The genes most clearly implicated all code for proteins that potentially have an impact, directly or indirectly, on the function of glutamate synapses.¹¹ The genes include dysbindin-1, neuregulin-1 (NRG1), D-amino acid oxidase (DAO), its activator DAOA (previously known as G72), and regulator of G protein signalling 4 (RGS4). For example, dysbindin-1 may influence the uptake of glutamate into synaptic vesicles, NRG1 is released from glutamate terminals and regulates NMDA glutamate receptors, and DAO, which is activated by DAOA, oxidises D-serine, an endogenous modulator of NMDA receptors.¹⁰ These functions imply that synapses, particularly glutamatergic ones, might be the site of primary abnormalities in schizophrenia, with downstream disruption of neural circuitry.¹⁰

The synaptic hypothesis of schizophrenia had already been attracting interest and, given these genetic clues, is likely to become a major research focus and a point of convergence between the genetics of schizophrenia and its neurobiology. Despite exciting recent findings we need to remain cautious in a field notorious for premature claims. The genetic evidence itself is incomplete, particularly for the genes with the most direct synaptic implications (DAO, DAOA, RGS4). The more strongly supported genes, however, especially NRG1, encode proteins with multiple functions, which could be relevant to schizophrenia without specifically involving the synapse.¹² Although the desire to fit the data into a unified pathophysiological theory is attractive and parsimonious, it may therefore be misguided. Schizophrenia is not a disorder where simple ideas generally prove to be true, and we should not slow down the hunt for novel schizophrenia genes. At the same time, we need to identify the specific mechanisms by which the current crop of genes alters risk of schizophrenia and the molecular processes that

link these primary events to altered function—synaptic or otherwise. We can then look forward to novel treatments that surpass the efficacy of existing medication, ameliorate the neglected cognitive and negative symptoms, and begin to modify the disease process itself.

Michael J Owen *professor of psychological medicine*
Michael C O'Donovan *professor of psychiatric genetics*

Department of Psychological Medicine, School of Medicine, Cardiff University, Cardiff CF14 4XN
(owenm@cardiff.ac.uk)

Paul J Harrison *professor of psychiatry*

University Department of Psychiatry, Warneford Hospital, Oxford OX3 7JX

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- Owen MJ, O'Donovan MC, Gottesman II. Schizophrenia. In: McGuffin P, Owen MJ, Gottesman II. *Psychiatric genetics and genomics*. New York: Oxford University Press, 2002:247-66.
- Seeman P, Chau-Wong M, Tedesco J, Wong K. Brain receptors for antipsychotic drugs and dopamine: direct binding assays. *Proc Natl Acad Sci USA* 1975;72:4376-80.
- Abi-Dargham A, Rodenhiser J, Printz D, Zea-Ponce Y, Gil R, Kegeles LS, et al. Increased baseline occupancy of D2 receptors by dopamine in schizophrenia. *Proc Natl Acad Sci USA* 2000;97:8104-9.
- Weinberger DR, Egan MF, Bertolino A, Callicott JH, Mattay VS, Lipska BK, et al. Prefrontal neurons and the genetics of schizophrenia. *Biol Psychiatry* 2001;50:825-44.
- Laruelle M, Kegeles LS, Abi-Dargham A. Glutamate, dopamine, and schizophrenia: from pathophysiology to treatment. *Ann N Y Acad Sci* 2003;1003:138-58.
- Weinberger DR. Implications of normal brain development for the pathogenesis of schizophrenia. *Arch Gen Psychiatry* 1987;44:660-9.
- Murray RM, Lewis SW. Is schizophrenia a neurodevelopmental disorder? *BMJ* 1987;295:681-2.
- Harrison PJ. The neuropathology of schizophrenia. A critical review of the data and their interpretation. *Brain* 1999;122:593-624.
- O'Donovan MC, Williams NM, Owen MJ. Recent advances in the genetics of schizophrenia. *Hum Mol Genet* 2003;12:R125-33.
- Harrison PJ, Weinberger DR. Schizophrenia genes, gene expression, and neuropathology: on the matter of their convergence. *Mol Psychiatry* 2005;10:40-68.
- Harrison PJ, Owen MJ. Genes for schizophrenia? Recent findings and their pathophysiological implications. *Lancet* 2003;361:417-9.
- Corfas G, Roy K, Buxbaum JD. Neuregulin 1-erbB signaling and the molecular/cellular basis of schizophrenia. *Nat Neurosci* 2004;7:575-80.

Would regional government have been good for your health?

England may have missed an opportunity to improve public health

The resounding “no” vote for a regional assembly in the North East of England has firmly put the lid on the prospect of elected regional government for the foreseeable future. There is considerable debate in the North East as to the reasons for the rejection of the proposal, which may have come down to a distaste for having more politicians, a suspected higher council tax, intraregional rivalries, too few powers, or perhaps a mix of these. In the white paper announcing the regional referendums, assemblies would not have any direct responsibility for health care,¹ although many would have liked to have seen such an outcome in the spirit of the government's devolution policy and commitment to localism.² But the assemblies would have had a specific remit for public health.

The white paper announcing the regional referendums pointed out the high impact that housing, transport, and economic development have on public

health and promoted the joining up of these policies to reduce health inequalities. Nevertheless, it remained a cautious document, produced against a background of little interest in the issue of elected regional assemblies.³

A public health presence already exists at regional level—a process that began with the *NHS Plan* and the move of regional directors of public health to the nine regional government offices in 2002. This was designed to enable the regeneration of regions to embrace health as well as environment, transport, and inward investment.⁴

What, if any, would have been the health benefits of regional government? Integrating public health with regional activities in social and economic development and inclusion would go some way towards meeting Derek Wanless's view that good health is also good economics.⁵ Regional development agencies are already investing in the regions, and an even closer

working relationship with those involved in health improvement could be facilitated by an elected regional assembly—to which regional development agencies would be directly accountable. Moreover, given the difficulties of joining up and integrating central government, doing so at a regional level for public health may have been easier.⁶ Regional devolution also potentially offered the democratisation of policy and its adaptation to place.⁷ It also fitted in with the government's declared wish to see more localism in public services.

Devolving responsibility is not without risks. Tensions between central and regional government, sometimes leading to poor policy formation and implementation, are a feature of countries such as Spain, which have strong regions. There were fears that regional government might have occurred at the expense of local government and increased, rather than decreased, the pull to the centre. Can assurances that regions will draw down powers from central government rather than suck up powers from local government be trusted? National policies in respect of data collection, and prevention programmes may have been vulnerable to regionalism and the fragmentation that could have occurred. Poor communication between regions, resulting in waste and duplication of effort, was also a possibility.

In contrast with England, which remains the most centralised country in Europe and beyond, regionalism is a strong movement in parts of Europe. Since the 1950s contiguous regions from European Union member states have created administrative "Euro-regions," which enable the sharing of services across borders to the mutual benefit of their populations.⁸

Elected regional assemblies in England would have had some important public health functions as well as being involved in many activities that have a bearing on public health. In particular they would have had a duty to promote the health of the region (through, for example, overview and scrutiny committees of local authorities to promote better health outcomes in the region) and support the development and implementation of a health improvement strategy for the region working with the regional directors of public health and other partner organisations.

Experience from devolved government in the United Kingdom can be gleaned from Scotland and Wales where political devolution has been happening since 1999 and administrative devolution for considerably longer. Health is regarded as a high level, cross cutting theme.

In Wales, unlike England, structural alignment and conterminosity of statutory bodies delivering public health functions have been maintained since the 1974 reorganisation. Both Scotland and Wales have developed their own detailed approaches to public health while pursuing common overarching policies to tackle inequalities in health.^{9–11} In Wales, the Richard Commission has recommended further development of devolved powers but has not specified added powers in the field of health, nor the inclusion of devolved powers as in Scotland, such as policing and justice that contribute to wider determinants of health.¹²

The experience of the Greater London Authority has also shown that progress is possible even when public health is not an executive function but an

influencing one. The London Health Commission is an advocacy coalition for public health. Its most important contribution has been to carry out health impact assessments on various of the mayor's strategies, including transport.

If regionalism is to become a potent political force in England with a remit for creating a health promoting economy, then the following issues are important. Health should not be ignored in the regional debate. An opportunity is provided to have a more coherent, and integrated, public health approach if regionalism proceeds. Some risks exist, notably in regard to central-local relations, which would need to be managed with appropriate safeguards introduced. Most European Union countries are looking to promote and develop their regions and health needs to be debated at this level.

With the publication of the English public health white paper,¹³ the issue is whether elected regional assemblies might have been well placed to take forward much of the ambitious agenda set out. The answer must be an unreserved "yes," for the reasons set out here. Although the white paper is firmly stamped as an NHS document, most of what is proposed to improve the public's health concerns other agencies and policy sectors. Certain functions are best undertaken or coordinated at a regional level, so regions will always be required. At issue is whether they should be democratically elected and transparent or appointed and largely invisible.

Regional government might have been good for health—but in England we shall never know.

David J Hunter *professor of health policy and management*

School for Health, University of Durham, Stockton on Tees TS17 6BH

John Wilkinson *director*

North East Public Health Observatory, School for Health, University of Durham, Stockton on Tees TS17 6BH
(john.wilkinson@nepho.org.uk)

Edward Coyle *director*

Wales Centre for Health, Cardiff CF11 9LJ

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- 1 Department of Transport Local Government and the Regions. *Your region, your choice*. London: Stationery Office, 2002.
- 2 Tomaney J, Hetherington P. *Nations and regions: the dynamics of devolution. The English regions. Q Rep*. London: Constitution Unit, UCL, 2004.
- 3 Sandford M. A commentary on the regional government white paper, "Your region, your choice: revitalising the English regions." London: Constitution Unit, UCL, 2002.
- 4 Department of Health. *The NHS plan. A plan for investment, a plan for reform*. London: Stationery Office, 2000. (Cmd. 4818.)
- 5 Wanless D. *Securing our future health: taking a long-term view. Final report*. London: HM Treasury, 2002.
- 6 Cabinet Office. *Reaching out: the role of central government at regional and local level*. London: Performance and Innovation Unit, 2000.
- 7 Greer S, Sandford M. Regional government and public health. London: Constitution Unit, UCL, 2001.
- 8 Perkmann M. Building governance institutions across European borders. *Regional Studies* 1999;33:657–67.
- 9 Welsh Office. *Better health—better Wales. A consultation paper*. Cardiff: Welsh Office, 1998.
- 10 Scottish Executive Health Department. *Review of the public health function in Scotland*. Edinburgh: Scottish Executive, 1999.
- 11 Townsend P. *Targeting poor health: Professor Townsend's report of the national assembly's national steering group on the allocation of NHS resources*. Vol 1. Cardiff: National Assembly for Wales, 2001.
- 12 National Assembly for Wales. *Report of the Richard Commission*. Cardiff: National Assembly for Wales, 2004.
- 13 Department of Health. *Choosing health: making healthy choices easier*. London: DoH, 2004. (CM 6374.) www.dh.gov.uk/assetRoot/04/09/47/51/04094751.pdf (accessed 16 Dec 2004).