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What causes the onset of psychosis?

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Abstract

It has become increasingly clear that the simple neurodevelopmental model fails to explain many aspects of schizophrenia including the timing of the onset, and the nature of the abnormal perceptions. Furthermore, we do not know why some members of the general population have anomalous experiences but remain well, while others enter the prodrome of psychosis, and a minority progress to frank schizophrenia. We suggest that genes or developmental damage result in individuals vulnerable to dopamine deregulation. In contemporary society, this is often compounded by abuse of drugs such as amphetamines and cannabis, which then propel the individual into a state of dopamine-induced misinterpretation of the environment. Certain types of social adversity such as migration and social isolation, as well as affective change can also contribute to this. Thereafter, biased cognitive appraisal processes result in delusional interpretation of the abnormal perceptual experiences. Thus, a plausible model of the onset of psychosis needs to draw not only on neuroscience, but also on the insights of social psychiatry and cognitive psychology.

Keywords: Psychosis; Schizophrenia; Prodromal; Aetiology/Etiology; Epidemiology; Imaging

1. Introduction

In this paper we consider what initiates psychosis. We start by describing the developmental and epidemiological context of prodromal symptoms. Then we discuss dopaminergic mechanisms implicated in the onset of functional psychosis as well as the role of social factors, and how cognitive psychological models may help to integrate these seemingly disparate lines of research.

1.1. The developmental perspective

It has been apparent for almost two decades that there is a developmental component to schizophrenia.

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In its simple form, this model postulates that genes involved in neurodevelopment (Jones and Murray, 1991) and/or environmental insults in early life lead to aberrant brain development, which in turn predisposes to the later onset of psychosis (Murray and Lewis, 1987; Bullmore et al., 1998; McDonald et al., 1999). However, more recent formulations incorporate the role of social factors such as urban upbringing, social isolation, and migration (Boydell et al., 2004), and point to an interaction between the biological and psychological in a cascade of increasingly deviant development (Howes et al., 2004).

Prospective studies show that children who later develop schizophrenia are more likely than peers to show subtle developmental delays and cognitive impairments, they also tend to be solitary and socially anxious (Cannon et al., 2002a; Jones et al., 1994). Some evidence suggests that individuals destined to develop schizophrenia fail to learn new cognitive skills as they enter adolescence, thus appearing to show a relative decline compared with their peer group (Jones et al., 1994; Fuller et al., 2002). The combination of neurocognitive and emotional deviance increases the likelihood of developing minor quasi-psychotic symptoms: indeed the Dunedin prospective study showed preschizophreniform individuals to be more likely to manifest such symptoms as early as age 11 years (Poulton et al., 2000; Cannon et al., 2002a) (see Tables 1 and 2). It is postulated that in those destined to develop psychosis, the strength, frequency, and associated distress, of the odd ideas and experiences increases, and at some ill-defined point, the individual crosses a threshold into the pre-psychotic or prodromal phase.

Table 1
Dunedin questions asked at age 11 (adapted from Poulton et al., 2000)

"Some people believe in mind reading or being psychic. Have other people ever read your mind?"
"Have you ever had messages just sent to you through television or radio?"
"Have you ever thought that people are following you or spying on you?"
"Have you ever heard voices other people can't hear?"
"Has something ever gotten inside your body or has your body changed in some strange way?" (not endorsed by any study participant).

Table 2
Dunedin prospective study data (adapted from Poulton et al., 2000)

Number of questions endorsed	Subjects (total $n=789$)	Symptom level at age 11	Diagnosis of schizophreniform disorder at age 26 (%)	Odds ratio
0	673	'Control'	2.0	
1	103	Weak	9.5	5.1
2 or more	13	Strong	25.0	16.1

1.2. Psychotic symptoms in the general population

Not only many children but also a proportion of the general adult population experience brief or isolated psychotic phenomena without coming into contact with psychiatric services (Johns and van Os, 2001). For example, in the Dunedin cohort, 25% of the entire population reported having experienced isolated or transient delusions or hallucinations at the age of 26 years though only 3.7% met criteria for a schizophreniform illness. Initially, there was considerable skepticism that such minor symptoms bore any relation to the frank and persistent hallucinations and delusions experienced by schizophrenic patients. However, van Os and his colleagues reported that the very same risk factors that are associated with clinical schizophrenia (single state, unemployment, urban living, etc) are also associated with the occurrence of minor psychotic symptoms in the Dutch general population. Johns et al. (2004) confirmed these findings in a large sample ($n=8580$) of the British general population. Factors independently associated with psychotic symptoms were lower IQ, poorer educational qualifications, cannabis dependence, alcohol dependence, victimisation, stressful life events, and neurotic symptoms. Such findings have suggested that psychosis is best considered as a dimension extending well into the general population (Verdoux and van Os, 2002).

1.3. The prodrome

Several research groups have identified characteristics of young people thought to be at 'ultra high risk' of developing frank psychosis (see Table 3). These individuals are described as experiencing cognitive dysfunction as the earliest detectable anomaly, followed by attenuated 'negative' symptoms such as dec-

Table 3
Cohorts of "at risk" subjects and their chances of transition to psychosis

Study	Sample	Follow up	Rate of transition (%)
Klosterkotter et al. (2001); Bonn Early Recognition Study	160; from 695 referrals for a second opinion	9.6 years average	49.4
Morrison et al. (2002, 2004); EDIE trial	58; from general practice referrals	12 months	6 (treated group); 22 (monitored group)
Woods et al. (2003); PRIME clinic	59 prodromals	1 year treatment and 1 year follow-up	33 (preliminary result)
Yung et al. (2003); PACE clinic	49; from 162 referrals	1 year	40.8
Lencz et al. (2003); RAP clinic	34 young at risk persons	2 years mean follow up	26.5
Broome et al. (in press); OASIS clinic	58	18 months	10.3
Hafner et al. (2004); Bonn and Cologne, Germany	123	12 months	14.8 (support group); 5.3 (CBT group)

A number of cohort studies following people with 'at risk' symptoms allow estimating the probability that they will experiment transition to schizophrenia or other psychoses. PPV: positive predictive value, NPV: negative predictive value.

reased motivation and socialisation (Cornblatt et al., 2001). Later, positive psychotic symptoms develop but are not sufficient in intensity or duration to meet formal criteria for frank psychotic illness. This constellation of symptoms has been combined with having: a) a first degree relative with psychosis or b) a diagnosis of schizotypal personality disorder plus a decline in function, to create what is termed an 'at risk mental state' or ARMS (Yung et al., 1998, 2003). If one accepts psychosis as a dimension, then the 'at risk mental state' is likely to cover a segment of it, and the point of transition to frank psychosis is somewhat arbitrary.

Nevertheless, Yung and colleagues reported that the presence of the "at risk" mental state in their clients predicted a 40% transition rate to frank psychosis within 12 months. Morrison et al. (2002) noted that 22% of those they identified became psychotic, while Cornblatt et al. (2002) studied a group of 15 individuals with 'schizophrenia-like psychosis' of whom one third developed schizophrenia within 6 months. Not all groups, however, have been so successful in identifying individuals at such a high risk of transition (Broome et al., in press). For example, Hambrecht et al. (2002) reported that at 15 month follow up five (9.8%) of 51 individuals identified as UHR met ICD-10 criteria for a psychotic disorder.

1.4. The prodrome in context

van Os and Delespaul (in press) point out that the highest transition rates occur in those "at risk" populations which have been most highly selected, and that the process of screening and referral into these populations makes a major contribution to the success of researchers in identifying individuals at such high risk of transition. Thus, the application of ARMS criteria to the general population may have much less predictive power than in a clinic to which individuals suspected of being in a pre-psychotic phase have been specially referred. One reason for this loss of power is the evidence discussed above that psychosis exists as a continuous phenotype in the general population. A second reason is that the commonest outcome of subclinical psychotic symptoms in a general population is remission (Hanssen et al., in press).

This is an obvious example of the more general problem that findings from cohort, epidemiological, and prodromal studies have not yet been fully integrated. Thus, neurodevelopmental theorists have struggled to explain what converts a developmentally impaired or socially isolated adolescent with odd ideas and experiences into a psychotic individual. Similarly, it is not yet clear what differentiates an individual in the community who experiences hallucinations and holds delusional beliefs but never sees a psychiatrist, from the individual who reaches a specialised clinic for those at risk of psychosis where he/she is considered as prodromal. The work of Hanssen et al. (in press) suggests that the intensity of the experiences is important but so too, they suggest, is depression. Escher et al. (2002) also believe that the co-existence of affective disturbance

is a major factor in determining whether young people who experience minor psychotic symptoms will progress to psychotic disorder that requires care.

Of course, cohort studies have consistently shown that preschizophrenic children have an excess of depression and social anxiety (e.g. Jones et al., 1994; Cannon et al., 2002a). Retrospective studies show that depression and anxiety are among the first noticeable psychological disturbances in individuals who later become psychotic; indeed most patients with a first episode of schizophrenia will have had a depressed mood, and at least one frank episode of depression, in the year prior to hospitalisation (an der Heiden and Hafner, 2000). From studies of those with the ARMS, it is clear that prior to the onset of frank psychosis there are prominent mood symptoms, many of which reach DSMIV diagnostic criteria (Yung et al., 2003; Broome et al., in submission). Such affective symptomatology may play a role in the genesis of positive symptoms such as hallucinations and delusions. Freeman and Garety (2003) suggest that anxiety also facilitates the development of aberrant cognitive schema and beliefs, and influences the generation of anomalous experiences and then the maintenance of delusions once formed (Freeman and Garety, 2003).

1.5. Dopamine as the wind of psychotic fire

While the neurodevelopmental hypothesis can explain neurocognitive and emotional deficits in preschizophrenic children, and some at least of the neuropsychological and neuroanatomical abnormalities found in those with established schizophrenia, neither it nor epidemiological or prodromal studies explain the biological processes that accompany the onset of frank psychosis. In considering this issue, it is worth examining what we know concerning the neurochemical basis of the positive symptoms experienced in acute psychosis.

Hemsley (1993) described how in the acutely psychotic individual "Meaningful connections are created between temporary coincident external impressions. . .or perceptions with thoughts that happen to be present, or events and recollections happening to occur in consciousness at the same time". He and his colleagues (Gray et al., 1991) pointed out that, normally, input from the hippocampus controls the mesolimbic dopamine system, and speculated that damage to it causes a loss of this control, with the resultant heightened dopamine transmission facilitating the formation of "meaningful connections" between coincident events. Relatively little attention was paid to this paper at the time for the dopamine hypothesis of schizophrenia was in the doldrums. Then Laruelle et al. (1996), who demonstrated increased striatal dopamine release following amphetamine challenge in acute schizophrenic patients, provided evidence demonstrating the long suspected link between dopamine dysregulation and psychosis. Furthermore, the degree of dopamine release correlated positively with extent of acute positive symptoms and with subsequent response to dopamine blockers (Laruelle et al., 1999; Abi-Dargham et al., 2000).

Kapur (2003) elaborated on the link between dopamine and the positive symptoms of psychosis, and drew on theories of the role of mesolimbic dopamine in the healthy brain derived from studies using experimental animals. It has been argued that in the normal individual, mesolimbic dopamine acts to provide significance or salience, transforming an affectively neutral mental representation of a stimulus into an attractive or aversive one (Berridge and Robinson, 1998). Thus, mesolimbic dopamine activity may determine whether an intrusion into awareness from either external perceptual or internal mental sources receives a positive or negative 'hedonic vector', and thus "grabs the attention" of the individual. If psychosis were associated with increased, often stimulus-independent, release of dopamine, salience would be granted to what would otherwise be relatively innocuous events and stimuli. In this way, it is argued, dopamine provides "the wind of psychotic fire" (Laruelle et al., 1999).

In normal health, interplay between the hippocampus and the amygdala helps to maintain the individual in emotional balance. As Gray et al. (1991) outlined, the hippocampus maintains focus on a task, and sets current environmental stimuli in the context of previous experience, allowing only response patterns that are appropriate to a given context to impact on mesolimbic dopamine; however, the amygdala can provide an emotional or affective override to this information. Grace (2004) points out that normally the prefrontal cortex provides a super-

visory input to the hippocampus and amygdala that tempers their reactions to stimuli and ensures that the responses are appropriate to the particular circumstances. However, in schizophrenia, this cortical–limbic circuitry malfunctions; many patients show deficits in prefrontal or executive functions, and much evidence demonstrates that the hippocampus and amygdala are decreased in volume in schizophrenia (Wright et al., 2000). Grace suggests that either excessive input from these limbic structures or a loss of the normal prefrontal 'brake' on the limbic system causes increased mesolimbic dopamine which results in the increased salience and overreaction to emotional stimuli, which leads ultimately to paranoia and psychosis.

1.6. Why are some individuals vulnerable to dopamine dysregulation?

1.6.1. Genes

Since a high proportion of the variance in liability to schizophrenia is genetic, we must suppose that some at least of the susceptibility genes influence the dopamine system. Recently there has been some success in identifying genes that increase risk of schizophrenia, particularly neuregulin, dysbindin, and DISC-1 (Harrison and Owen, 2003; Owen et al., 2004). These have been noted to have effects on the glutamate system which is well known to regulate dopamine, while another candidate gene, catechol-*O*-methyl transferase gene (COMT), is involved in the breakdown of prefrontal dopamine and the latter's effect on cognition (Egan et al., 2001; Malhotra et al., 2002; Rosa et al., 2004).

1.6.2. Early environmental insult

Individuals exposed to a range of obstetric hazards are at increased risk of later schizophrenia (Verdoux et al., 1997; Cannon et al., 2002b), and schizophrenic subjects who have been exposed to obstetric complications are particularly likely to show decreased volume of the hippocampus (Stefanis et al., 1999; Schulze et al., 2003). Animal studies have modelled such insults. For example, Lipska and colleagues (Lipska et al., 1993, 2003; Weinberger and Lipska, 1995) showed that lesioning the ventral subiculum in the neonatal period produced adult rats with a mesolimbic dopaminergic system prone to overreaction to an amphetamine challenge. Neonatal rats and guinea pigs which have been subject to Caesarean section and global anoxia show dopaminergic abnormalities, and such early insults effect how dopamine is regulated in response to stress in adulthood (Boksa and El-Khodor, 2003). Flagstad et al. (2004) suggest that late gestational disruption of neurogenesis in rats not only leads to behavioural changes that mimic psychotic symptoms, but also to a dysregulation of subcortical dopamine transmission.

1.6.3. Drug-induced psychosis

Many studies have shown that animals repeatedly exposed to amphetamines become sensitised to the drug, and with successive exposures release increasing amounts of dopamine. There is some evidence that a similar process of dopamine sensitisation occurs in humans exposed to intermittent amphetamine in experimental conditions (Curran et al., 2004). Of course, the common situation of human exposure to amphetamine is in the context of abuse of the drug, which is well known to induce schizophrenia-like psychosis (Murray et al., 2004; Curran et al., 2004; Chen et al., 2003). Such evidence has given rise to the notion that not only amphetamine-induced psychosis (Tsapakis et al., 2003) but also psychosis in general is the consequence of sensitisation in mesolimbic cortical striatal circuits mediated by dopamine (Lieberman et al., 2001; Lewis and Lieberman, 2000). This is increasing evidence that heavy use of cannabis in adolescence can increase the risk of later schizophrenia (Arseneault et al., 2004) and that effects on dopamine also mediate this. A recent study (Caspi et al., in press) has shown that liability to psychosis induced by cannabis is strongly influenced by a polymorphism in the COMT gene that determines the rate of catabolism of frontal dopamine.

1.6.4. The role of social factors

Any plausible aetiological model of schizophrenia needs to incorporate the growing evidence that social factors can also modulate risk. Urban birth and upbringing are risk factors (Boydell et al., 2004), and several cohort studies have shown the quality of maternal–child relationship to be a predictor of risk of later schizophrenia (Jones et al., 1994; Cannon et al., 2002a). A recent meta-analysis has confirmed that migration increases risk of schizophrenia (Cantor-

Graae and Selten, 2005), the most striking findings being the evidence that African-Caribbeans living in the UK show an incidence of schizophrenia at least 6 times that of the native white population. Sharpley et al. (2001) and Boydell et al. (2001) demonstrated that the risk was especially high where the migrant group was a small minority, suggesting that social isolation and lack of social support may play a role.

Boydell et al. (2004) also note that isolation rearing of rats leads to a sensitised dopamine system (Heidbreder et al., 2001), and argue by analogy that social factors may have a similar impact in humans. Another proposal suggests that factors such as urbanicity, ethnic minority status, and low IQ operate by subjecting the individuals repeatedly to the experience of social defeat (Selten and Cantor-Graae, in submission); in animal studies, repeated social defeat leads to an enhanced behavioural response to dopamine agonists.

In an interesting animal analogy, a primate's standing in the social hierarchy can influence occupancy at D2 receptors. Using positron emission tomography (PET) Morgan et al. (2002) found that, upon being transferred from individual to social housing, socially dominant macaque monkeys show an increase, and more subordinate monkeys no change, in availability of dopamine D2 receptors (Morgan et al., 2002). The authors suggest that this is because individually-housed and socially subordinate monkeys have high levels of synaptic dopamine, whereas those who are able to attain dominance in social housing are able to return to 'normal' dopamine levels. Hence, living alone or being in a lower position in the social hierarchy may be, at least for macaque monkeys, associated with a hyperdopaminergic state.

1.7. Psychological mechanisms

Most psychological effort has been expended in demonstrating that people with schizophrenia show deficits on neuropsychological tasks. In recent years an increasing number of cognitive models of positive psychotic symptoms have also been proposed. These can be roughly divided into those that attempt to understand the cognitive basis of anomalous perceptual experiences and those which attempt to explain abnormal belief systems; the former tend to be more biologically grounded than the latter.

1.7.1. Anomalous perception

Garety et al. (2001) propose that the most common route to psychosis is via a "basic cognitive dysfunction" or disturbance of automatic processing. Possible mechanisms include difficulties in a) integrating information into its temporal and spatial context, or b) in the self-monitoring of intentions and actions that lead to the individual's own actions being experienced as alien (Frith, 1992). These disturbances are assumed to lead to anomalous conscious experiences, such as heightened perception, actions experienced as unintended, thoughts appearing to be broadcast, thoughts experienced as voices, and events that are unconnected appearing to be causally linked.

In the light of our earlier discussion of the role of dopamine, it may be that Garety's "basic cognitive dysfunction" is a cognitive parallel of heightened mesolimbic dopamine transmission (Gray et al., 1995; Kapur, 2003). Hippocampal dysfunction may contribute to this, as described earlier, but it may also contribute directly to the misinterpretation of incoming stimuli since it plays a crucial role in the comparison of the past and present environment. As Gray et al. (1991, 1995) point out, damage to the hippocampus will therefore result in a 'weakening of the influence of stored memories of regularities of previous input on current perception', and this in turn will lead to ambiguous and unstructured sensory input (Hemsley, 1993, p.635).

The role of attention is central to this and many cognitive models. In a classic description of the subjective experience of acute psychosis, McGhie and Chapman (1961) quote a patient as stating, "My thoughts get all jumbled up. . . .Things are coming in too fast. I loose my grip and get lost. I am attending to everything at once and as a result I do not attend to anything." Normally, individuals become aware of only those aspects of the internal and external environment to which attentional resources are deployed. When a stimulus intrudes into awareness, this implies that attentional resources have been devoted to the content of that intrusion. Intrusions are normal phenomena experienced by all people, and include external stimuli, body state information, or cognitive state information (intrusive thoughts and images) (Rachman and de Silva, 1978; Salkovskis and Harrison, 1984). Morrison's (2001) model of psychosis

emphasises that such intrusions into awareness become problematic when they are appraised as a threat, as this may result in emotional, cognitive, and behavioural responses that in turn increase the frequency of further intrusions. Since the relative salience of information that might potentially enter awareness is influenced by dopamine, increased dopaminergic activity will result in attention being deployed inappropriately, with the consequence that inappropriately salient intrusions intrude into awareness. Inappropriate deployment of attention might also be explained by poor contextual integration because this would result in a decrease in the influence of temporal context on attentional control. Thus, theories implicating impaired contextual integration and abnormal appraisal on the one hand and dopamine dysregulation on the other may be attempts at explaining the same processes at the different levels of information processing and neurochemistry, respectively.

1.7.2. Abnormal beliefs

Several groups have gone on to attempt to explain how anomalous perceptual experiences are transformed into psychotic symptoms. Maher (1988) pointed out that the experiences are often puzzling and associated with intense emotion, and may seem extremely personally relevant to the individual; not surprisingly, they trigger a search for explanation as to their cause. Kapur (2003) makes a similar point that the experience of being bombarded by apparently salient stimuli causes great anxiety and arousal in the acutely psychotic individual, and this in turn might lead to a continued disruption of contextual integration and consequent vulnerability to intrusions into awareness. One way to resolve this anxiety and arousal is to develop a delusional explanation of the experiences.

However, resolving anxiety and arousal by developing a delusional explanation is counterproductive. In an epidemiological sample of non-psychotic individuals, Krabbendam et al. (2004) found that the presence of delusional ideation in combination with hallucinatory experience significantly increased the risk of developing a psychotic disorder and needing psychiatric care relative to hallucinatory experience alone.

Biased conscious appraisal processes may contribute to a judgement that the anomalous experiences are externally caused. Garety et al. (2001) describe several cognitive biases that may adversely influence how the perceptual experience is appraised. Firstly, there is a "jumping-to-conclusions" data-gathering bias (Garety and Hemsley, 1994; Garety et al., 2001). If this bias operates, individuals prematurely terminate their search for an explanation of their experience. Such a bias seems to be present in subjects with an ARMS, prior to the onset of frank delusions (Broome et al., 2004). A second bias is that of externalising attributions which causes individuals to attribute negative events to an external cause. Bentall et al. (1994) found that people with persecutory delusions are more likely than normal controls to attribute negative events that they experience to other people than circumstances or fate. Frith's (1992) ideas of theory of mind represent a third possible bias. Thus, a failure to construct accurate representations of the contents of other people's minds may cause the individual to misrepresent the intentions of others in a paranoid manner.

Morrison (2001) claims that any factor that increases the probability of making a culturally unacceptable appraisal of an intrusion will increase the risk of psychosis. The way in which individuals appraise intrusions will be influenced by their experience, and certain types of experience, for example bullying, victimization, racism and alienation from mainstream culture, increase the probability of culturally unacceptable appraisals and thus the risk of psychosis. Several groups have pointed out that social isolation reduces access to alternative and normalising explanations for anomalous experiences (Hodges et al., 1999; van Os et al., 2000), and that the failure to be part of a normalising social network distinguishes those who develop psychosis from those who have anxiety and mood disorders. As we noted earlier, in animal experiments, isolation and subordination increases dopamine transmission.

1.8. The possible role of structural brain changes

There has been renewed interest in the possibility of progressive brain changes in schizophrenia (Woods, 1998). These have been most clearly demonstrated in childhood onset cases (Thompson et al., 2001) but several groups have claimed that progressive processes occur at, or immediately before, the onset of the first

episode of psychosis (Phillips et al., 2002; Pantelis et al., 2003; Cahn et al., 2002; Lawrie et al., 2002; Whalley et al., 2004). While there is a degree of agreement that some brain changes can be seen on MRI scans, there is much dispute as to what they represent (Weinberger and McClure, 2002; Weinberger and Marenco, 2003). The findings could reflect developmental changes occurring in late adolescence and early adult life, be degenerative, or even in some cases be consequent upon antipsychotic medication.

One possibility is that the changes may be consequent upon the stress that accompanies the onset of psychosis. Cotter and Pariante (2002) point out that stress is well known to induce elevated cortisol and this may induce secondary brain changes such as hippocampal volume reduction. Further observations have suggested that the HPA axis is elevated in psychotic patients who are acutely unwell but normal in patients who are clinically remitted and receiving medication (Tandon et al., 1991; Pariante et al., 2004). Increased volume of the pituitary on MRI imaging is a marker of HPA activity, and Pariante et al. (2004) demonstrated that those in a first episode of psychosis had larger pituitary volumes, and those with a chronic illness, smaller volumes than controls. The temporally closer a prodromal subject was to the onset of psychosis, the larger was the pituitary (Pariante et al., 2004). In the acute phase of the psychosis, the increased pituitary volume could represent a consequence of the distress and arousal associated with the psychotic experience; alternatively, it could represent an increased activation of the stress response preceding the development of psychosis, for an increased susceptibility to daily life stress, an increased level of independent stressors, or both (Bebbington et al., 1993; Myin-Germeys et al., 2001). This cross-sectional study does not allow a clarification of this point; however, but recent data suggests that the enlarged pituitary volume precedes the onset of psychosis, in a group of subjects at ultra-high risk of developing psychosis, and hence seems to support the latter model (Pariante et al., in submission).

2. Conclusions

Schizophrenia has a multifactorial aetiology in which genes and early environmental brain insults interact to cause neurodevelopmental impairment and set pre-schizophrenic children on a trajectory of increasing deviance (Bramon et al., 2001; Murray and Fearon, 1999). However, the neurodevelopmental hypothesis has struggled to explain the timing of the onset of psychosis. The initial view was that an early brain abnormality interacts with normal events during adolescence. The latter potentially include hormonal changes, axonal myelination, and as well as environmental risk factors such as those we have just discussed—drug misuse and social stress. Synaptic pruning has been much invoked and in what has become known as the ‘late neurodevelopmental model’, previously quiescent aberrant neuronal circuitry is postulated to become clinically problematic due to as result of excessive or aberrant pruning (Murray et al., 1998; Keshavan, 1999; Lieberman et al., 2001). Although an attractive theory, there is little evidence at present that directly bears on the issue.

Another view, proposed by Diamond (1990), suggests that the timing of the onset of psychosis is related to the fact that during childhood the hippocampus carries out crucial working memory functions whilst the prefrontal cortex is developing, but then attempts to off-load this cognitive responsibility on to the prefrontal cortex when the latter reaches functional maturity. Pathology of the prefrontal cortex may prevent this transfer of responsibility occurring from the hippocampus. As noted earlier, the prefrontal cortex controls the amygdala and as such dampens emotional responses to stimuli that are determined to be benign or non-threatening. A disruption of this prefrontal control would lead to a pathological increase in emotional responsivity of the subject, which in turn could be mediated via the amygdala’s influence over the hypothalamic–pituitary–adrenal (HPA) axis. This in turn may influence the ventral hippocampus most markedly.

Thus, the developmental impaired hippocampus may be compromised by two further factors—the inability to pass on the working memory tasks to the prefrontal cortex coupled with the effects of stress and high circulating cortisol. Such a model proposes that transition to psychosis is a consequence of primary prefrontal dysfunction leading to secondary enhanced subcortical stress response and dopamine transmission (due to an impairment of prefrontal modulation), compounded by stress-induced damage to the hippo-

campus. Drug use and chronic social adversity may compound dopamine dysregulation and project the susceptible individual over the threshold for the expression of frank psychosis.

Some cognitive theorists have argued that abnormal perceptual experience per se is relatively benign and that it is the cognitive appraisal that determines the pathology (Morrison, 2001). This approach is as misguided as the view of reductionists who claim that cognitive abnormalities are simply epiphenomena of a biological process. In our view, both neurobiological vulnerability and particular social adversities are important, and Gray et al. (1995), Kapur (2003), and Pariante et al. (2004) provide models that are both testable and bridge the explanations offered by neuroscience and cognitive psychology.

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