Severity of Hypoperfusion in Distinct Brain Regions Predicts Severity of Hemispatial Neglect in Different Reference Frames

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Background and Purpose—Hemispatial neglect is among the most common and disabling consequences of right hemisphere stroke. A variety of variables have been associated with the presence or severity of neglect but have not evaluated the independent effects of location, severity, and volume of ischemia. Few have determined areas involved in different types of neglect. We identified the contributions of these variables to severity of viewer-centered versus stimulus-centered neglect in acute ischemic right hemisphere stroke.

Methods—We studied 137 patients within 24 hours of stroke onset with MR diffusion- and perfusion-weighted imaging and a test of hemispatial neglect that distinguishes between viewer-centered and stimulus-centered neglect. Using multivariable linear regression, we identified the independent contributions of severity of ischemia in specific locations, volume of ischemia, and age in accounting for severity of each neglect type.

Results—Severity of hypoperfusion in angular gyrus was the only variable that significantly and independently contributed to severity of viewer-centered neglect. Volume of dysfunctional tissue and hypoperfusion in posterior frontal cortex also accounted for some variability in severity of viewer-centered neglect. Severity of hypoperfusion of superior temporal cortex was the only variable that independently and significantly contributed to severity of stimulus-centered neglect.

Conclusions—Location, severity, and volume of ischemia together determine the type and severity of neglect after right hemisphere stroke. Results also show that perfusion-weighted MRI can be used as a semiquantitative measure of tissue dysfunction in acute stroke and can account for a substantial proportion of the variability in functional deficits in the acute stage. (Stroke. 2009;40:3563-3566.)

Key Words: acute stroke ■ cognitive impairment ■ magnetic resonance ■ map cortex

Hemispatial neglect is a common and debilitating consequence of right hemisphere stroke. The severity of hemispatial neglect depends on volume of infarct, age, and degree of atrophy in the intact hemisphere, but not sex.1–4 Previous studies have shown that volume of tissue hypoperfusion (measured with perfusion weighted imaging time-to-peak [TTP] maps) is even more strongly associated with severity of hemispatial neglect than is volume of infarct in acute stroke.5–7 Reduction in volume of hypoperfusion by restoring blood flow also correlates with degree of early recovery of neglect.8 These findings indicate that TTP maps represent dysfunctional brain tissue and can show areas where dysfunction results in neglect in acute stroke (irrespective of the more controversial issue of whether TTP maps are useful in predicting tissue that will progress to infarct). Severity of neglect may also depend on location of infarct or tissue dysfunction. Many studies have identified an association between hemispatial neglect and damage to the inferior parietal cortex or temporoparietal junction.9–11 Others conclude superior temporal gyrus lesions are most common in patients with neglect.12 We previously found that the presence of ischemia in temporal, parietal, and frontal regions is associated with different forms of hemispatial neglect in acute stroke, distinguished by modality13 or by reference frame.14 The presence of hypoperfusion of the right parietal cortex was associated with left viewer-centered neglect (neglect of the contralesional side of the viewer), and the presence of hypoperfusion in the right temporal cortex was associated with left stimulus-centered neglect (neglect of the contralesional side of individual stimuli, irrespective of the side of the viewer on which they are presented).14,15

Complementary evidence for the role of the parietal lobe in viewer-centered representations and the temporal lobe in stimulus-centered spatial representations would be obtained if severity of dysfunction in the parietal cortex predicted severity of viewer-centered neglect and severity of dysfunction in...
the temporal cortex predicted severity of stimulus-centered neglect after acute ischemic stroke. This hypothesis can be tested by identifying areas where the severity of ischemia is independently associated with severity of each type of neglect. Previous studies have indicated that severity of language impairment reflects severity of hypoperfusion in the left temporal cortex in the first 24 hours after stroke. After the acute stage, chronic hypoperfusion can lead to reorganization of structure/function relationships. Therefore, we evaluated the association between severity of each type of neglect and severity of hypoperfusion in dorsal and ventral regions of interest in the first 24 hours of stroke onset, before substantial reorganization. We also evaluated the independent contributions of locations and volumes of tissue dysfunction and age in predicting severity of each type of neglect.

Methods

Participants
We studied a consecutive series of 137 consenting patients with right hemisphere acute ischemic stroke who had neglect testing, diffusion-weighted imaging (DWI) and perfusion-weighted imaging (PWI) within 24 hours. This study involved a new population compared with our previously published studies; and viewer-centered and stimulus-centered neglect were defined somewhat differently (using a single test in this study, as described subsequently). Exclusion criteria included: reduced level of consciousness (as indicated by the ability to understand the task directions and to remain awake and responsive throughout the task), left-handedness (scores of <0.70 on the Edinburgh Handedness Scale), previous neurological disease or uncorrected visual loss, sedation, or hemorrhage. All patients provided informed consent for the study using methods and consent forms approved by the Johns Hopkins Institutional Review Board.

Imaging
MRI sequences included axial T2, fluid-attenuated inversion recovery, gradient echo, DWI trace images, apparent diffusion coefficient (ADC) maps, dynamic contrast PWIs, and MR angiogram of the circle of Willis. The reported analyses used DWI (after acuity of the lesion was confirmed on ADC maps) and PWI (coregistered to T2 to provide anatomic boundaries less visible on PWI), DWI and PWI scans were 5 mm thick with whole-brain coverage. Severity of hypoperfusion in various regions was determined on TTP maps using ImageJ (http://rsb.info.nih.gov/ij). A trained technician without knowledge of the neglect test results outlined 8 regions of interest (ROIs) in each hemisphere and determined the mean delay in TTP in each right hemisphere ROI relative to the homologous region in the left (normal) hemisphere.

Areas that were entirely bright on DWI and dark on ADC maps were assigned a relative delay in TTP of 7 seconds, because previous studies have indicated that a relative delay in TTP of 7 seconds is equivalent to infarct in terms of total dysfunction. Delays of <7 seconds appear to be associated with less severe dysfunction, at least in the language cortex. ROIs included atlas-based definitions of Brodmann’s area (BA) 6, 7, 9, 22, 37, 39, 40, and 44/45. We recognize that atlas-defined Brodmann’s areas do not necessarily reflect underlying cytoarchitecture due to individual variability in the cytoarchitectural fields but are widely recognized as general cortical regions that may have associated functions and allow a reproducible methodology. We use BA numbers to provide the reader information about the location within the frontal, parietal, or temporal region designated as each ROI by referring to the published template. This information makes the study reproducible; we do not mean to imply that a particular cytoarchitecture was present in that ROI in any given individual. These ROIs were selected because they have been previously implicated in neglect or because they have shown activation in functional imaging of spatial attention.

Neglect Testing
Patients were given a battery of tests of hemispatial neglect, described previously. However, for this study, we analyzed performance with only a gap detection test that can distinguish between viewer-centered and stimulus-centered neglect in a single test with a single set of directions. In this test, 30 circles are presented on a page: 10 with left gaps, 10 with right gaps, and 10 without gaps. Patients are instructed to circle the complete circles and draw an “X” through any circles with gaps. Severity of viewer-centered neglect was measured as percent of circles, with or without gaps, that were ignored on the left sides of the pages (including any circle to the left of the left most marked stimulus). Severity of stimulus-centered neglect was measured as total percent of circles with left gaps that were marked as complete circles (failure to detect left gaps) irrespective of the side of the page. Among 59 healthy control subjects, with a mean age of 64 (range, 42 to 81 years), there were no errors made on this test (unpublished data).

Statistical Analysis
First, stepwise linear regression analysis determined ROIs where degree of hypoperfusion/infarct was independently associated with severity of each neglect type. The α level to include a ROI was P<0.05; α level to exclude a ROI was P>0.1. 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 severity of hypoperfusion/infarct in all ROIs (for all 137 patients), total volume of tissue dysfunction, and age. Total volume of tissue dysfunction was determined by measuring the total area of dense ischemia on DWI and/or hypoperfusion on PWI defined as a >4-second delay in TTP compared with the homologous voxels in the left hemisphere.

Results
Age ranged from 31 to 90 years (mean, 62.9±14.0 years); 50.8% were female. Education ranged from 3 to 20 years (mean, 12.0±3.1 years). Of the 137 patients, 22 (16.1%) had some degree of viewer-centered neglect. Scores ranged from 7% to 100% (mean, 55.7%±27.7%) errors in detecting stimuli on the left side of the page. A total of 25 (18.2%) patients had some degree of stimulus-centered neglect. Scores ranged from 10% errors to 90% (mean, 23.05%±19%) errors in detecting left gaps in stimuli on the both sides of the page. Patients with viewer-centered neglect and those with stimulus-centered neglect did not differ in terms of volume of dysfunctional tissue (80.6±85.3 versus 67.6±77.8 mL) or age (67.0±12.3 versus 69.2±13.1 years). Stepwise linear regression revealed that right BA 39 (angular gyrus) was the area where relative delay in TTP or infarct most strongly predicted severity of viewer-centered neglect independently of delay in TTP in other regions (r=4.1; P<0.0001). This variable alone accounted for a small amount of the variability (r²=0.16) in severity of viewer centered neglect (r=0.40; F=16.8; P<0.0001). When we regressed severity of hypoperfusion/infarct in each area along with total volume of dysfunctional tissue and age, the following model accounted for more of the variability (r²=0.38) in severity of viewer-centered neglect (where BA represents severity of hypoperfusion in each right hemisphere Brodmann area):
The only variables that were positively correlated with viewer-centered neglect severity were delay in TTP in BA 9 (dorsal prefrontal cortex), BA 39 (angular gyrus), BA 44/45 (inferior frontal cortex), age, and total volume of dysfunctional tissue. Relative delay in TTP in other regions included in the model was negatively correlated with severity of viewer-centered neglect.

In contrast, using stepwise linear regression, right BA 22 (superior temporal cortex) was the only ROI where relative delay in TTP or infarct predicted severity of stimulus-centered neglect measured by percentage of left gaps missed independently of delay in TTP of other ROIs \( (r=3.2; P=0.002) \). No other area showed a relationship between severity of hypoperfusion and severity of stimulus-centered neglect after controlling for severity of hypoperfusion in right BA 22. However, this variable alone accounted for only a small proportion of the variability of severity of stimulus-centered neglect \( (r^2=0.10; F=9.99; P=0.002) \). However, when we regressed severity of hypoperfusion/infarct in each area along with total volume of dysfunctional tissue and age, the following model accounted for more of the variability \( (r^2=0.22) \) in severity of stimulus-centered neglect (where BA represents severity of hypoperfusion in each right hemisphere Brodmann area):

\[
\text{Severity of Neglect} = \text{BA 22 (0.31)} + \text{BA 44/45 (0.07)} + \text{age (0.02)} + \text{vol dys tissue (0.01)} - \text{BA 37 (0.25)} - \text{BA 39 (0.13)} - \text{BA 6 (0.09)} - \text{BA 40 (0.05)} - \text{BA 9 (0.04)} - 0.82.
\]

The only variable that was positively and significantly correlated with neglect severity independently of the other variables was delay in TTP or severity of hypoperfusion in BA 22 \( (P<0.001) \). Volume of dysfunctional tissue did not independently account for variability in severity of stimulus-centered neglect \( (P=0.06) \). Relative delay in TTP in other significantly associated regions was negatively correlated with severity of neglect (see the Figure for illustrative cases). In these analyses, collinearity was acceptable with a VIF of 1.113 to 3.010 for variables included in the models.

**Discussion**

Results confirmed the hypothesis that severity of hypoperfusion (or infarct) in the right parietal cortex (specifically, BA 39) predicted severity of viewer-centered neglect; whereas severity of hypoperfusion within more ventral right cortical areas (specifically BA 22) predicted severity of stimulus-centered neglect. We also found that hypoperfusion of the right posterior frontal cortex, BA 44/45 and BA 9, independently contributed to the severity of viewer-centered neglect. Neglect due to right frontal regions has been previously described after stroke and may form part of a dorsal network of spatial attention critical for modulating attention in an viewer-centered reference frame.\(^{10}\) The localization of the different types of neglect is similar to those of previous studies,\(^ {14,15} \) although the precise BAs are not identical. BAs vary across individuals, but those implicated in viewer-centered neglect are reliably more dorsal (frontal and parietal), whereas those implicated in stimulus-centered neglect are more ventral (temporal) across studies. Results are consistent with the hypothesis that viewer-centered spatial representations are processed in parietal (and frontal) cortex, whereas stimulus-centered representations are processed more ventrally in the temporal cortex.

The role of right BA 22 in neglect is controversial. Karnath and colleagues found it to be the cortical region where infarct was most associated with neglect\(^ {12} \); but others report that chronic lesions in angular gyrus are more strongly associated with neglect,\(^ {11,14} \) although ischemia in right BA 22 is associated with stimulus-centered but not viewer-centered neglect.\(^ {14} \) The current results provide novel evidence for this last hypothesis. Results confirm an essential role of the posterior parietal cortex for representing where an object is relative to the viewer and how to respond to it and an essential role of the posterior temporal cortex for stimulus-centered representations necessary for identifying objects. Correlational evidence for these distinct roles of the posterior parietal cortex and more ventral temporal cortex was provided in a positron emission tomography study in normal subjects that showed bilateral temporo-occipital activation associated with object-centered processing and right posterior parietal activation associated with viewer-centered processing.\(^ {23} \)

The clinical importance of our results is 2-fold. First, many patients with acute stroke are unable to have perfusion imaging either because of unavailability of hardware, software, or technical expertise or because contraindications to contrast or lack of intravenous access. Our results provide the basis for predicting the site and severity of hypoperfusion, which in combination with imaging of the completed infarct on DWI or CT, allows the clinician to estimate the location of...
dysfunctional, but potentially salvageable, tissue. This sort of information can be useful in clinical decision-making. Second, stimulus-centered and viewer-centered neglect are likely to be amenable to different rehabilitation approaches. The site of dysfunctional tissue can therefore be useful in planning rehabilitation of neglect. Patients with parietal lesions, who are more likely to have viewer-centered neglect, may respond more to treatment directed toward shifting the window of attention toward the contralesional side (eg, prism adaptation). Patients with temporal infarcts are more likely to have stimulus-centered neglect and respond to treatment designed toward expanding the window of attention toward individual stimuli (irrespective of their location relative to the viewer) so that the entire stimulus is processed.

Finally, our results demonstrate that TTP maps can be used as semiquantitative indications of tissue dysfunction whether or not they predict the risk of the tissue proceeding to infarct (a more controversial topic). Although maps of regional cerebral blood flow, calculated with appropriate territorial arterial input functions, are likely to provide more precise and quantitative measures of tissue dysfunction, software for computing TTP maps is more widely available. Our study shows that delay in TTP in particular brain regions is correlated with severity of functional deficits associated with those regions.

There are also limitations of this study. First, we elected to analyze results by BAs where ischemia predicted each type of neglect rather than using a voxel-based approach, because this ROI analysis allowed us to identify significant lesion deficit associations, even after correcting for multiple comparisons with a relatively small population. We recognize the individual variability in the precise location of cytoarchitecture (BAs) in the brain. However, almost certainly, the cytoarchitecture rather than the location or voxel itself is related to function, so it is reasonable to estimate the location of BAs. Additionally, mean delay in TTP in a region of interest must be compared with the mean TTP in the homologous region in the opposite hemisphere. A single voxel is too small to serve as the ROI, because brains are not precisely symmetrical. A more important limitation of our study is that it was based on subjects whose location of tissue dysfunction was a result of poor perfusion. The cortex is not homogeneous with respect to its vulnerability to ischemia. Only areas where there are sufficient numbers of patients who have ischemia (as well as those who do not) will have the power to show a significant association with the deficit. It is likely that more ventral areas of the temporal cortex are associated with stimulus-centered neglect, but these areas (eg, BA 20, 21) are less commonly ischemic. Nevertheless, this study provides evidence for the broad conclusion that severity of tissue dysfunction in the right parietal and frontal cortex and volume of tissue dysfunction together account for severity of viewer-centered neglect; and severity of tissue dysfunction in the right temporal cortex accounts for severity of stimulus-centered neglect in acute ischemic stroke.

Disclosures
None.

References
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