed additional light on neural networks underlying spatial attention and computation of allocentric and viewer-centered spatial representations in the brain. Already, several investigators have demonstrated the importance of frontoparietal disconnections and functional disconnections and as well as other white matter tract disruptions in causing neglect in both humans and primates (see Gaffan and Hornak, 1997; Deuel and Collins, 1993; Doricchi and Tomaiuolo, 2003; Doricchi et al., 2008; He et al., 2007; Bartolomeo et al., 2007). There are several causes of cortical hypoperfusion; diaschisis from disruption of white matter tracts disconnecting the cortex from remote critical input or diaschisis from thalamic lesions (Vallar et al., 1988) are important mechanisms of cortical hypoperfusion in some cases. However, we suspect the cortical hypoperfusion reported in the present cases was due to large vessel stenosis independent of the subcortical lesion, such that mechanical reperfusion that did not affect the subcortical lesion resulted in recovery of neglect (see also Hillis et al., 2002 and Nadeau and Crosson, 1997 for discussion).

In summary, our study provides evidence that the right frontoparietal cortex is not only *associated* with viewer-centered perceptual representations for visuospatial and exploratory tasks, but also that left viewer-centered hemispatial neglect recovers when function of right frontoparietal cortex is restored. Likewise, our study shows that not only is the right temporal lobe associated with allocentric, stimulus-centered spatial representations and allocentric neglect, but that allocentric neglect recovers when function of right temporal cortex is restored through reperfusion.

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