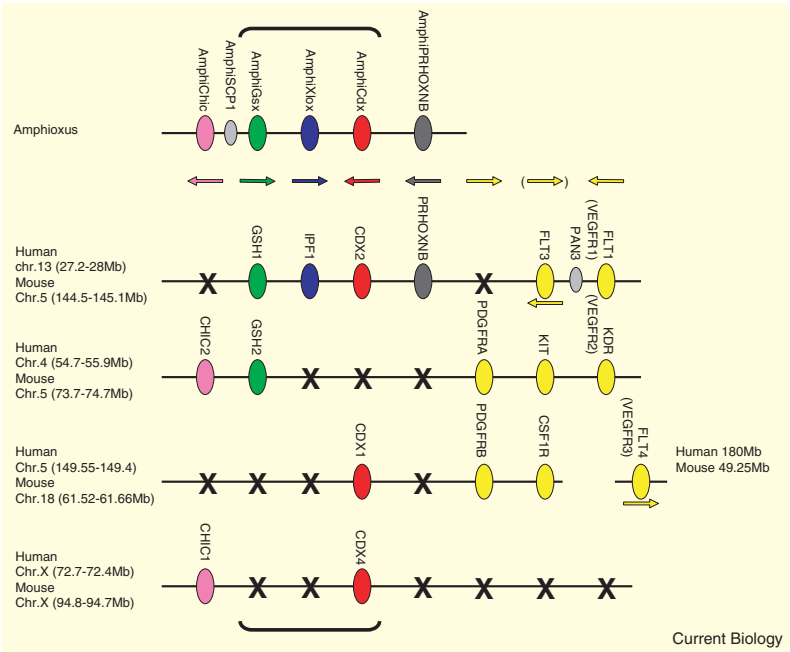

Figure 2. Maintenance of ParaHox clusters.

Schematic of the amphioxus ParaHox cluster (top), with flanking genes, and the mammalian ParaHox clusters with the mammalian ParaHox paralogy regions. The amphioxus cluster has retained the organisation present in the chordate ancestor. Arrows denote transcriptional orientation, which has been conserved between the ParaHox clusters and the paralogy regions. The pattern of gene linkage and orientation indicates that the mammalian genomic regions arose from duplications of the entire region, followed by extensive gene loss (indicated by 'X'). Only a single intact ParaHox cluster remains in mammals, and genomic rearrangements have occurred up to its edges, but not within it. Each column of receptor tyrosine kinase genes (yellow) is a distinct paralogy group (i.e. PDGFRA is a paralogue of PDGFRB). FLT4 has been transposed to a different location on the chromosome, and the orientation of FLT3 is the reverse of that of its paralogues KIT and CSF1R, the orientation of KIT and CSF1R presumably being the same as the ancestral organisation. AmphiSCP1 is reduced to indicate the possibility that it is a retrotransposition (see Supplemental Data). Mammalian PAN3 is reduced because it is not a receptor tyrosine kinase gene and hence is not analysed here.

NHGRI. The authors' work is supported by the BBSRC (D.E.K.F.), NIH and NSF (C.A., A.H-F.).

Supplemental data

Supplemental data including experimental procedures are available at http://www.current-biology.com/cgi/content/full/15/20/R820/DC1/

References

1. Brooke, N.M., Garcia-Fernàndez, J., and Holland, P.W.H. (1998). The ParaHox gene cluster is an evolutionary sister of the Hox gene cluster. Nature *392*, 920–922.
2. Ferrier, D.E.K., and Holland, P.W.H. (2001). Ancient origin of the Hox gene cluster. Nat. Rev. Genet. *2*, 33–38.
3. Minguillón, C., and Garcia-Fernàndez, J. (2003). Genesis and evolution of the Evx and Mox genes and the extended Hox and ParaHox gene clusters. Genome Biol. *4*, R12.
4. Holland, P.W.H. (1999). Gene duplication: past, present and future. Semin. Cell Dev. Biol. *10*, 541–547.
5. Ferrier, D.E.K., Minguillón, C., Holland, P.W.H., and Garcia-Fernàndez, J. (2000). The amphioxus Hox cluster: deuterostome posterior flexibility and Hox14. Evol. Dev. *2*, 284–293.
6. Chambeyron, S., Da Silva, N.R., Lawson, K.A., and Bickmore, W.A. (2005). Nuclear re-organization of the Hoxb complex during mouse embryonic development. Development *132*, 2215–2223.
7. Kmita, M., Fraudeau, N., Hérault, Y., and Duboule, D. (2002). Serial deletions and duplications suggest a mechanism for the colinearity of Hoxd genes in limbs. Nature *420*, 145–150.

[1]Department of Zoology, University of Oxford, Tinbergen Building, South Parks Road, Oxford OX1 3PS, UK. [2]The Whitehead Institute/MIT Center for Genome Research (now: Broad Institute), 320 Charles Street, Cambridge, Massachusetts 02141, USA. [3]Department of Human Genetics (McGill University) and McGill University and Genome Quebec Innovation Centre, 1650 Avenue Cedar, Montreal, Quebec, Canada H3G 1A4. [4]Molecular Genetics Program, Benaroya Research Institute at Virginia Mason, 1201 Ninth Avenue, Seattle, Washington 98101, USA.
*E-mail: david.ferrier@zoo.ox.ac.uk

Weak suppression of visual context in chronic schizophrenia

Steven Dakin[1], Patricia Carlin[2] and David Hemsley[2]

Several theories propose that diverse cognitive deficits associated with schizophrenia are attributable to an impaired ability to use information (context) to interpret stimuli [1–3]. We asked how such a deficit might influence vision, a modality that depends heavily on low-level contextual processing — for example, 90% of cells in primary visual cortex, V1, are subject to suppression by their neighbours [4].

Recent evidence suggests that some contextual interactions in vision may be weaker in schizophrenia. Must *et al.* [5] reported that, in schizophrenic observers, the detection of an oriented target is less facilitated by the presence of collinear 'flanks' than usual. It is unclear, however, whether this reduced performance level arises from impaired lateral connectivity in V1, as the authors conclude, or is the result of other cognitive deficits associated with schizophrenia.

To differentiate these possibilities we require a task for which reduced contextual interactions actually improve performance. Against a backdrop of generalised cognitive impairment, tasks at which schizophrenic observers excel are both rare and revealing: enhanced performance cannot be attributed to general factors and serves to illuminate the condition's underlying neural mechanism [6].

Figure 1A illustrates how contextual suppression can influence normal visual perception by causing the ringed target to appear lower contrast when presented within a high-contrast surround than in isolation [7]. Convergent data from psychophysics and functional magnetic resonance imaging

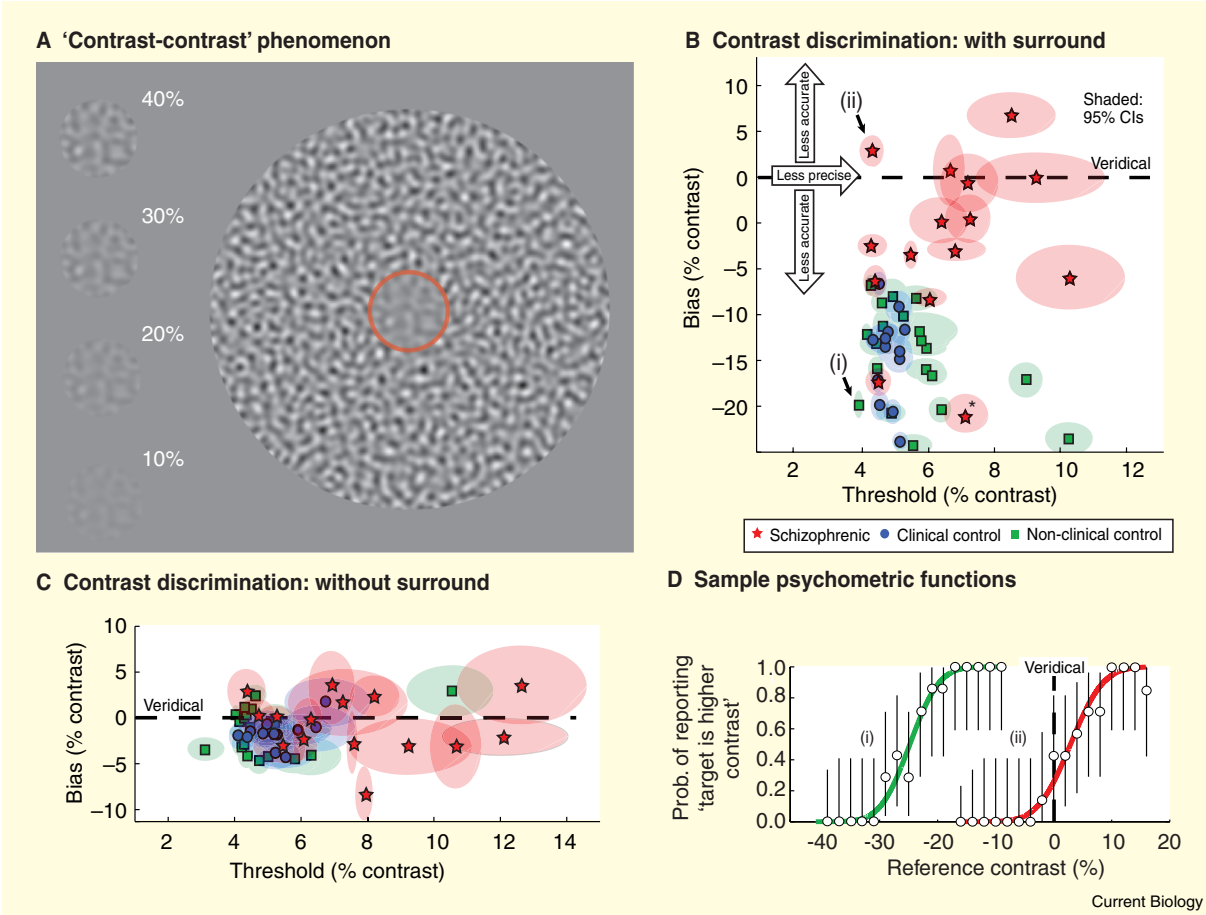

Figure 1. Contextual suppression and visual perception.

(A) Although the physical contrast of the ringed target is 40%, surround suppression makes it appear much lower. (Note that no ring was present in the psychophysical experiment.) (B,C) Contrast-matching performance, with or without a surround, for schizophrenic (stars) and control (squares and circles) subjects. Shaded regions show associated 95% confidence intervals. The abscissa indicates precision (minimum contrast difference supporting discrimination), the ordinate indicates accuracy (contrast of the isolated patch producing a 'match' to the surrounded patch). All groups produce near-veridical matches without surrounds, but schizophrenic observers are less biased than controls, with the surround. (D) Psychometric functions associated with data marked (i) and (ii) in (B). Schizophrenic data can be similar to controls, but are largely unbiased.

(fMRI) [8] indicate that this so-called 'contrast–contrast' phenomenon is linked to response gain control within V1 (likely driven both by low-level visual input and by higher-level 'object-level' knowledge [9]). Prompted by evidence that schizotypal observers are less prone to a size illusion [10] based on context, we hypothesised that weaker contextual suppression might also make schizophrenic observers less vulnerable to the 'contrast–contrast' illusion: that is, more accurate at judging contrast under conditions that disrupt control subjects' ability to make the judgment.

In order to test this we measured contrast discrimination performance of 15 observers with chronic schizophrenia, 13 psychiatric controls — including individuals with personality, bipolar and severe affective disorders — and 20 non-psychiatric control subjects. Either a small isolated target patch (Figure 1A, left hand side) or a similar patch within a high-contrast surround (Figure 1A, right hand side) was presented, followed by an isolated reference patch. Subjects reported which patch appeared to be of higher contrast.

By manipulating reference-contrast we were able to collect a psychometric function (Figure 1D) for contrast discrimination, and then estimated its slope, which gives precision, the smallest discernable contrast-difference, and bias, which gives accuracy, the contrast-offset producing a perceptual 'match'.

The clustering of schizophrenic data in the upper-right part of Figure 1B indicates less precise (mean threshold 6.6%), but more accurate (mean bias –7.2%) performance than control subjects (mean threshold 5.2%; mean bias –19.4%) in the surround condition, (t = –6.12, p = 0.0000002). The schizophrenic group's immunity to the contrast illusion is remarkable: 12 out of 15 were more accurate than the most-accurate control. We note that one of the two outliers in the schizophrenic group (indicated with an asterisk in Figure 1B) has subsequently been re-diagnosed as having bipolar disorder.

With respect to precision, best-fitting psychometric functions indicate that people with schizophrenia required a larger contrast difference to perform reliably (no-surround: $t = -3.06$, $p = 0.0037$; surround: $t = -4.73$, $p = 0.000022$). Note, however, that this did not somehow lead to higher accuracy; accuracy and precision were not significantly correlated within any group for any condition.

We also assessed if our findings might in part be attributable to stimulus-independent error — random 'key-presses' — possibly as a result of attentional drift, as in the limit a completely random observer is bias-free. To examine this issue, we refit our data incorporating a stimulus-independent error term which allows the height of the tails of our psychometric functions — floor and ceiling performance — to vary. Using the resulting threshold estimates we find that schizophrenics are not significantly more prone to random errors than control groups (mean random error for schizophrenic group: 2.4%, control: 3.3%; $t = -1.1$; p = 0.28), that they were still significantly more accurate than control observers in the surround condition ($t = -6.0$; $p = 0.00000025$) but less precise across all conditions (for example, surround: $t = -2.12$, $p = 0.04$).

Our results clearly cannot be attributed to higher levels of random response amongst the schizophrenic group. However, note that we are only able to draw these inferences because we collected full psychometric functions suggesting that detailed psychophysical characterisation of people with schizophrenia may prove to be more revealing than large-population studies using measurements whose interpretation may be limited by 'noisy' data.

Our findings cannot be attributed to medication; 11 out of 15 of the schizophrenic group received atypical antipsychotic medication, which only minimally affect visual sensitivity, while older antipsychotic drugs cause global impairment in contrast sensitivity [11]. Neither can generalised effects of mental illness explain these results; improved accuracy was not found in the psychiatric control group which included individuals with major mental illness (some of whom were, incidentally, treated with low-dose anti-psychotics).

This work has implications for how we understand schizophrenia. With respect to neural mechanism, Bleuler [12], described sufferers as "flooded with an undifferentiated mass of incoming sensory data". A century on, this description accords with our finding that contextual suppression — the neural process that quells the visual 'flood' — is weaker in schizophrenia. In particular, our finding that chronic schizophrenics were more accurate at contrast-matching allows us to link their performance to the failure of a specific visual mechanism (rather than to general cognitive factors such as attention). Furthermore, that this behaviour is manifest on a task that has been linking the earliest stages of neural processing of visual information [7,8] suggests that weak suppression may be a general and pervasive difference in 'style' of cortical processing associated with the illness. The challenge is now to test if abnormal contextual suppression extends into other sensory modalities (and even domains such as language and memory) and so determine if it represents a common deficit across the schizophrenic syndrome [1].

Acknowledgements
We thank our subjects, and Roger Watt, Bill Phillips, Sarah Griffiths and Dan Stott for comments. Support: BBSRC (31/S17766).

Supplemental data
Supplemental data including experimental procedures are available at http://www.current-biology.com/cgi/content/full/15/20/R822/DC1/

References

1. Hemsley, D.R. (2005). The schizophrenic experience: taken out of context? Schizophr. Bull. *31*, 43–53.
2. Phillips, W.A., and Silverstein, S.M. (2003). Convergence of biological and psychological perspectives on cognitive coordination in schizophrenia. Behav. Brain Sci. *26*, 65–82.
3. Silverstein, S.M., and Schenkel, L.S. (1997). Schizophrenia as a model of context deficient cortical computation. Behav. Brain Sci. *20*, 696–697.
4. Jones, H.E., Grieve, K.L., Wang, W., and Sillito, A.M. (2001). Surround suppression in primate V1. J. Neurophysiol. *86*, 2011–2028.
5. Must, A., Janka, Z., Benedek, G., and Keri, S. (2004). Reduced facilitation effect of collinear flankers on contrast detection reveals impaired lateral connectivity in the visual cortex of schizophrenia patients. Neurosci. Lett. *357*, 131–134.
6. Chapman, L.J., and Chapman, J.P. (1973). Problems in the measurement of cognitive deficit. Psychol. Bull. *79*, 380–385.
7. Chubb, C., Sperling, G., and Solomon, J.A. (1989). Texture interactions determine perceived contrast. Proc. Natl. Acad. Sci. USA *86*, 9631–9635.
8. Zenger-Landolt, B., and Heeger, D.J. (2003). Response suppression in v1 agrees with psychophysics of surround masking. J. Neurosci. *23*, 6884–6893.
9. Lotto, R.B., and Purves, D. (2001). An empirical explanation of the Chubb illusion. J. Cogn. Neurosci. *13*, 547–555.
10. Uhlhaas, P.J., Silverstein, S.M., Phillips, W.A., and Lovell, P.G. (2004). Evidence for impaired visual context processing in schizotypy with thought disorder. Schizophr. Res. *68*, 249–260.
11. Chen, Y., Levy, D.L., Sheremata, S., Nakayama, K., Matthysse, S., and Holzman, P.S. (2003). Effects of typical, atypical, and no antipsychotic drugs on visual contrast detection in schizophrenia. Am. J. Psychiatry *160*, 1795–1801.
12. Bleuler, E. (1950). Dementia praecox or the group of schizophrenias (New York: International Universities Press).

[1]Institute of Ophthalmology, University College London, Bath Street, London EC1V 9EL, UK. [2]Kings College London, Institute of Psychiatry, De Crespigny Park, London SE5 8AF, UK.