

Stress and the progression of the developmental hypothesis of schizophrenia

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The neurodevelopmental hypothesis of schizophrenia proposes that an early insult to the developing brain could result in brain changes that are 'fixed', 'non-progressive' and lie 'dormant' until made manifest in adolescence or early adulthood. This hypothesis was promoted most recently in the 1980s (Lewis & Murray, 1987; Weinberger, 1987), but similar models were proposed by earlier researchers (Clouston, 1891; Southard, 1915; Pasamanick *et al*, 1956). The success of this theory has been in its capacity to explain many of the known features of schizophrenia. Thus, the season-of-birth effect, the reported excess of obstetric complications, minor physical anomalies, dermatoglyphic abnormalities and childhood developmental impairments may all be successfully and usefully explained in relation to the influence of environmental and epigenetic factors on normal foetal brain development. Crucial supportive evidence for the theory was given by studies showing that classical degenerative brain changes were largely absent, by the presence of microscopic brain changes indicative of abnormal brain development, and by the absence of clear evidence for progressive ventricular dilation among people with schizophrenia.

However, these latter findings are no longer secure. For example, the absence of excess cortical gliosis is no longer accepted as indicating a lack of perinatal or post-natal cerebral inflammation, and firm cyto-architectural evidence of abnormal brain development has yet to be consistently presented (Harrison, 1999). Furthermore, some neuroimaging studies have shown evidence for progressive brain volume reductions over time (Mathalon *et al*, 2001) and others have shown that hippocampal volume reductions occur during the phase of a first psychotic episode (Lawrie *et al*, 2000; Pantellis *et al*, 2000). Reversibility of superior temporal gyrus volume reductions has also been described during the first episode of psychosis (Keshavan *et al*,

1998), and progressive cortical reductions are observed in people with early-onset schizophrenia (Thompson *et al*, 2001). Thus, evidence is accumulating to support the view that plastic changes in macroscopic cytoarchitecture may occur with illness.

The microscopic basis of these cortical volume reductions is not known, but clues are provided by recent neuropathological studies which show reductions in cortical neuronal size, dendritic complexity and synaptic proteins in schizophrenia (Harrison, 1999). Smaller neurons with fewer and less elaborate branches would result in a diminution in the amount of neuropil, more compacted cells, and thus increased neuronal density. It is certainly feasible to suggest that these alterations underlie the regional cortical volume reductions observed in schizophrenia. The current challenge, however, is to understand the mechanism underlying these changes. The term 'atrophic' is preferred to 'degenerative' because evidence of cell death and of the gliotic response so characteristic of degenerative diseases is absent. However, regardless of terminology, the findings necessitate a re-evaluation of the neurodevelopmental hypothesis of schizophrenia as described by Lewis & Murray (1987).

EVIDENCE FOR A COMMON NEUROPATHOLOGY IN MAJOR DEPRESSION, BIPOLAR DISORDER AND SCHIZOPHRENIA

The microscopic neuropathological changes in schizophrenia may be either a vulnerability factor, or an intrinsic component or consequence of the illness. Neuropathological studies cannot tell which interpretation is correct. Some histological changes, such as those of reduced neuronal density in bipolar disorder but not in schizophrenia (Rajkowska *et al*, 2001) and

alterations in hippocampal kainate receptor function in schizophrenia but not in bipolar disorder (Benes *et al*, 2001) argue for disease-specific processes. However, similarities in the neuropathology of schizophrenia, major depressive disorder and bipolar disorder suggest that a common process of change might be involved. These findings are not discordant, for they argue that the observed pathology in these disorders might be the product of both disease-specific and non-specific processes.

What pathological changes are shared? First, macroscopic neuroanatomical investigations of brain changes in schizophrenia, bipolar disorder and major depressive disorder show differences that are generally quantitative rather than qualitative. For example, ventricular dilation and reduced hippocampal and frontal brain volumes are seen in schizophrenia, but they are also present to a lesser degree in major depressive disorder and bipolar disorder (McCarley *et al*, 1999). The single main departure from this pattern is that the volume of the amygdala may be specifically enlarged in bipolar disorder (Altshuler *et al*, 1998), possibly because of drug treatment, although this is not yet resolved. Second, at the microscopic level, reductions in dendritic spine density (Rosoklija *et al*, 2000), neuronal size (Rajkowska *et al*, 1999; Cotter *et al*, 2001a, 2002) and synaptic proteins (Eastwood & Harrison, 2001) have been described in both mood disorders and schizophrenia (Harrison, 1999). Finally, it has now become apparent that glial cell deficit may also be a feature of major depressive disorder, bipolar disorder and schizophrenia (Rajkowska *et al*, 1999; Cotter *et al*, 2001a, b, 2002), depending possibly on the coexistence of affective symptoms and on which region of the brain is investigated. Although the latter finding's functional and aetiological significance is not yet clear, it further demonstrates a similar brain pathology in these disorders and may provide an important clue to identifying aspects of the underlying disease processes.

The similarity of these patterns of changes in cortical cellular architecture in schizophrenia and mood disorders suggests that a common biological mechanism may underlie aspects of these psychiatric diseases. What aspects of illness common to major depressive disorder, bipolar disorder and schizophrenia could cause changes in keeping with the known cellular changes described above? We do not propose that

this common process is necessarily primary to the pathophysiology of these disorders – rather, that a single biological mechanism might participate in an important way in the development of the observed neuropathological (micro- and macroscopic) abnormalities. Glucocorticoid-related neurotoxicity is a candidate that needs to be considered.

ROLE OF GLUCOCORTICOIDS

There is substantial evidence that hyperactivity of the hypothalamic–pituitary–adrenal (HPA) axis is involved in the pathogenesis of mood disorder (Pariante & Miller, 2001). Impaired function of the glucocorticoid receptor and subsequent altered feedback inhibition by endogenous glucocorticoids probably represents the mechanism by which the HPA axis is activated in depression. In contrast, until recently there was no firm evidence that HPA hyperactivity is part of the pathogenesis of schizophrenia. The rate of non-suppression to the dexamethasone suppression test in schizophrenia varies from 0% to 70%, with a mean rate of approximately 20% (Sharma *et al*, 1988), which is much lower than that described in depression (Evans *et al*, 1983) but still higher than in the normal population (Sharma *et al*, 1988). The range appears to reflect the type of patient, the activity of the patient, the presence of associated symptoms of depression and the effect of hospitalisation. Indeed, in schizophrenia there is evidence that patients who are clinically stable and receiving treatment tend to have a normal HPA axis (Tandon *et al*, 1991; Ismail *et al*, 1998), but patients who are drug-free or in the acute phase of the illness have an activated HPA axis (Holsboer-Trachslers *et al*, 1987; Tandon *et al*, 1991). This suggests, crucially, that the inconsistencies of the HPA axis changes observed in schizophrenia may be because fewer studies have assessed patients during the acute phase of the schizophrenic illness, which is the very period most likely to be associated with a stress-related elevation of glucocorticoids. Moreover, reduced glucocorticoid receptor gene expression has been described in the frontal cortex in schizophrenia and major depressive disorder (Webster *et al*, 2000), providing some evidence that HPA axis abnormalities may indeed be present in both these disorders, albeit mediated by different mechanisms.

Several other lines of investigation support the view that glucocorticoid-related neurotoxicity may be implicated in depression and schizophrenia. First, investigations *in vitro* have shown that high levels of glucocorticoid hormones result in reduced neuronal volume and dendritic arborisation (Sapolsky, 2000), and these changes have been observed in both disorders. Second, elevated plasma glucocorticoid levels are associated with hippocampal volume reductions in major depressive disorder, post-traumatic stress disorder, Cushing's disease and normal ageing, and such reductions have been observed in the phase of a first psychotic episode (Lawrie *et al*, 2000; Pantellis *et al*, 2000). Third, the functional effect of glucocorticoids on reducing hippocampal glial cell activation and proliferation (Crossin *et al*, 1997) mirrors the glial deficit observed in major depressive disorder, bipolar disorder and possibly schizophrenia. Consequently the glial deficit found in these disorders may also relate to glucocorticoid-related effects.

At present one can only speculate whether this putative link between glucocorticoid hormones and macroscopic brain changes in schizophrenia is exerted mainly through permanent damage of the brain cells or through reversible changes in the neuropil structure. In animals, stress-induced changes in dendritic arborisation are reversible after the stressor is eliminated, unless the stress is severe and protracted over weeks or months (Sapolsky, 1996). Moreover, the hippocampal volume reduction in people with Cushing's disease is also reversible after normalisation of cortisol levels (Sapolsky, 2000). Evidence in psychiatric disorders is less clear and the mechanisms may be different in different phases of the disorders. For example, the temporal gyrus volume reductions described during the first episode of psychosis seem to be reversible (Keshavan *et al*, 1998), but the hippocampal reductions described in patients with a long history of major depressive disorder are present even in stable patients with normal cortisol levels, and are correlated with the length of illness (Sapolsky, 2000). Reassuringly, a recent study has found minimal or no evidence of apoptosis in the post-mortem analysis of the hippocampus from patients with major depression (Lucassen *et al*, 2001), suggesting that the main alterations may involve potentially reversible changes to neuropil, glia and dendrites.

Despite this evidence supporting the view that interactions between glucocorticoid hormones and the brain might be abnormal in major depressive disorder and schizophrenia, there remain some unanswered questions. First, it is not at all clear whether the mechanism of neurotoxicity *in vivo* is mediated through elevated or lowered levels of cerebral glucocorticoids, for very low levels also have neurotoxic effects (Sapolsky, 2000). Second, reduced glucocorticoid receptor function is observed in individuals with major depression (Pariante & Miller, 2001) or undergoing severe psychological stress (Bauer *et al*, 2000), suggesting that elevated plasma cortisol levels could represent a compensatory strategy. Third, studies indicate that levels of cortisol in the human brain are regulated by efflux systems at the blood–brain barrier (De Kloet *et al*, 1998), and that both the glucocorticoid receptor and the cortisol efflux systems may be influenced by psychotropic drugs (Pariante & Miller, 2001; Pariante *et al*, 2001). This indicates that peripheral cortisol levels may not necessarily dictate cerebral levels, as is often assumed in studies. Finally, adjuvant antidepressant effects have been demonstrated not only with compounds that stimulate glucocorticoid receptor function (e.g. dexamethasone, prednisolone) but also with compounds that inhibit its function (e.g. RU486, ketoconazole). Therefore, whether patients with major depression or schizophrenia have elevated or lowered activation of the glucocorticoid receptor within the brain is yet to be fully elucidated.

Further development of this hypothesis will require research into HPA function in these disorders, such as post-mortem brain investigations into levels of corticotrophin-releasing hormone in the paraventricular nucleus of the thalamus in schizophrenia and bipolar disorder, and *in vivo* study of the relationship between glucocorticoid receptor function, cortisol levels and brain changes in patients with depression and schizophrenia at various stages of these illnesses.

CONCLUSION

Evidence is accumulating that brain changes occur during and possibly after the period of the first acute psychosis – changes that are not purely developmental in the traditional sense. Furthermore, these

alterations are not specific to schizophrenia, in terms of either macroscopic or microscopic brain structure, for they are also present to a generally milder degree in people with mood disorder, and are in keeping with glucocorticoid-related brain changes. Although it is possible – even likely – that these brain changes are secondary to stress-related changes in glucocorticoid hormones rather than primary pathogenetic pathways, they may none the less have crucial clinical effects through diminishing neuronal and cortical function. This is because these brain changes may complicate recovery from the primary illness. In the future, it may be possible to reverse these changes by therapies that protect against glucocorticoid-related neurotoxicity or promote neuroprotective cell signalling pathways. In the meantime, however, the developmental theory of schizophrenia as presented by Lewis & Murray (1987) and Weinberger (1987) is challenged, for alone it is insufficient to explain the unfolding neuroanatomy of the disorder, which now seems likely to involve both early developmental and later atrophic processes. Targeting these later processes may offer crucial therapeutic opportunities.

DECLARATION OF INTEREST

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