for future work to explore these possibilities.

One very interesting observation, apparently conserved between multiple systems, is that the effect of a perturbation changes over time. The immediate effect of the temperature-sensitive kinesin mutant is to knock-out kinesin function rapidly but leave minus-end transport unaltered. However, over time, all transport ceases. This is interpreted to reflect the need for an anterograde motor to ship retrograde motors back out of the flagellum, but other forms of longer-term feedback are possible. For instance, in the lipid droplet case, similar to the temperature-sensitive effects described above, when a function-blocking anti-kinesin antibody is injected, kinesin function is selectively blocked, and there is net minus-end motion. Further, a kinesin-null mutant also blocks all minus-end motion driven by dynein [11]. However, when kinesin dosage is decreased by 50%, although droplet motion is unaffected from a transport point of view (i.e., the number of moving droplets is unaffected, and their travel distances and velocities are not decreased, and thus any effects cannot be due simply to an inability to come into contact with dynein), the number of engaged motors in both directions is decreased by 50% [11]. Thus, the observed longer-time impairment in the flagella case may also reflect subtle effects or feedback.

It is likely that the activity of opposing motors is regulated using different strategies for different classes of cargo. One of the immediate challenges facing the field is to determine how many such classes there are — is each type of cargo really different, or are there are a few general classes of cargo transport, each with its associated regulation of the underlying motors? At this stage we cannot arrive at a single general model of cargo transport, but the studies here develop an important new system that will help us approach this long-term challenge. Clearly, there will be a lot of back-and-forth before we understand how back-and-forth motion works in the cell.

References

1. Welte, M.A. (2004). Bidirectional transport along microtubules. Curr. Biol. *14*, R525–R537.
2. Gross, S.P. (2004). Hither and yon: a review of bi-directional microtubule-based transport. Phys. Biol. *1*, R1–R11.
3. Muller, M.J., Klumpp, S., and Lipowsky, R. (2008). Tug-of-war as a cooperative mechanism for bidirectional cargo transport by molecular motors. Proc. Natl. Acad. Sci. USA *105*, 4609–4614.
4. Gross, S.P., Tuma, M.C., Deacon, S.W., Serpinskaya, A.S., Reilein, A.R., and Gelfand, V.I. (2002). Interactions and regulation of molecular motors in Xenopus melanophores. J. Cell Biol. *156*, 855–865.
5. Rogers, S.L., Tint, I.S., Fanapour, P.C., and Gelfand, V.I. (1997). Regulated bidirectional motility of melanophore pigment granules along microtubules in vitro. Proc. Natl. Acad. Sci. USA *94*, 3720–3725.
6. Laib, J.A., Marin, J.A., Bloodgood, R.A., and Guilford, W.H. (2009). The reciprocal coordination and mechanics of molecular motors in living cells. Proc. Natl. Acad. Sci. USA *106*, 3190–3195.
7. Vershinin, M., Carter, B.C., Razafsky, D.S., King, S.J., and Gross, S.P. (2007). Multiple-motor based transport and its regulation by Tau. Proc. Natl. Acad. Sci. USA *104*, 87–92.
8. Mallik, R., Petrov, D., Lex, S.A., King, S.J., and Gross, S.P. (2005). Building complexity: an in vitro study of cytoplasmic dynein with in vivo implications. Curr. Biol. *15*, 2075–2085.
9. Kunwar, A., Vershinin, M., Xu, J., and Gross, S.P. (2008). Stepping, strain gating, and an unexpected force-velocity curve for multiple-motor-based transport. Curr. Biol. *18*, 1173–1183.
10. Ashkin, A., Schutze, K., Dziedzic, J.M., Euteneuer, U., and Schliwa, M. (1990). Force generation of organelle transport measured in vivo by an infrared laser trap. Nature *348*, 346–348.
11. Shubeita, G.T., Tran, S.L., Xu, J., Vershinin, M., Cermelli, S., Cotton, S.L., Welte, M.A., and Gross, S.P. (2008). Consequences of motor copy number on the intracellular transport of kinesin-1-driven lipid droplets. Cell *135*, 1098–1107.
12. Bloodgood, R.A. (1977). Motility occurring in association with the surface of the Chlamydomonas flagellum. J. Cell Biol. *75*, 983–989.
13. Gross, S.P., Welte, M.A., Block, S.M., and Wieschaus, E.F. (2000). Dynein-mediated cargo transport in vivo. A switch controls travel distance. J. Cell Biol. *148*, 945–956.
14. Gennerich, A., and Schild, D. (2006). Finite-particle tracking reveals submicroscopic-size changes of mitochondria during transport in mitral cell dendrites. Phys. Biol. *3*, 45–53.
15. Bananis, E., Nath, S., Gordon, K., Satir, P., Stockert, R.J., Murray, J.W., and Wolkoff, A.W. (2004). Microtubule-dependent movement of late endocytic vesicles in vitro: requirements for dynein and kinesin. Mol. Biol. Cell *15*, 3688–3697.
16. Bananis, E., Murray, J.W., Stockert, R.J., Satir, P., and Wolkoff, A.W. (2003). Regulation of early endocytic vesicle motility and fission in a reconstituted system. J. Cell Sci. *116*, 2749–2761.
17. Pollock, N., Koonce, M.P., de Hostos, E.L., and Vale, R.D. (1998). In vitro microtubule-based organelle transport in wild-type Dictyostelium and cells overexpressing a truncated dynein heavy chain. Cell. Motil. Cytoskeleton *40*, 304–314.
18. Gross, S.P., Welte, M.A., Block, S.M., and Wieschaus, E.F. (2002). Coordination of opposite-polarity microtubule motors. J. Cell Biol. *156*, 715–724.

[1]Department of Biological Sciences, Tata Institute of Fundamental Research, Mumbai, India. [2]Department of Developmental and Cell Biology, University of California-Irvine, Irvine, California.
E-mail: roop@tifr.res.in, grosslab@gmail.com

DOI: 10.1016/j.cub.2009.04.007

Functional Neuroanatomy: The Locus of Human Intelligence

A new study mapping the functional effects of brain lesions has revealed a surprising map of human intelligence, stimulating a re-evaluation of data from purely correlative methods such as functional magnetic resonance imaging.

Parashkev Nachev[1], Yee-Haur Mah[3] and Masud Husain[1,2]

Where in the brain are the sites that determine intelligence? For some researchers, such a question is nonsensical: they would argue no single brain function could subserve something so complex. For others, though, the possibility of a discrete set of brain regions governing intelligence might not seem so bizarre [1]. Many behavioural studies show strong correlations between an individual's performance across a range of mental ability tests, pointing to a common, general factor [2,3].

But how do we find the neuroanatomical underpinnings of such a commonality? Because the defining feature of intelligence is the generality of its operations, there is no easy way of constructing a single set of tasks that uniquely isolates it. Most neuroanatomical studies have therefore focused on differences between people measured using a battery of mental tasks, exploring their putative biological basis using

functional magnetic resonance imaging (fMRI) or voxel-based morphometry (VBM). Although frontal lobe involvement appears to be a dominant theme, the picture these studies paint is remarkably variable [4].

A recent study [5] employing a very different experimental tool — voxel-based lesion-function mapping — has produced yet another map of intelligence, at odds with traditional views. The authors studied the intellectual performance, as gauged by the widely used Wechsler Adult Intelligence Scale, of 241 patients with focal brain damage to various parts of the brain. The number and diversity of lesion locations allowed them to establish lesion-deficit relationships across most, but not all, of the brain.

The statistical maps revealed a remarkable degree of anatomical segregation: language-centred deficits localized to the left inferior frontal lobe; perceptual-centred deficits to the right parietal, occipito-parietal, and superior temporal cortex; and impairments in working memory predominantly to the left dorsal frontoparietal areas. Not only was there surprisingly little overlap between different domains, the frontal lobes — for so long assumed to be of primary importance in abstract operations of any kind — did not show the dominance many might have expected. These findings suggest that if intelligence is indeed based on a discrete, unitary substrate, its neuroanatomy must be far more intricate than might have been thought.

Critically, there is good reason to give this study [5] greater weight than those derived from established neuroimaging methods. Frustratingly, fMRI has serious limitations as a tool for exploring intelligence. First, a global ability cannot be easily isolated with a specific set of paradigms — necessarily the form imaging experiments take — unless we presuppose that the paradigm inevitably recruits it, which begs the question we are trying to answer. Second, we have no way of knowing whether functional imaging should reveal lower signal in high-performance subjects — because their brains are better organised, requiring less 'effort' [6] — or higher signal — because they are able to recruit these areas to a greater extent [7]. Neither result can therefore be unequivocally interpreted. Most importantly, functional imaging does not establish the necessity of a given region for a putative function, but merely establishes a correlation.

If measuring brain volumes by VBM escapes many of these criticisms, it brings problems of its own. Whether or not the focal volume of a brain region will correlate with intellectual performance will depend not only on the extent of its involvement in the underlying neural processes but also on the (unquantifiable) relation between volume and neural function. The picture presented by VBM will therefore be distorted by this unknown relation in a way we cannot easily characterise, and, like functional imaging, the relation it describes remains a purely correlative one.

By contrast, much stronger inferences about the relation between structure and function in the brain could be made if we were able to study the consequences of focal inactivation across the entire brain. We might then distinguish the parts of the brain that are essential to intelligence from those that are not. The closest we can come to this in practice is to study the behaviour of patients with focal brain damage from incidental causes: lesion–function mapping.

Unfortunately, the natural causes of focal brain lesions are generally unsympathetic to our aims: the size, shape, and distribution of lesions are strikingly non-random. Lesions announce their presence generally only after their behavioural consequences have become manifest, making it difficult to determine their unique contribution to the intellectual deficit. Moreover, co-existent deficits may mask or distort our inference. A disturbance of language, for example, will inevitably interact with the patient's capacity to understand and respond to the task, making it difficult to characterise his true underlying abilities. For all their potential power, lesion studies have therefore been slow to emerge. The remarkably large number of patients surveyed by Gläscher *et al.* [5] has allowed them to overcome many of these problems.

If this study is a milestone, the road it marks remains a long and winding one. Although the authors deal with one major difficulty in lesion-mapping — the striking variability in detection power across the brain — by examining each brain volume unit independently, they do so inevitably at the cost of ignoring correlations across disparate areas of the brain. Such correlations arise from the essential non-randomness of lesion data, for example from the vascular supply to brain areas in stroke. It is likely that they distort the inference in a way that is very hard to predict, especially if more than one area of the brain is critical to a syndrome [8].

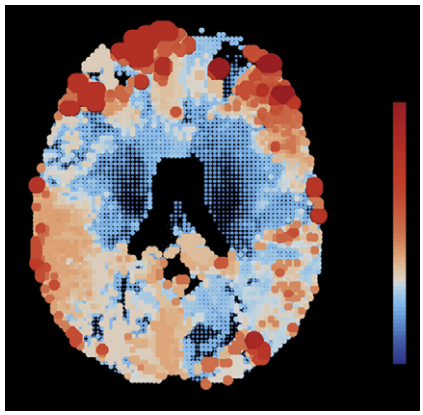

Figure 1. Map of the spatial distribution of mean volume of 485 unselected lesions of patients with stroke.

The colormap and the size of the circle at each point index the mean volume of all lesions (in 2 mm isotropic voxels) affecting that point. The slice corresponds to z = 20 in Montreal Neurological Institute normalized stereotactic space. Note that the distribution of lesion volume is highly non-random: lesions affecting the periphery are generally larger than those affecting subcortical regions.

Note, for example, the remarkable variation in mean volume for lesions affecting different parts of the brain depicted in Figure 1 (our unpublished data). Damage to certain areas is much more likely to occur if a lesion is large than small, the converse is true for others. Although a simple parameter such as total lesion volume can be easily corrected for in the statistical model, other global features of the lesion — its shape for example — are much harder to parameterize. Nevertheless, the study by Gläscher *et al.* [5] is a key landmark in the study of the anatomy of human intelligence, opening the way for even more sophisticated approaches of lesion–function correlation in the near future.

References

1. Jung, R.E., and Haier, R.J. (2007). The parieto-frontal integration theory (P-FIT) of intelligence: Converging neuroimaging evidence. Behav. Brain Sci. *30*, 135–154.

2. Spearman, C. (1927). The Abilities of Man: Their Nature and Measurement (London: Macmillan & Co. Ltd).
3. Duncan, J., Seitz, R.J., Kolodny, J., Bor, D., Herzog, H., Ahmed, A., Newell, F.N., and Emslie, H. (2000). A neural basis for general intelligence. Science *289*, 457–460.
4. Haier, R.J., Jung, R.E., Yeo, R.A., Head, K., and Alkire, M.T. (2004). Structural brain variation and general intelligence. NeuroImage *23*, 425–433.
5. Gläscher, J., Tranel, D., Paul, L.K., Rudrauf, D., Rorden, C., Hornaday, A., Grabowski, T., Damasio, H., and Adolphs, R. (2009). Lesion mapping of cognitive abilities linked to intelligence. Neuron *61*, 681–691.
6. Neubauer, A.C., Fink, A., and Schrausser, D.G. (2002). Intelligence and neural efficiency The influence of task content and sex on the brain–IQ relationship. Intelligence *30*, 515–536.
7. Gray, J.R., Chabris, C.F., and Braver, T.S. (2003). Neural mechanisms of general fluid intelligence. Nat. Neurosci. *6*, 316–322.
8. Husain, M., and Nachev, P. (2007). Space and the parietal cortex. Trends Cogn. Sci. *11*, 30–36.

[1]Institute of Neurology, UCL, London WC1N 3BG, UK. [2]Institute of Cognitive Neuroscience, UCL, London WC1N 3AR, UK. [3]Department of Clinical Neuroscience, Imperial College London, London W6 8RP, UK.
E-mail: p.nachev@imperial.ac.uk

DOI: 10.1016/j.cub.2009.04.002