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 dilatation 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 postnatal cerebral inflammation, and firm cytoarchitectural 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 vulnerable 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 (Altschuler 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 neuro-
pathological (micro- and macroscopic)
abnormalities. Glucocorticoid-related neuro-
toxicity is a candidate that needs to be
considered.

ROLE OF
GLUCOCORTICOIDS

There is substantial evidence that hyper-
activity 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 activ-
ated in depression. In contrast, until recently
there was no firm evidence that HPA hyper-
activity is part of the pathogenesis of schizo-
phrenia. The rate of non-suppression to the
dexamethasone suppression test in schizo-
phrenia varies from 0% to 70%, with a mean
rate of approximately 20% (Sharma et al,
1988), which is much lower than that de-
scribed in depression (Evans et al, 1983)
but still higher than in the normal popu-
lation (Sharma et al, 1988). The range
appears to reflect the type of patient, the
activity of the patient, the presence of asso-
ciated symptoms of depression and the
effect of hospitalisation. Indeed, in schizo-
phrenia 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 (Holboer-Trachster et al, 1987;
Tandon et al, 1991). This suggests, cru-
ically, 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 schi-
zophrenic illness, which is the very period
most likely to be associated with a stress-
related elevation of glucocorticoids. Mor-
over, reduced glucocorticoid receptor gene
expression has been described in the fron-
tal 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 sup-
port the view that glucocorticoid-related
neurotoxicity may be implicated in depres-
sion 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 re-
ductions in major depressive disorder,
post-traumatic stress disorder, Cushing’s
disease and normal ageing, and such reduc-
tions 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 hippo-
campal glial cell activation and prolifera-
tion (Crosin et al, 1997) mirrors the glial
deficit observed in major depressive dis-
order, bipolar disorder and possibly schizo-
phrenia. 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 gluco-
corticoid 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 elimi-
nated, unless the stress is severe and pro-
tracted 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 differ-
ent phases of the disorders. For example,
the temporal gyrus volume reductions
described during the first episode of psy-
chosis seem to be reversible (Keshavan
et al, 1998), but the hippocampal reduc-
tions 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). Re-
assuringly, a recent study has found mini-
mal 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 glucocorti-
coid hormones and the brain might be
abnormal in major depressive disorder
and schizophrenia, there remain some un-
answered questions. First, it is not at all
clear whether the mechanism of neurotoxi-
city 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 cor-
tisol 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 psy-
chotropic drugs (Pariante & Miller, 2001;
Pariante et al, 2001). This indicates that
peripheral cortisol levels may not necess-
sarily dictate cerebral levels, as is often
assumed in studies. Finally, adjuvant anti-
depressant effects have been demonstrated
not only with compounds that stimulate
glucocorticoid receptor function (e.g. dexa-
methasone, 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 corticosterone-
releasing hormone in the paraventricular
nucleus of the thalamus in schizophrenia
and bipolar disorder, and in vivo study of
the relationship between glucocorticoid re-
ceptor 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 in 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 glucocorticoids 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.

DEопределATION OF INTEREST

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REFERENCES


