

Neuropsychological and neuroimaging evidence for the involvement of the frontal lobes
in depression: 20 years on.

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Abstract

In 1997, neuropsychological and neuroimaging evidence supported the involvement of the frontal lobes, and indeed the brain in depression. This was a challenge to conventional phenomenology and linked with the imperative to use neuroscience to understand major mental illness. Since that time, we are seeing ever more convincing evidence for the genetic basis of mental illness (including depression), relevant abnormality in grey and white matter and neuropsychological analysis of brain function. It has proved more difficult to pin down structural abnormality in major depression at the cellular level, but a focus on glial cells is increasingly justified by the evidence. Neuroscience continues to be a buttress against anti-scientific impulses in psychiatry and can attract young people to enter it as a profession.

Keywords: Frontal lobes, Major depression, cognition, glia, astrocytes

Introduction

I wrote this review for an edition of the journal based on a meeting that had focused on the prefrontal cortex and psychiatry, held at the Wellcome Trust. It represents a point of view, held at a particular point in time. In it, I placed an emphasis on brain anatomy and neuropsychology as domains through which to understand major depression. It exemplified the position, which I had articulated in a very brief commentary (Goodwin, 1996), and still hold, that psychiatry must become applied neuroscience. Which in turn simply requires that research in psychiatry adheres to the scientific method in developing its understanding and practice. This may seem unremarkable to neuroscientists, but UK psychiatry has faced and continues to face a determined antipsychiatry movement, which is anti-scientific to the core. The thrust of its argument is that psychiatric disorders are unlike physical disorders. It often starts from the linguistic confusions of dualism: brain versus mind. It claims that diagnoses are false and non-specific and that medications do not work (any evidence that they do work is the fraudulent marketing of drug companies). It asserts that to speak of disease diminishes the status of patients who seek help with psychiatric symptoms. These views deny the need for neuroscience, and those

who hold them necessarily deny that clear scientific advances based on the medical model can ever occur.

Unfortunately, a fair proportion of psychiatrists are themselves somewhat anti-science; it is their conceit that somehow psychiatrists offer their patients more than mere doctors and surgeons can. Anyway, the proposal in 1996 to create a section for neuroscience in the Royal College of Psychiatrists was never accepted. However most psychiatrists with strong opinions on the subject hold them weakly, so the psychopharmacology section endures as a Trojan horse. The UK Department of Health's antipsychiatry position is much more hard line and has not really wavered since the 1990s; nor will it in the immediate future. It has also been expressed in NICE guidelines that prefer ideology to evidence when the two are in conflict (Taylor and Perera, 2015; Jauhar et al., 2016).

The key, perhaps definitive, challenge to antipsychiatry is molecular genetics. For me, the landmark moment came in 2014 when the common polymorphisms associated with schizophrenia were described in a very large clinical sample (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). The corresponding genetic data for depression will require even larger samples (Ripke et al., 2013), although there is little reason to doubt that they will eventually be established too because of the substantial heritability shown in conventional twin and family studies. Molecular genetic association permits only one direction of causation. Indeed, genetics confound almost all the associations claimed for the social environment and mental illness. It has recently been shown that the urban clustering invoked as a cause of schizophrenia may be explained by essentially genetic causes (Sariaslan et al., 2016). Exposure to life events, confidently judged to be independent by observers, and usually described as causing depression, have also long been known to be 'heritable' and are associated with genetic polymorphisms (Power et al., 2013). The determinism that this implies is uncomfortable, but like other inconvenient truths, unwise to deny.

Twenty years ago, identification of the brain correlates of depression provided another persuasive argument that the brain is implicated in disorders of mood. The broad thrust

of my original review was that the neuroanatomy of emotion was an obvious clue to the neurobiology of mood disorder which would be elaborated by functional imaging and structural abnormalities associated with the risk of depression. It was unusual at the time also to describe memory and executive function as key impairments in depression. I thought they were profoundly important because they showed that the depressive syndrome was more than just a temporary emotional bias and when we speak of functional impairments in depression they are failures of brain function, not just failures of motivation. I also believed that they could be preferable to rating scales as outcome measures in clinical trials; I was singularly unsuccessful in taking the field with me on that one. However, interest has shown a little late blooming with the development of vortioxetine; it appears to have an effect on cognition independent of an effect on mood (Browning et al., 2014; McIntyre et al., 2014). Debate still rages whether executive and memory impairment are simply a component of the unitary depressive syndrome (i.e. a pseudo-specific phenomenon), or better regarded as a semi-independent dimension which may be a legitimate target for drug treatment. But, this is a regulatory dispute; the impairments are real and now recognized more universally to be important (McIntyre, 2016).

In 1997, neuroimaging was still something of a novelty. The methods available for simple structural imaging were CT or MRI, and for functional imaging, SPECT (single photon emission tomography) and PET (positron emission tomography). Structural imaging was conducted on service equipment which offered very limited automation and very crude quantitation compared with now. Functional imaging was based on detecting changes in blood flow. The BOLD method had just been described and was the basis for what would turn out to be an explosion in interest and availability of research-dedicated MR scanners. Oxygen-15 PET had been the expensive precursor, which had stimulated whole brain statistical analysis, voxel-by-voxel, now applied universally in the analysis of structural and functional data. Brain imaging has been important in confirming that brain structure and function correlates with the risk, the presence and the consequences of major depression.

The brain volume in Major Depression

The availability of research scanners has led to a relatively large number of structural MRI studies in mood disorder patients. The main findings using voxel-based morphometry (VBM) relate to differences in grey and white matter (GM and WM) structures. Individual imaging studies in psychiatry have tended to be small and so pooling of data either using published results or, better by pooling individual patient data has resulted in much more confidence that differences actually exist between patients and controls. Published data from MRI studies has demonstrated reduced GM in prefrontal and limbic cortex in mature patients (Wise et al., 2016b). In contrast, relatively well powered and controlled studies have not confirmed brain volume changes in first episode MDD (Zhang et al., 2016) and adequate studies of at risk subjects have not been published. Therefore, reductions in GM may relate to illness duration (Cheng et al., 2010). It is a reasonable hypothesis that GM structural changes in MDD are acquired as a function of illness duration, intensity or recurrence. Hypercortisolaemia or other aspects of the biology of MDD, like inflammation, may contribute to this change in brain. The meaning of such volumetric changes has not been established. It implicates the brain but leaves us wanting more. Some of the possibilities are discussed below.

Brain connectivity in Major Depression

The 1997 review highlighted the emerging interest of neuroscientists in specifying the normal functions of the frontal lobes. This was based on detailed anatomy established primarily in animal studies. Such studies taught us that, even if, as appears, abnormalities of frontal or limbic cortex are present, function is very unlikely to be ‘localized’; instead, to implicate an area of the frontal cortex is to implicate a network of connections that include basal ganglia and thalamus. Hence there might be important functional consequences from abnormal brain connections, perhaps because of abnormal WM. Indeed, WM abnormality in patients with mood disorder date had been reported from the early days of structural CT and MR imaging. So-called WM hyperintensities in older patients are attributed to vascular pathology (Brown et al., 1992) and appear to correlate with the severity of systemic vascular disease (Sexton et al., 2012b).

A most interesting development since 1997 has been the detailed study of anatomical connections using MR-based diffusion weighted imaging (DTI). DTI estimates the diffusibility of water in different brain structures. Nerve axons constrain the direction of travel to be along the axis of the fibre tracts, and it turns out that if one seeds a particular brain area, its connections can be traced and remarkably displayed across the brain. It has proved possible to reconstruct almost all the major WM tracts in the living human brain with remarkable precision. This in vivo ‘tractography’ in man can then be set beside the classical axonal tracing methods used in animals. For example, the connectivity of the subgenual region, long of interest in mood disorder, suggests projections to nucleus accumbens, amygdala, hypothalamus, and orbitofrontal cortex (Johansen-Berg et al., 2008). In addition, tractography can be performed in post-mortem tissue and can demonstrate the anatomical consequences of, for example, thalamic lesions in mood disorder (McNab et al., 2009).

The detail of the anatomy *within individuals* revealed by tractography suggests that it should be possible to decide whether the density of connections between key structures varies between individuals and diagnoses. Unfortunately, this appears to have been difficult to achieve in practice. The focus has instead been on the average properties of large tracts carrying many connections, admittedly a much cruder measure of functional WM integrity. The key measure for comparing cases with controls using DTI is the fractional anisotropy (FA). A high value for FA is associated with limited diffusion; unconstrained diffusion as in a simple solution of saline or cerebrospinal fluid has zero FA. Systematic review suggests widespread FA reductions in corpus callosum, not just confined to WM in frontal areas (Wise et al., 2016a).

Such reductions could imply white matter disorganization either as a developmental or an acquired property of the brain. Twin studies suggest that FA is under genetic control (Brouwer et al., 2012) and FA increases during adolescence at different rates in different brain structures. Abnormal development of WM could be reflected in reduced FA profiles. There are studies describing FA reductions in subjects at familial risk (Bracht et

al., 2015) and in young people with hypomanic experience at risk of mood disorder (Yip et al., 2013). Decreased fibre coherence or glial distribution (Song et al., 2002) appears to be the likely underlying anatomy. Reduced FA may be a rather general neurodevelopmental marker of vulnerability to functional disorders of the brain in young people. However, FA may still be a useful biomarker for stratification in clinical trials, although as yet there has been no consistent correlate with psychopathology or cognition in young people. WM investigation at higher magnetic fields and with more refined methods are eagerly awaited.

While reduced FA may imply developmental abnormality, it also signals WM changes in ageing. A progressive reduction is seen with age in a normally ageing population. Reductions in FA correlated selectively with working memory and with the neuronal marker, *N*-acetyl aspartate (Charlton et al., 2008). In depression with onset over 60 years, FA reductions were much more striking than in age matched controls (Sexton et al., 2012a), in the absence of GM volume change or WM hyperintensities. Impaired neuropsychological performance correlated with reduced FA in a number of anatomical structures. While exploratory, there appeared to be a closer link between cognitive impairment/slowness and acquired white matter disruption, than with the superficially similar reductions in FA seen in young people with major depression (Sexton et al., 2012b). The actual structural change may be explained by different microstructural elements in the acquired versus the neurodevelopmental case; WM abnormality is a candidate for understanding gene and gene x environment interactions on the one hand and cognitive impairment on the other.

The cellular structure of brain in Major Depression

In contrast with the ever expanding literature on imaging, classical neuropathological approaches to mood disorder have remained limited in number and scope. Notwithstanding the obvious limitations for a disorder of function, this is still the only approach offering direct observation of cellular abnormality in previously depressed brains. As (Harrison, 2002) commented ‘all findings remain preliminary due to a lack of

unequivocal replication and the failure to control fully for other potential confounders and co-morbid conditions. There are also basic questions to be answered concerning the clinical correlates, magnitude, progression and heterogeneity of the pathology. Nevertheless, it must now be considered likely that changes in brain structure, both macroscopic and microscopic, are a feature of primary mood disorder, a fact to be taken into account when interpreting functional imaging, neuropsychological and neurochemical data.'

There is a consensus that major depression is associated with reduced numbers of glial cells (Rajkowska and Stockmeier, 2013) but not neurones. This is demonstrated by cell counting and with biochemical markers for astrocytes in both GM and WM. The observation may be most striking in frontal/limbic cortex and associated subcortical areas, although it is difficult to exclude reporting bias. It is not known how far these findings are unique to major depression (and not seen in other functional psychiatric disorders).

Historically, glia were the poor relations of neuroscience: little regarded and so little studied, even though they are more numerous than neurones. They were viewed as 'supporting' in a rather dismissive and passive way. Oligodendrocytes and Schwann cells do respectively provide myelination to the central and the peripheral nervous systems and hence provide functional electrical insulation and metabolic support to axons (Bercury and Macklin, 2015). But the supporting role for astrocytes is now recognized to be much more pivotal for neuronal survival, synaptogenesis and synaptic pruning and interaction with the microvasculature. By their interaction with neurones and the vasculature (Belanger et al., 2011), astrocytes play a crucial role in neurovascular coupling. The increased blood flow to brain regions with active neurones is the basis of the blood flow measures that have contributed so fundamentally to functional imaging. In addition, astrocytes may contribute to the 'glymphatic' system, a CNS equivalent of the lymphatic system, which appears to regulate the circulation of cerebral spinal fluid (Jessen et al., 2015) and provides a linkage to sleep and circadian function.

Of course, post mortem studies have access to very limited sample numbers and on tissue subjected to the many complications of relatively prolonged tissue death and post mortem delay. Convincing correlations between in vivo and post mortem findings have not been demonstrated but new approaches to biochemical analysis are being applied all the time (Nagy et al., 2015). It would be surprising if glial cells have not had a major influence on MRI findings. In the case of WM, although axons are present in very large numbers, oligodendrocytes and astrocytes appear to extend over a disproportionately large area (almost 50%) of any WM voxel (Walhovd et al., 2014). Changes in FA seem very likely to implicate glial cell organization as well as neurones.

There is a final twist in the glial story. Unlike neurones, glial cells are not excitable tissue and so do not transmit electrical action potentials. However, they may contribute to functions requiring extensive spatial and temporal integration. This may be what is required for complex cognitive constructs to be represented in the human brain. Glial cells may eventually provide the key to solving some of the current mysteries in cognition (Fields et al., 2014). Their dysfunction could accordingly predict the failures of cognition we actually observe in depression.

Functional imaging in Major Depression

The application of fMRI to major depression might have been expected to lead to fundamental advances. Instead it has done little more than add supporting (brain) substance to what can be observed in behavioural paradigms. Patients have changes in function related blood flow when tested with a host of informative neuropsychological paradigms. But it is difficult to argue that this has changed our understanding of what makes patients vulnerable to depression or what really happens when they are depressed. The technology simply offers too indirect a measure of underlying cellular change. However, functional imaging has given a major boost to the work (and arguably the credibility) of neuropsychologists. Our understanding of the regulation of the emotions has been enhanced and in relation to the emotional heart of decision making, a whole new field – neuroeconomics - has been born. The impact of brain lesions on emotional

experience continues to inform theories of normal emotion and the development of neuropsychology as cognitive neuroscience.

Conclusions

Having highlighted the pivotal role of genetics in supporting a neuroscience-first approach to psychiatry, it is worth remembering that size has been everything in creating definitive findings. The perennial problem with imaging studies has been inadequate sample size. New, very welcome initiatives to create very large data sets by pooling data have started (ENIGMA at <http://enigma.ini.usc.edu/> is a superb example) and will generate definitive findings within the limits of existing scanner technology. Moreover, genetics will inform imaging in potentially very interesting ways and anatomy will remain important because it is so intrinsically an expression of function and vice versa.

The molecular basis of major depression remains elusive because obviously the brain is the hardest organ to invade for direct measurement of its chemistry. A convergence between the astrocyte story in major depression and the acknowledgement of cognition as central to MDD offers a very tempting synthesis. Should we be thinking of depression as a glial dysfunction? Since astrocytes can be produced from induced pluripotent stem cells, and derived from individual depressed patients, perhaps the brain basis of depression will not remain the challenge it has been hitherto.

Finally, how we best harness neuroscience to serve psychiatric patients remains uncertain. We need to persuade neuroscientists that mental illness is the most interesting thing in neuroscience. As a fascinating if distorted window on normal experience, and a source of enormous burdens for individuals and society, mental illness deserves to be better served by the best people in neuroscience. By the same token, psychiatry needs to embrace neuroscience. Our best medical students and clinical psychologists need to be drawn to psychiatry via neuroscience so they can help re-think a different future for our patients. We need much better, more creative services, better treatments and better outcomes. Only science will deliver them.

References

- Belanger M, Allaman I and Magistretti PJ. (2011) Brain energy metabolism: focus on astrocyte-neuron metabolic cooperation. *Cell Metab* 14: 724-738.
- Bercury KK and Macklin WB. (2015) Dynamics and mechanisms of CNS myelination. *Dev Cell* 32: 447-458.
- Bracht T, Linden D and Keedwell P. (2015) A review of white matter microstructure alterations of pathways of the reward circuit in depression. *J Affect Disord* 187: 45-53.
- Brouwer RM, Mandl RC, Schnack HG, et al. (2012) White matter development in early puberty: a longitudinal volumetric and diffusion tensor imaging twin study. *Plos One* 7: e32316.
- Brown FW, Lewine RJ, Hudgins PA, et al. (1992) White matter hyperintensity signals in psychiatric and nonpsychiatric subjects. *Am J Psychiatry* 149: 620-625.
- Browning M, Smith J, Conen S, et al. (2014) Vortioxetine Reduces BOLD Signal during Performance of the N-Back Task in Subjects Remitted from Depression and Healthy Control Participants. *Neuropsychopharmacology* 39: S480-S480.
- Charlton RA, Landau S, Schiavone F, et al. (2008) A structural equation modeling investigation of age-related variance in executive function and DTI measured white matter damage. *Neurobiol Aging* 29: 1547-1555.
- Cheng YQ, Xu J, Chai P, et al. (2010) Brain volume alteration and the correlations with the clinical characteristics in drug-naïve first-episode MDD patients: a voxel-based morphometry study. *Neuroscience Letters* 480: 30-34.
- Fields RD, Araque A, Johansen-Berg H, et al. (2014) Glial biology in learning and cognition. *Neuroscientist* 20: 426-431.
- Goodwin GM. (1996) Special Interest Group for Neuroscience in psychiatry. *Psychiatric Bulletin* 20: 304-305.
- Harrison PJ. (2002) The neuropathology of primary mood disorder. *Brain* 125: 1428-1449.
- Jauhar S, McKenna PJ and Laws KR. (2016) NICE guidance on psychological treatments for bipolar disorder: searching for the evidence. *Lancet Psychiatry* 3: 386-388.
- Jessen NA, Munk AS, Lundgaard I, et al. (2015) The Glymphatic System: A Beginner's Guide. *Neurochem Res* 40: 2583-2599.
- Johansen-Berg H, Gutman DA, Behrens TE, et al. (2008) Anatomical connectivity of the subgenual cingulate region targeted with deep brain stimulation for treatment-resistant depression. *Cereb Cortex* 18: 1374-1383.
- McIntyre RS. (2016) Cognitive impairment in major depressive disorder. 351.
- McIntyre RS, Lophaven S and Olsen CK. (2014) A randomized, double-blind, placebo-controlled study of vortioxetine on cognitive function in depressed adults. *Int J Neuropsychopharmacol* 17: 1557-1567.
- McNab JA, Voets NL, Jenkinson N, et al. (2009) Reduced limbic connections may contraindicate subgenual cingulate deep brain stimulation for intractable depression. *J Neurosurg* 111: 780-784.

- Nagy C, Suderman M, Yang J, et al. (2015) Astrocytic abnormalities and global DNA methylation patterns in depression and suicide. *Mol Psychiatry* 20: 320-328.
- Power RA, Wingenbach T, Cohen-Woods S, et al. (2013) Estimating the heritability of reporting stressful life events captured by common genetic variants. *Psychological Medicine* 43: 1965-1971.
- Rajkowska G and Stockmeier CA. (2013) Astrocyte pathology in major depressive disorder: insights from human postmortem brain tissue. *Curr Drug Targets* 14: 1225-1236.
- Ripke S, Wray NR, Lewis CM, et al. (2013) A mega-analysis of genome-wide association studies for major depressive disorder. *Mol Psychiatry* 18: 497-511.
- Sariaslan A, Fazel S, D'Onofrio BM, et al. (2016) Schizophrenia and subsequent neighborhood deprivation: revisiting the social drift hypothesis using population, twin and molecular genetic data. *Transl Psychiatry* 6: e796.
- Schizophrenia Working Group of the Psychiatric Genomics Consortium. (2014) Biological insights from 108 schizophrenia-associated genetic loci. *Nature* 511: 421-427.
- Sexton CE, Allan CL, Le Masurier M, et al. (2012a) Magnetic resonance imaging in late-life depression: multimodal examination of network disruption. *Arch Gen Psychiatry* 69: 680-689.
- Sexton CE, Le Masurier M, Allan CL, et al. (2012b) Magnetic resonance imaging in late-life depression: vascular and glucocorticoid cascade hypotheses. *Br J Psychiatry* 201: 46-51.
- Song SK, Sun SW, Ramsbottom MJ, et al. (2002) Dysmyelination revealed through MRI as increased radial (but unchanged axial) diffusion of water. *Neuroimage* 17: 1429-1436.
- Taylor M and Perera U. (2015) NICE CG178 Psychosis and Schizophrenia in Adults: Treatment and Management - an evidence-based guideline? *Br J Psychiatry* 206: 357-359.
- Walhovd KB, Johansen-Berg H and Karadottir RT. (2014) Unraveling the secrets of white matter--bridging the gap between cellular, animal and human imaging studies. *Neuroscience* 276: 2-13.
- Wise T, Radua J, Nartjes G, et al. (2016a) Voxel-Based Meta-Analytical Evidence of Structural Disconnectivity in Major Depression and Bipolar Disorder. *Biol Psychiatry* 79: 293-302.
- Wise T, Radua J, Via E, et al. (2016b) Common and distinct patterns of grey-matter volume alteration in major depression and bipolar disorder: evidence from voxel-based meta-analysis. *Mol Psychiatry*.
- Yip SW, Chandler RA, Rogers RD, et al. (2013) White matter alterations in antipsychotic- and mood stabilizer-naïve individuals with bipolar II/NOS disorder. *Neuroimage Clin* 3: 271-278.
- Zhang H, Li L, Wu M, et al. (2016) Brain gray matter alterations in first episodes of depression: A meta-analysis of whole-brain studies. *Neurosci Biobehav Rev* 60: 43-50.