

**LETTER TO THE EDITOR****Reply: 'The anatomy underlying acute versus chronic spatial neglect' also depends on clinical tests****Hans-Otto Karnath,<sup>1,2</sup> Johannes Rennig,<sup>1</sup> Leif Johannsen<sup>1,3</sup> and Chris Rorden<sup>2</sup>**

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Sir, earlier this year we published the first longitudinal study of spatial neglect in your journal (Karnath *et al.*, 2011). Longitudinal studies of this profoundly debilitating disorder are crucial to unlock one of the great mysteries of this disorder: some individuals spontaneously recover while others are left with long-term deficits. Recently, Saj *et al.* (2011) responded to our work, noting that there are actually a variety of attentional deficits that are common following right hemisphere brain injury. Saj *et al.* (2011) warn that scientists need to be careful that they do not pool across different underlying syndromes, which may each rely on different anatomy and exhibit different patterns of recovery. We think their recent work adds to a growing consensus regarding the complex interaction of anatomy, recovery phase and symptoms observed following right hemisphere injury. While we believe this type of work will prove theoretically crucial (demonstrating the unique functional roles of different anatomical nodes) and clinically vital (providing improved long-term prognosis based on acute behaviour and acute imaging), we do think it is appropriate to fully describe the historical precedence for Saj *et al.*'s (2011) work. Further, we describe some of the methodological advances required in order to accurately address the issues raised by these authors.

Saj *et al.*'s (2011) work hinges on the idea that there is not a single, unitary perceptual deficit associated with right hemisphere damage, but rather a series of relatively independent syndromes. Indeed, one of the striking features of right hemisphere injury is

the variability of the symptoms observed. For example, stimuli might be missed on the left side of the patient's space (egocentric neglect) or the left side of individual stimuli might be ignored regardless of position with respect to the body (object-centred or allocentric neglect). There is now compelling evidence that consolidating all symptoms under the catch-all term 'spatial neglect' is a misguided approach. Instead, a clear framework for core and satellite symptoms exists (Karnath and Rorden, 2011) based on the observation that individual symptoms correlate with specific anatomy. While Saj *et al.* (2011) describe some of the recent findings, it should be noted that these behavioural-anatomical dissociations have a long history. For example, Binder *et al.*'s (1992) seminal work noted that individuals with neglect who had difficulty accurately determining the midpoint of a line (a measure of allocentric deficits) had more posterior lesions than individuals who only had errors on cancellation tasks (a measure of egocentric neglect). This effect has been replicated (Rorden *et al.*, 2006; Verdon *et al.*, 2010; Vossel *et al.*, 2011), and this behavioural distinction can even be used retrospectively to explain anatomy in individual patients in prior studies (*cf.* Mort *et al.*, 2003). While much early work relied solely on the line bisection task to measure allocentric neglect, other tasks that attempt to dissociate egocentric and allocentric deficits appear to support the same anatomical dichotomy (Grimsen *et al.*, 2008; Medina *et al.*, 2009; Chechlacz *et al.*, 2010; Verdon *et al.*, 2010; however, see Hillis *et al.*, 2005).

In addition, there is some evidence that extinction [an inability to detect the contralesional stimulus when confronted with two brief and simultaneous stimuli, a symptom that is also seen in isolation of any other florid symptoms (e.g. Becker and Karnath, 2007)] appears to be associated with relatively posterior injury (Karnath *et al.*, 2003). Further, measures of personal neglect appear to predict more posterior injury than conventional tasks that tap into extrapersonal neglect (Committeri *et al.*, 2007). Patterns of patient performance as well as convergent evidence from healthy adults and primates has suggested that the attentional system of the human brain is based on a network of tightly integrated but functionally and spatially distinct modules (e.g. Corbetta and Shulman, 2002; Husain and Rorden, 2003; Karnath, 2009). In a recent review (Karnath and Rorden, 2011) we discuss these findings in more detail, coming to the conclusion that there is a wide degree of agreement regarding the core deficits and their relative anatomy (at least as observed on structural scans), and as a corollary that using tasks that accurately identify the true underlying syndromes should reduce the variability in studies seeking to identify the relevant anatomy. Therefore, there is clear evidence from cross-sectional studies that the tasks used to define neglect and the ability to dissociate different forms of attentional deficit are crucial for understanding these syndromes.

Saj *et al.* (2011) present two analyses, one based on the composite scores (their Fig. 1A) from the same two tests of neglect we used (two cancellation tasks) plus a copying task (different from the one we used), and a second analysis (their Fig. 1B) based on eight measures, which include various tests such as line bisection, drawing, reading, writing and cancellation. The authors emphasize the resemblance to our own findings, but focus on the fact that their analysis, which only includes three tests (their Fig. 1A), appears to highlight superior parietal regions and the occipital lobe (in addition to inferior parietal and superior/middle temporal involvement). This is an interesting observation and we do feel regions near the intraparietal sulcus are involved with spatial attention. For example, in our recent neuroimaging study contrasting adaptations of the line bisection to cancellation tasks in healthy adults we found this region was specifically activated during bisection tasks (Revill *et al.*, 2011), consistent with similar findings from other groups. Indeed, some suggest that neglect may often be due to functional disruption of these regions caused by distant anatomical injury (e.g. Corbetta *et al.*, 2005; see Karnath and Rorden, 2011 for a review of this literature and our own reflections on this intriguing hypothesis). However, we do think that the evidence provided by Saj *et al.* (2011) really requires further testing. As they acknowledge, the first paradox is that analyses of all eight tests maps closest to our findings based on three tests, yet it seems that they have a bias to prefer the results from their data restricted to only three tests.

The authors argue that using a composite score based on numerous tests will pool across different symptoms, and may fail to identify regions that are detected with only one or two subtests. The primary danger here is that we do not know ground truth. Combining tests may have poor sensitivity for symptoms that are only detected by one test, but on the other hand relying on only a small number of tests may not provide a stable measure of the deficit. Indeed, one could look at the same data set of Saj *et al.*

(2011) and conclude that the superior parietal result is objectively the least reliable region, as it is not consistently found.

While we agree that pooling across subtests that measure different attentional deficits (e.g. egocentric and allocentric neglect) is unwise, we wish to emphasize that in our own study (Karnath *et al.*, 2011) we carefully selected tests that appear to correlate very strongly with each other as well as with clinical measures for the core deficits of egocentric neglect (Ferber and Karnath, 2001; Karnath and Rorden, 2011). Therefore, our aim was to have a stable measure for a single syndrome (as suggested by the previously reviewed anatomical and behavioural studies). For example, we chose to measure neglect on cancellation tasks using the 'Centre of Cancellation' (Binder *et al.*, 1992; Rorden and Karnath, 2010), which attempts to measure the magnitude of spatial bias rather than the traditional method of counting omission rate (which combines both spatial and non-spatial attentional deficits). In contrast, Saj *et al.* (2011) present results based on omission rates. We were somewhat perplexed by the authors' comment 'We also calculated a "centre of cancellation" score for the cancellation tests (as Karnath *et al.*, 2011), but results were identical when using this measure as it was highly correlated ( $r > 0.91$ ) with the number of left omissions'. Do the authors mean the voxel-wise results were visually indistinguishable, or not statistically different from each other (and if so by what threshold) or actually numerically precisely identical? It is hard not to feel like a linguist who has just read the sentence 'chimpanzees and humans are identical as their genetics are highly correlated ( $r > 0.98$ )'. Presumably, the authors have conducted the analyses and reasonably decided that any differences observed by visual inspection of the statistical image are of no substantive value, and the authors have just used shorthand. We certainly expect omission/hit rates and centre of cancellation to be highly correlated in cancellation tasks, but logically it seems that centre of cancellation should be the preferred measure. This measure is specific to spatial bias and therefore attenuates influence of non-spatial attentional and motor deficits. In contrast, omission/hit scores in cancellation tasks cannot distinguish between spatially biased performance versus inattentive performance or motor deficits. For example, some patients may miss items specifically on the contralesional side whereas others may miss the same number of targets but evenly distributed across space. While the first observation is indicative of spatial neglect; the latter does not support this diagnosis because it does not exhibit the spatial bias that is so unique to spatial neglect. This is of course not only a serious problem in behavioural studies but in particular in anatomical studies that use omission/hit scores (like the study by Saj *et al.*, 2011) instead of centre of cancellation scores.

While Saj *et al.* (2011) prefer the results of their analysis based on three tests to the results of all eight tests, they do not objectively demonstrate a difference between these results nor do they disentangle the contribution of the different measures. The authors are interpreting differences based on which voxels survive a stringent test for multiple comparisons: it is actually possible that the results from all three analyses (the two in Saj *et al.* as well as our recent work) are statistically not different from each other. Rather, due to random noise the regions that survive thresholding appear different to the human eye. In other words, we really need

tests to identify the interactions between symptoms: which tasks reliably dissociate between brain regions. Indeed, cross-sectional studies have already employed measures that attempt to assess the independent contribution of different factors (Bates *et al.*, 2003; Karnath *et al.*, 2004). These techniques can allow us to objectively test whether different tasks directly track to different anatomy. Further, by potentially being able to account for variability that would have been counted as noise in a single-factor test, such analyses may actually provide better statistical power for identifying crucial brain regions. Ultimately, the latter attribute may prove vital for providing reliable prognosis.

In closing, spatial neglect has traditionally been seen as an enigmatic diagnosis due to the variability in symptoms, anatomy and outcome. Saj *et al.* (2011) argue that each of these factors must be considered if one wants to truly understand this disorder and provide sound clinical guidance. We fully endorse this notion (see Karnath and Rorden, 2011 for further arguments), and while one could suggest that these ideas were foreshadowed by others (Binder *et al.*, 1992), the recent development of imaging sequences, behavioural measures and tools for lesion analysis finally make this a tractable topic for exploration.

## Funding

Deutsche Forschungsgemeinschaft (KA 1258/10-1) and the National Institutes of Health (R01 NS054266).

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