A real red-letter day

Edward M Hubbard

Synesthesia, in which letters or numbers elicit color perception, could be due to increased brain connectivity between relevant regions, or due to failure to inhibit feedback in cortical circuits. Diffusion tensor imaging now provides evidence for increased connectivity in word processing and binding regions of the brain.

If looking at this page of text causes you to see a cascade of colors, you have grapheme-color synesthesia, in which viewing letters and numbers in black and white elicits the experience of seeing colors[1,2]. For a grapheme-color synesthete, the letter 'A' might always be tinged red, a '5' might have a blue overlay, or the word 'synesthesia' might be associated with yellow and green because of the colors of the individual letters. Grapheme-color synesthesia occurs in as many as 2 out of every 100 people[3] and is the most intensively studied form of synesthesia. Although behavioral[4,5] and neuroimaging studies[6,7] have shown consistent differences between synesthetes and nonsynesthetes, the underlying neural basis for these differences has been a matter of substantial debate. Some researchers propose that the additional experiences of synesthetes are due to increased connectivity between relevant brain regions, such as those involved in word and color perception, perhaps because of incomplete pruning[1,6]. Others argue that synesthesia does not depend on anatomical differences, but is instead due to a failure of inhibition in cortical feedback circuits[8]. To date, these models have been supported by indirect evidence, as neither behavioral nor neuroimaging data can distinguish between these two neural mechanisms.

In this issue, Rouw and Scholte[9] provide direct evidence of increased structural connectivity in synesthetes, supporting the first hypothesis that synesthesia is a result of increased connectivity between relevant brain regions. The authors combined two neuroimaging techniques to provide insights into the neural basis of this condition. First, the authors used diffusion tensor imaging (DTI), a neuroimaging technique that measures the diffusion of water molecules in the living human brain. Water molecules diffuse more easily parallel than perpendicular to the direction of white-matter fibers, because of the myelin sheaths and axonal membranes. By measuring relative differences in how easily water diffuses along different axes (termed fractional anisotropy), it is possible to infer the size, orientation and degree of myelination of white matter tracts *in vivo*. Rouw and Scholte[9] used this technique to demonstrate increased structural connectivity in synesthetes compared with controls in three brain regions: the right fusiform gyrus, which is near regions involved in word and color processing,

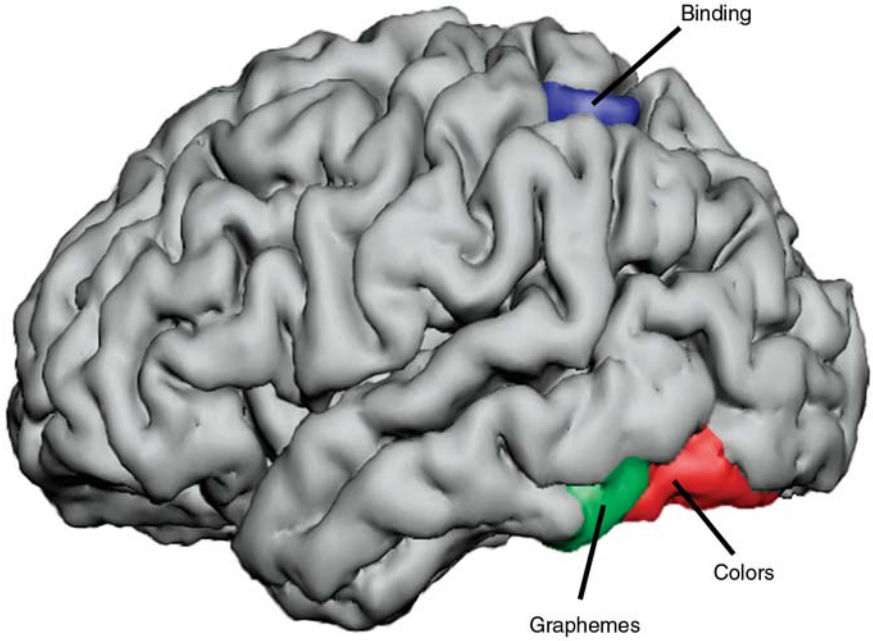

Figure 1 The outer cortical surface with relevant brain regions indicated. The color-selective hV4 is indicated in red, and the visual word form area is indicated in green. Cross-activation between these regions, mediated by increased anatomical connectivity, correlates with the generation of the additional experiences of grapheme-color synesthesia, and the degree of connectivity determines their strength. The posterior IPS, thought to be involved in binding, is in blue. Additional anatomical connectivity in this region may be critical for synesthetic binding, which must operate on the colors generated by the cross-activation between grapheme regions and hV4. These regions have been projected to the left hemisphere for simplicity.

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and the left intraparietal sulcus (IPS) and frontal cortex, both of which are part of a network of regions involved in binding and consciousness (**Fig. 1**). Although differences in structural connectivity may coexist with differences in inhibitory processes, and may even be the consequence of such differences[10], the present study clearly shows increased connectivity in regions thought to be critical to the genesis of grapheme-color synesthesia. This is consistent with previous proposals supported by indirect evidence[1,6].

In addition to the group differences between synesthetes and nonsynesthetes, behavioral[6,11] and neuroimaging studies[6] have shown stable individual differences among synesthetes. Some synesthetes ('projectors') report strong experiences projected into the external world, whereas others ('associators') report weaker experiences that appear in their mind's eye[11]. Rouw and Scholte[9] assessed the intensity of synesthetic experiences using a structured questionnaire, in which subjects rated their experiences on a five-point scale. They found that the degree of fractional anisotropy in the right temporal cortex was positively correlated with the reported intensity of synesthetic experience, suggesting that such differences in intensity are due to differences in connectivity in the temporal cortex. In addition, by showing that phenomenological differences correlate with anatomical differences among different synesthetes, these findings constitute an essential replication of reports of stable individual differences among synesthetes[6,11] using a different group of subjects and a different imaging modality. These individual differences may be important for understanding some of the contradictory findings in the literature[1] and must be taken into consideration in future investigations of synesthesia.

Rouw and Scholte[9] also identified regions of increased fractional anisotropy in the IPS and frontal cortex, which is consistent with neuroimaging[12] and transcranial magnetic stimulation (TMS)[13] data showing that the parietal cortex is essential for synesthetic binding of color and form. Notably, the degree of fractional anisotropy in parietal and frontal regions did not correlate with the subjective reports of their synesthetes, suggesting that differences in the parietal cortex may be important for determining whether or not someone is a synesthete, but not for determining the strength of their experiences. Taken together, these results suggest a two-stage model of grapheme-color synesthesia (**Fig. 1**). In the first stage, anomalous color experiences are generated via cross-activation in ventral visual areas. Every time a synesthete looks at a letter or number, additional excitatory activity passes from the regions involved in grapheme processing to those involved in color processing, with the degree of connectivity determining the strength of those experiences. After synesthetic colors are generated via this cross-activation, they are then bound by stronger than normal parieto-frontal binding mechanisms, which may elicit a kind of 'hyperbinding'[12,13].

In the same session, Rouw and Scholte[9] tested the same subjects using standard whole-brain functional magnetic resonance imaging (fMRI). Consistent with previous reports[6,7], the authors found increased activation in the ventral-occipital cortex, in the human V4 complex (hV4). Unlike previous investigators[6], they did not find a correlation between fMRI activation and their subjective report measure, despite their larger sample size. However, as the authors note, this lack of a correlation may be due to anatomical variability in the location of hV4 and the exact location of activated cortex, which cannot be detected without using retinotopic mapping in individual subjects. Additional studies combining retinotopic mapping and diffusion tensor tractography may clarify these issues.

Because they collected DTI and fMRI data in the same subjects, Rouw and Scholte[9] were able to compare the locations of the anatomical and functional differences. Although both were in the right temporal cortex, the anatomical differences were anterior to the location of increased blood oxygenation level–dependent signal, suggesting that the interplay between anatomical and functional differences is more complex than is suggested by the simple direct cross-activation hypothesis[1]. Some of this unexpected complexity might be due to the presence of multiple stages involved in reading. In the past five years, models of the neural basis of reading have become more sophisticated, moving from the notion of a single visual word form area[14] to suggesting a hierarchy of stages beginning in early visual areas and increasing in complexity, invariance and receptive field size across the entire ventral visual pathway[15]. A better understanding of the mechanisms of reading will be critical for interpreting these neuroanatomical and functional differences.

The new anatomical data also have relevance to the question of the laterality differences, if any, in synesthesia. Previous fMRI studies (for example, refs. 6,7) showed either left-lateralized or bilateral activation in hV4. Contrary to this, Rouw and Scholte[9] find increased fractional anisotropy and increased fMRI blood oxygenation level–dependent signals in the right temporal cortex. Similarly discrepant lateralization is found in fMRI and TMS studies examining the role of parietal cortices in synesthetic binding. Increased activity in the left, but not right, IPS is seen by fMRI during synesthetic binding[12], whereas synesthetic binding is disrupted only after TMS stimulation of the right IPS[13]. Consistent with the fMRI results, but not the TMS results, Rouw and Scholte[9] found significant anatomical differences between synesthetes and nonsynesthetes only in the left hemisphere. Given the small number of subjects commonly tested and the differing lateralizations obtained using different techniques, assertions of the laterality in synesthesia should be taken with caution until larger studies are conducted to examine these questions.

In sum, this study demonstrates anatomical differences between synesthetes and nonsynesthetes. Not only do these results provide clear support for the hypothesis that anatomical differences underlie at least some aspects of synesthetic experience, they also suggest that pre-existing neuroanatomical differences may underlie differences in conscious experience more generally. Future investigations into the neural correlates of unusual sensory experiences, including other forms of synesthesia, Charles Bonnet syndrome and even schizophrenic hallucinations, should use methods such as these to investigate whether they depend on similar functional and anatomical differences in the relevant brain regions.

COMPETING INTERESTS STATEMENT
The author declares no competing financial interests.

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