Time to abandon the bio-bio-bio model of psychosis: Exploring the epigenetic and psychological mechanisms by which adverse life events lead to psychotic symptoms

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Abstract. Mental health services and research have been dominated for several decades by a rather simplistic, reductionistic focus on biological phenomena, with minimal consideration of the social context within which genes and brains inevitably operate. This 'medical model' ideology, enthusiastically supported by the pharmaceutical industry, has been particularly powerful in the field of psychosis, where it has led to unjustified and damaging pessimism about recovery. The failure to find robust evidence of a genetic predisposition for psychosis in general, or 'schizophrenia' in particular, can be understood in terms of recently developed knowledge about how epigenetic processes turn gene transcription on and off through mechanisms that are highly influenced by the individual's socio-environmental experiences. To understand the emerging evidence of the relationship between adverse childhood events and subsequent psychosis, it is necessary to integrate these epigenetic processes, especially those involving the stress regulating functions of the HPA axis, with research about the psychological mechanisms by which specific types of childhood trauma can lead to specific types of psychotic experiences. The implications, for research, mental health services and primary prevention, are profound.

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THE FAILURE OF THE SEARCH FOR A GENETIC PREDISPOSITION

The originators of the stress-vulnerability model of schizophrenia (Zubin & Spring, 1977) assumed that vulnerability to stress could be *acquired* "due to the influence of trauma, specific diseases, perinatal complications, family experiences, adolescent peer interactions, and other life events". Most genetic and brain researchers, however, have either ignored the psycho-social causes of psychosis or relegated them to the role of triggers or exacerbators of a vulnerability which they assumed to be genetic. Meanwhile brain researchers identified abnormalities in 'schizophrenics' without considering what might have happened in their lives to have caused them. The ratio of biological to psycho-social etiology studies, 16 to one, has become increasingly imbalanced (see Table I).

The hypothesis that there is a specific genetic predisposition for schizophrenia may be one of the costliest blind alleys in the history of medical research. Recent editorials suggest that 'the inconsistent results and disappointing findings of genetic research on schizophrenia' arise from 'failure to demonstrate the existence of a unitary disease process' (Ruggeri & Tansella, 2009) and that 'the difficulty in gaining a consistent and clear-cut picture of the genetics of schizophrenia mirrors the marked clinical and neurobiological heterogeneity of the disorder' (Tosato & Lasalvia, 2009).

The construct of 'schizophrenia' is indeed heterogeneous. It is also disjunctive and has little reliability or validity (Bentall, 2003; 2009; Read, 2004a), rendering it very difficult to identify any specific cause, genetic or otherwise. Reviewing the methodologies and concepts deployed in the search for a genetic predisposition shows that there is no robust evidence for it (Joseph, 2006). A recent paper in the American Journal of Psychiatry (Sanders *et al.*, 2008), described by the editor as "The most comprehensive genetic association study of genes previously reported to contribute to the susceptibility to schizophrenia" (Hamilton, 2008), found that "none of the polymorphisms were associated with the schizophrenia phenotype at a reasonable threshold for statistical signif-

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Table I – *Proportions of 'schizophrenia' research investigating child abuse, poverty, biological etiology and drug treatment.*

	All	% of all schizophrenia research	Before 2000	% of all schizophrenia research	2000 -May 2009	% of all schizophrenia research
Schizophrenia	75,063		48,061		27,002	
…and…						
Child abuse and neglect[1]	262	0.3%	142	0.3%	120	0.4%
Poverty[2]	704	0.9%	462	1.0%	242	0.9%
Biological causes[3]	15,481	20.6%	8,023	16.7%	7,458	27.6%
Drug Therapy[4]	14,077	18.8%	7,832	16.3%	6,345	23.1%
Ratio of Biological causes to Social causes[5]	16.0:1		13.3:1		20.6:1	

key words entered:
[1]'child abuse' 'child neglect' 'emotional abuse' 'sexual abuse' psysical abuse'
[2]'poverty' 'socioeconomic status'
[3]'neurotransmitters' 'brain' 'genetics'
[4]'drug therapy' 'antipsychotics'
[5]Ration of 3 to (1 + 2)

icance' and 'of the 69 SNPs (single nucleotide polymorphisms) ... only four showed even nominal association. ... The distribution of test statistics suggests nothing outside of what would be expected by chance" (p. 421).

The failure of this expensive enterprise is understandable given what we now know about the role of epigenetic processes in the control of DNA transcription. An array of processes in the chromatin in the cell nucleus turn gene transcription on and off through mechanisms that are highly influenced by the individual's socio-environmental experiences. DNA is able to fit within the cell nucleus by being tightly wrapped around histone proteins, which have "tails" that function as the target for acetyl groups. Gene transcription is made possible when acetyl groups bind to histone tails through an enzymatic process. Without this binding DNA is closed for expression. A complementary epigenetic process occurs when a methyl group binds to the cytosine part of a cytosine-guanine base pair on the DNA, termed methylation, leading to the suppression of gene expression. We now know that the functional properties of DNA are controlled by complex interactions between histone acetylation, cytosine methylation and a range of other epigenetic processes that change the properties and structure of the chromatin in the cell nucleus (Champagne & Curley, 2009).

In the central nervous system, these processes are specifically sensitive to an individual's psycho-social experience; hence neuropsychological development from birth to adulthood is governed by epigenetic mechanisms which are shaped by interactions with the environment (Champagne & Curley, 2009). This is particularly pronounced in limbic structures such as the hippocampus, where the processing of psycho-social stress factors as well as the general dynamics of learning and memory are tightly coupled to modification of epigenetic state. This means that, at the cellular level, a new picture is emerging of how our biological heritage interacts with the environment, and in this picture, the environment seems to play a much more crucial role than hitherto thought. This emerging view also suggests that the idea that specific DNA polymorphisms provide a vulnerability to mental health problems may be seriously flawed (Fosse, in press).

THE PSYCHO-SOCIAL CAUSES OF PSYCHOSIS

The psycho-social factors which increase the risk of psychosis fall primarily in the domain of relational stress. Their impact is often, directly or indirectly, on the quality of relationships with other people, mediated (as discussed later) by psychological and brain adaptations to the original stressors.

Poverty, which operates in multiple ways to increase exposure to stress and to inhibit self-esteem and secure attachments, was first implicated in psychosis 70 years ago (Faris & Dunham, 1939). By 1980 the relationship between poverty and 'schizophrenia' was described as 'one of the most consistent findings in the field of psychiatric epidemiology' (Eaton, 1980). Attempts to explain away its causal role with the 'social drift' hypothesis failed to produce convincing evidence (Read, 2004b). Contrary to the notion that 'schizophrenia' is a particularly biologically-based disorder it has repeatedly been demonstrated that poverty is even more strongly related to the diagnosis and to psychosis in general than to other disorders (Read, 2004b). For example, British children raised in economic deprivation were found to be four times more likely to develop 'non-schizophrenic' disorders but eight times more likely to grow-up to be 'schizophrenic' (Harrison *et al.*, 2001). Among those with no

family history of psychosis, the deprived children were seven times more likely to develop schizophrenia. The relationship between urban living and psychosis also remains after controlling for family history of psychiatric disorder (Lewis *et al.*, 1992; Mortensen *et al.*, 1999).

Other social factors (many related to poverty) now known to have a causal role, or to be significant risk factors, for psychosis include: mother's health, nutrition and stress during pregnancy; being the product of an unwanted pregnancy; early loss of parents via death or abandonment; separation of parents; witnessing inter-parental violence; dysfunctional parenting (often intergenerational) – particularly affectionless over-control; childhood sexual, physical and emotional abuse; childhood emotional or physical neglect; bullying; war trauma; rape or physical assaults as an adult; racist or other forms of discrimination; and heavy marijuana use early in adolescence (Bentall & Fernyhough, 2008; Conus *et al.*, 2009; Janssen *et al.*, 2003; Larkin & Morrison, 2006; Larkin & Read, 2008; Morgan & Fearon, 2007; Moscowitz *et al.*, 2009; Read *et al.*, 2004a; 2005; 2008; Schreier *et al.*, 2009; Shevlin *et al.*, 2009a, b; Verdoux & Tournier, 2004; Welham *et al.*, 2009; and see Table II). Many of these events occur in childhood, are in the domain of relational stress, and seem to increase the probability of subsequent psychosis via the creation of long-lasting insecure attachment patterns (Read & Gumley, 2008).

It should not be surprising that psychosis, which can involve severely distressing symptoms, is caused by adverse events in childhood. Child abuse is related to disturbance severity no matter how it is measured. Patients abused as children have earlier first admissions and longer and more frequent hospitalisations, spend longer in seclusion, receive more medication, self-mutilate more, have higher global symptom severity (9, 11-15) and try to kill themselves more often (Read *et al.*, 2005; 2008; Conus *et al.*, 2009).

The idea that psychosis is socially caused is not surprising to the public. Studies in 16 countries find that when asked what causes 'schizophrenia' most people, including patients and their family members, place far more emphasis on social factors like abuse and poverty than on faulty brains or genes (Magliano *et al.*, 2009; Read, 2007; Read *et al.*, 2006) Furthermore, attempts to improve 'mental health literacy' (the term used by biological psychiatrists for the extent to which others agree with them), by promulgating the 'medical model', increase fear and prejudice (Angermeyer & Matschinger, 2003; Read, 2007; Read *et al.*, 2006).

After having been ignored for decades, the relationship between psychosis and childhood trauma has recently been studied intently (Bendall et al., 2008; Morgan & Fisher, 2007; Read *et al.*, 2005; Johnstone, 2009). A recent review found, from an analysis of 59 studies, that an average of 55% of male, and 65% of female, psychiatric inpatients had been either sexually or physically abused as children (Read *et al.*, 2008). These reviews report numerous studies, using clinical diagnoses or research measures, showing that childhood emotional, physical and sexual abuse, and childhood neglect, are related to psychosis.

Ten out of eleven recent large-scale general population studies have found, even after controlling for other factors including family history of psychosis, that child maltreatment is significantly related to psychosis (Table II). For example, a prospective Netherlands study controlled for both family mental health care and history of hallucinations or delusions in first-degree relatives and found that people who had been abused as children were nine times more likely than non-abused people to experience pathology-level psychosis (Janssen et al., 2004).

Nine of the 11 studies tested for, and found, a dose-response relationship. The most recent prospective study, of 6,437 British children, found that those who had been exposed, at age eight or ten, to either overt bullying or relational bullying (rejection by peers) were twice as likely to experience psychotic symptoms at age 12; while those who were victims of both types of bullying were 4.7 times more likely to experience psychotic symptoms (Shreier *et al.*, 2009). The dose response relationship between severity of abuse and psychosis is also found in smaller studies targeting psychotic or abused samples (eg Kilcommons *et al.*, 2008).

The reviews also report studies showing a relationship between abuse and the actual content of hallucinations and delusions (e.g. Read *et al.*, 2003). They also conclude that abuse disclosures by people diagnosed 'schizophrenic' are reliable (Fisher *et al.*, in press; Read *et al.*, 2003; 2005; 2008).

Even within samples diagnosed psychotic or 'schizophrenic', child abuse is related to longer duration of untreated psychosis, poorer premorbid functioning, substance abuse, other diagnoses (especially depression and PTSD), unemployment, poor engagement with services, low medication compliance, low satisfaction with diagnosis and treatment, and, most importantly, suicidality (Lecomte *et al.*, 2008; Read *et al.*, 2005; 2008).

The relationship between adverse events in childhood and negative outcomes is confirmed by seven studies of first episode psychosis (see Conus *et al.*, 2009). One (Fisher *et al.*, 2009) found the abuse-psychosis relationship in women but not in men (which might be explained by gender-specific responses to trauma, and the greater

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Table II – *Large-scale general population cross-sectional and prospective studies.+*

Study, country, design#, n	Psychosis measure	Adverse Childhood Event	Odds Ratio	Adjusted Odds Ratio	Factors controlled for in Adj. OR	Dose-Response: Odds Ratios for different levels of abuse/trauma
Bebbington *et al.* 2004 UK, C, 8580	Diagnosis of psychotic disorder	sexual abuse (not all childhood) bullied violence in home running from home children's institution	15.5 4.2 9.0 11.5 11.9	2.9** 1.4 1.4 2.8** 1.5	1,2	Not tested (see Shevlin *et al.* 2007)
Janssen *et al.* 2004 Netherlands, P, 4045	Psychosis severity a. any psychosis b. pathology level c. need for care	physical, sexual, emotional or psychological abuse	a. 3.6 b. 13.0 c. 11.5	a. 2.5* b. 9.3** c. 7.3*	3-14	Abuse: Mild Severe a. 1.4 9.8*** b. 2.0 48.4*** c. 1.0 31.7***
	d. hallucinations e. delusions		d. 4.0 e. 3.9	d. 2.5 2.2.8*		
Spataro *et al.* 2004 Australia, P, 3141357	Treatment for schizophrenic disorder	sexual abuse	male 1.5^{RR} female 1.3			Not tested
Whitfield *et al.* 2005 USA, C, 17337	Hallucinations	sexual abuse physical abuse emotional abuse battered mother	1.8 1.7 2.5 1.6	1.7* 1.7* 2.3* 1.5*	3-5, 7	1 event: 1.1 4 events: 1.8 ≥7 events: 6.7 ***
Lataster *et al.* 2006 Netherlands, C, 1290 (adolescents)	Non-clinical psychotic experiences	sexual trauma bullied	5.1 3.1	4.8* 2.9*	1, 3, 4, 15	bullied once/twice: 1.9 bullied once/twice per month: 3.5 ***
Spauwen *et al.* 2006 Germany, P, 2524 (aged 14-24)	Three or more positive symptoms	sexual abuse any trauma before 13yrs	3.4 2.6	1.55 2.2*	4, 8, 10, 14-16	1 severe event 1.8 2 severe events 3.1 **
Shevlin *et al.* 2007 UK, C, 5877 (subsample of Shevlin 2007 UK sample)	Visual Hallucinations	'sexually molested' 'rape' 'physical abuse' 'serious neglect'	1.7 2.4 1.5 2.1	1.6*** 2.4*** 1.0 1.6*	1-4, 8, 14, 15, 17	1 trauma: 2.7 4 traumas: 7.8 *
	Auditory Hallucinations	'sexually molested' 'rape' 'physical abuse' 'serious neglect'	1.8 1.8 1.5 1.7	1.9*** 1.7* 1.2 1.3		1 trauma: 1.9 4 traumas: 4.5 **
	Tactile Hallucinations	'sexually molested' 'rape' 'physical abuse' 'serious neglect'	2.1 1.9 2.4 1.5	1.8*** 1.7* 1.9*** 0.8		1 trauma: 2.7 4 traumas: 8.7 *
Shevlin *et al.* 2007 UK, C, 8580 (same as Bebbington)	Diagnosis of psychotic disorder	sexual abuse violence in home	15.5 9.0	5.7* 2.2*	1-5, 7, 8, 14, 15, 18	1 trauma: 1.7 3 traumas: 18.0* 5 traumas: 193.0**

(segue)

Table II – *Segue*

Study, country, design#, n	Psychosis measure	Adverse Childhood Event	Odds Ratio	Adjusted Odds Ratio	Factors controlled for in Adj. OR	Dose-Response: Odds Ratios for different levels of abuse/trauma
Shevlin *et al.* 2007 USA, C, 5782	Diagnosis of non-affective psychotic disorder	sexually molested physical abuse		2.5** 4.2*	1-5, 7, 8, 14, 15, 18	1 trauma: 1.6 3 traumas: 7.4* 5 traumas: 30.2**
Scott *et al.* 2007 Australia, C, 10641	Delusions	'sexually molested' (not all childhood)	7.1	2.3***[RR]	19	1 or 2 traumas: 2.5 3 or 4 traumas: 2.9 ≥5 traumas: 9.5 ***[RR]
		any trauma without PTSD any trauma with PTSD	2.7 9.2	2.0*** 6.4***	3, 4, 14, 20	
Schreirer *et al.* 2009 UK, P, 6437	one or more of 12 psychotic symptoms at age 12	bullied at age 8 or 10 ('overt' or 'relational')	1.9 1.9	1.8* 1.8*	2, 3, 4, 10, 15 21, 22	at age 8 or 10: 1.6 at age 8 and 10: 3.4* overt only: 2.2 relational only: 2.0 overt and relational: 4.7*

+Update from Table in Read *et al.* (2008) with acknowledgment *to Clinical Schizophrenia & Related Psychoses*

#P – prospective; C – cross-sectional

RR'Relative Risk'

*p ≤ .05;
**p < .01;
***p < .001

1. interrelationship between adverse events; 2. Depression; 3. Age; 4. Gender; 5. education level; 6. Discrimination; 7. Ethnicity; 8. Urbanicity; 9. Marital status; 10. non-psychotic; diagnosis; 11. family history of psychiatric care; 12. family history of psychosis; 13. Unemployment; 14. substance use; 15. socio-economic status; 16. 'psychosis proneness' on SCLR-90 at start of study; 17. family history of depression; 18. living arrangements; 19. PTSD. [7.1 = with PTSD; 2.3 = without PTSD]; 20. past diagnosis of schizophrenia; 21. IQ; 22. Family Adversity Index, measuring family functioning during pregnancy and including: young maternal age, housing problems, financial difficulties, problematic parental relationship, maternal depression, anxiety, substance abuse or involvement with crime.

likelihood of abused males entering the criminal justice system or killing themselves). The largest first-episode study to date found that child physical or sexual abuse was significantly related to numerous outcomes including substance abuse and suicide attempts, and, crucially, that the trauma preceded the psychosis in 98% of the cases (Conus *et al.*, 2009).

UNDERSTANDING THE PSYCHO-SOCIAL CAUSES: EPIGENETICS AND THE HPA AXIS

The interactive dynamics of epigenetic processes make clear how psychosocial adversities can give rise to mental health problems. A recent example of the basic science research on this topic has been performed by Meaney and his co-workers in Canada, using rodent models of maternal care. This research shows that the frequency of licking and grooming by the dam in early life governs the development of brain and behaviour in the offspring with effects that lasts into adult life (Champagne & Curley, 2009). Poor and absent maternal care directly affects and shapes the activity of the hypothalamus-pituitary-adrenal (HPA) axis, the main stress system of the brain, as well as its forebrain regulation systems, where crucial roles are played by the hippocampus and the medial prefrontal cortex (mPFC). Pups exposed to poor maternal care developed a modified, often increased, HPA axis reactivity and a breakdown in the normal down-regulation of this system following structural changes that are particularly well described in the hippocampus. Behaviourally, the exposed pups exhibited increased anxiety, fear and startle responses, passivity, and reduced explorative behaviour in novel situations in adult life, and females tended to exhibit the same behaviour towards their own pups as they had experienced postnatally. The molecular mechanisms involved are epigenetic processes, which become shaped by the psychosocial experience and in turn modify gene expression and thus brain development to fit the "forecast" provided by the postnatal environment. Meaney and co-workers showed that rodent maternal care affects the transcription of genes that support glucocorticoid receptors (GRs), which are central to the forebrain regulation of the HPA axis, with poor care leading to a down-regulation of these receptors through increased methylation of DNA regions in the nuclei of hippocampal neurons.

Marked changes in structure and function are documented within the HPA axis as well as its forebrain regulation regions in both first-episode and sustained psychosis.

MRI studies show an increased size of the hypothalamus, including the paraventricular nucleus that governs the HPA-axis (Goldstein *et al.*, 2007). The normal, dynamic development of the pituitary from childhood to adult life also is changed, with increased size prior to and during psychosis debut, followed by a decreased size in more chronic states as compared to normal healthy people (Pariante *et al.*, 2005; Pariante, 2008). In line with these changes are altered diurnal levels of cortisol elicited from the adrenal gland and increased release of cortisol following challenge (e.g. Newcomer *et al.*, 1991).

Changes in the forebrain regulation of the HPA-axis in psychosis are evident in the decreased level of mRNA expression for glucocorticoid receptors (GRs), being documented in the hippocampi, amygdalae, and prefrontal cortices (Perlman *et al.*, 2004; Webster *et al.*, 2002). Volume loss in gray matter is well documented in the hippocampus and found also in the mPFC, including the control regions of emotion and motivation in the anterior cingulate (Shenton *et al.*, 2001). The hippocampal and prefrontal changes include the density, size and shape of pyramidal cells and interneurons, and in the former region, reduced receptor expression, dendrite branching, and messenger RNA expression (Benes & Berretta 2001; Harrison, 2004; Shenton *et al.*, 2001). Moreover, the volume loss in the medial temporal cortex, that includes the hippocampus, correlates markedly with the reductions seen in the anterior cingulate and in the superior temporal lobe which includes the primary auditory cortex (see Shenton *et al.*, 2001), suggesting an integrated change in forebrain regions. This plethora of findings is fully consistent with models suggesting a primary role of trauma in the development of psychosis, such as the Traumagenetic Neurodevelopmental (TN) Model (Read *et al.*, 2001). An explicit test of the TN model found that within a sample of schizophrenia patients those abused as children (especially those emotionally abused) to have greater HPA axis dyregulation, measured by cortisol levels, than their non-abused counterparts (Brahler *et al.*, 2005). Similarly, problems in childhood attachment can alter the structures, neuro-chemicals, and connectivity of the brain. Like CPA and CSA, severe child neglect affects the ability of the HPA axis to regulate the body and brain's stress response (Corbin. 2007).

UNDERSTANDING THE PSYCHO-SOCIAL CAUSES: PSYCHOLOGICAL PROCESSES IN HALLUCINATIONS AND DELUSIONS

In parallel to the brain's adaptations to trauma and neglect psychological processes are also, of course,

affected. Obviously, for example, there is a psychological equivalent to the brain's over-reactivity to stress following early trauma. Psychological adaptation to adverse events, especially in childhood, tend, understandably to be in the domains of attachment and how we experience other people, including the extent to which we blame others when negative or stressful events occurs. As we shall see, however, other, perhaps less obvious, processes can also be at work. In order to understand the psychological mechanisms involved in pathways from trauma to psychosis it can be helpful to focus on specific types of trauma and specific types of psychotic experiences. For example, early childhood trauma, such as sexual abuse, seems to be particularly implicated in auditory verbal hallucinations (Hammersley *et al.*, 2003; Read *et al.*, 2003; Shevlin *et al.*, 2007) but less so in paranoid delusions.

HALLUCINATIONS

Researchers have converged on a consensus account of the mechanisms involved in hallucinations, which assumes that they occur when internal, self-generated mental contents are attributed to a source that is alien or external to the self (Bentall, 1990). In the case of auditory-verbal hallucinations (AVHs), it is inner speech (the internal dialogue which forms an important role in everyday thinking) that is misattributed. The primary evidence that this is the case comes from studies that have recorded the physiological concomitants of inner speech in hallucinating patients. For example, it has been known for more than half a century that AVHs are accompanied by covert activations of the speech musculature that can be detected by electromyography (Gould, 1948; Inouye & Shimizu, 1970; McGuigan, 1966); these kind of covert activations, known as subvocalisations, occur during normal verbal thought, and are thought to be neuromuscular echoes of the phase of childhood when children learn to speak to themselves, first out aloud and then silently (Berk, 1994). Recent PET and fMRI studies have confirmed that AVHs are accompanied by activations of the frontal brain regions involved in speech generation, and in the more posterior regions involved in speech perception (Jones & Fernyhough, 2007).

Psychological studies using signal detection (Barkus et al., 2007; Bentall & Slade, 1985; Rankin & O'Carrol, 1995) and other methodologies (Bentall *et al.*, 1991; Brebion *et al.*, 2000; Johns *et al.*, 2001; Morrison & Haddock, 1997) have confirmed that ordinary people who have a high predisposition towards hallucination, and also patients who hear voices, are impaired at source monitoring (the skill of distinguishing between self-generated thoughts and perceptions) compared to appropriate controls. In a series of elctrophysiological studies, Ford & Mathalon (2004) showed that, whereas normal inner speech is associated with signals from the frontal cortex which suppress activity in the auditory cortex, these signals are absent in patients with AVHs. Hence it seems likely that the poor source monitoring of hallucinating patients is a consequence of the failure of this mechanism which, in ordinary people, prevents self-generated speech from being mistaken from the speech of other people.

There are two possible psychological mechanisms that might link trauma to this impairment. First, poor source monitoring might be a vulnerability factor which only causes AVHs when a person experiences uncontrollable, trauma-related thoughts and memories. This hypothesis is plausible because the uncontrollable intrusive thoughts of PTSD victims are, in many ways, phenomenologically similar to AVHs and because experimental studies show that spontaneous thoughts of this kind are particularly difficult to source monitor (Johnson *et al.*, 1993). An alternative possibility is that trauma directly interferes with the source monitoring mechanism.

PARANOID DELUSIONS

Paranoid beliefs tend to arise against a background of chronic victimization and powerlessness (Janssen *et al.*, 2003; Mirowsky & Ross, 1983). There is also evidence that both patients (Dozier & Lee, 1995) and ordinary people with sub-clinical paranoia (Pickering *et al.*, 2008) tend to have severe attachment difficulties. These observations may help to explain why early separation from parents (Morgan *et al.*, 2007) and being unwanted at birth (Myhrman *et al.*, 1996) increase the risk of later psychosis, and also why immigrant groups (who are vulnerable to victimization) are especially likely to develop psychosis, typically with paranoia (Harrison *et al.*, 1988; Selten *et al.*, 2001).

The core of paranoia is the excessive estimation of personal threat (Bentall *et al.*, 2009). As the striatal dopamine system plays a role in anticipating aversive events, it seems likely that, at the neurochemical level, dopaminergic abnormalities (long implicated in psychosis; Laruelle & Abi-Dargham, 1999) underlie this excessive threat anticipation (Moutoussis *et al.*, 2007). This abnormality, in turn, seems to be associated with problems of emotion and reasoning which are quite distinct from the source monitoring difficulties of hallucinating patients.

Three separate mechanisms have been proposed in the psychological literature, with some evidence to support each. First, it has been suggested that delusions in general are associated with a tendency to jump to conclusions, that is, a tendency to make decisions on the basis of very little information. Although the precise nature of this deficit are currently a matter of controversy, the balance of evidence suggests that it is more evident in deluded patients than in patients with other kinds of symptoms (Dudley & Over, 2003; Garety *et al.*, 1991; 2005; Moritz & Woodward, 2005). Second, it has been argued that paranoid patients may have a difficulty in 'Theory of Mind'; the ability to understand others' mental states. Frith (1994) argued that a sudden loss of ToM skills would be likely to lead to persecutory beliefs if the patient assumes that others are concealing their true intentions. Consistent with this idea, empirical studies have clearly demonstrated that ToM skills are impaired during acute episodes of psychosis, but the evidence for a specific association with paranoia is equivocal (Brune, 2005; Corcoran *et al.*, 1997; 2008; Drury *et al.*, 1998).

Perhaps more importantly in the present context, it has been argued that paranoia arises as a consequence of severe problems of self-esteem and an external locus of control, especially if the individual attempts to defend against feelings of low self-worth by attributing the causes of misfortunes to malevolent others (Bentall *et al.*, 1994; 2001). Arguably, these kinds of cognitive biases are especially likely to develop against a background of attachment insecurity and victimization. Consistent with this account, paranoid patients show highly unstable self-esteem (Thewissen *et al.*, 2007; 2008) and also marked discrepancies between implicit and explicit self-esteem (McKay *et al.*, 2007; Moritz *et al.*, 2006). However, an externalizing attributional bias (the specific tendency to attribute negative events to the actions of others) only seems to be present during acute episodes of paranoia (Janssen *et al.*, 2006) when the individual is also grandiose (Jolley *et al.*, 2006) and believes that persecution is completely undeserved (Janssen *et al.*, 2006).

It is not known how these mechanisms, implicated in specific symptoms and related to specific types of adverse experience, relate to the epigenetic processes described earlier. However, the role of disrupted attachment in paranoia provides one point of contact between the two research literatures. Moreover, external locus of control and low self-esteem has been associated with HPA dysregulation and reduced hippocampal volume in young adults (Pruessner *et al.*, 2005) In the case of hallucinations, matters are likely to be more complex because acute stress increases source monitoring accuracy in healthy individuals (Smeets *et al.*, 2008) whereas, in people with hallucinations, the opposite effect seems to occur.

IMPLICATIONS

Research

A lot of money have has been wasted on well-intentioned but ultimately useless genetic research, with similar amounts poured into context-less brain research. The genuinely integrated socio-bio-psychological approach proposed in this paper, and increasingly being adopted internationally, will lead to genuinely productive research programmes, at both the theoretical and clinical levels. One review identified 37 research areas opened up by giving appropriate emphasis to all three domains in the bio-psycho-social paradigm and to the complex interactions within and between those domains (Read *et al.*, 2004b). There is an urgent need to develop research designs which will allow the measurement of childhood adversity, the epigenetic mechanisms discussed above, or index measures (e.g. HPA functioning), together with the psychological mechanisms that are implicated in particular symptoms of psychosis.

Assessment

Many researchers advocate the screening of all mental health service users, including those diagnosed 'schizophrenic', so as to make comprehensive formulations and effective treatment plans (e.g. Conus *et al.*, 2009). Progress towards this goal has been slow to date, but is beginning to gather pace (Read *et al.*, 2006). Training is essential (Read *et al.*, 2007).

Treatment

Another consequence of the over emphasis on de-contextualised biological factors has been the unsubstantiated assumptions that virtually everyone who experiences psychosis benefits from anti-psychotic medication and that psychological interventions are somehow adjunctive to drugs. These drugs, which benefit only between a third to two-thirds of recipients (in terms of relapse prevention or symptom reduction), have serious health risks (Ross & Read, 2004; Mosher *et al.*, 2004), including increased mortality risk (Weinmann *et al.*, 2009), for all recipients, leading to high levels of 'non-compliance'. A recent review of

five studies of early psychosis found that those treated without medication fared better than those on medication (Bola *et al.*, 2009). Meanwhile a range of psychological interventions that address the psycho-social causes and the maladaptive mechanisms identified above, have been found to be effective, at least for some patients, and are free from health risks for all (Gleeson *et al.*, 2008; Read *et al.*, 2004c; Alanen, 2009; Morrison, 2009). These include, but are no means limited to, cognitive therapy based on the understanding of the psychological mechanisms described earlier (Kindon & Turkington, 2005; Morrison, 2004; 2009). Starting from the client's understanding of their experiences (Geekie & Read, 2009), of the causes, of their problems (Magliano *et al.*, 2009) and of how best to measure recovery (Neil *et al.*, 2009), is paramount.

Prevention

Another consequence of a simplistic bio-genetic approach is the failure of the mental health community to lobby for primary prevention programmes aimed at keeping children securely attached and safe in the first five years of life. (Davies & Burdett, 2004). For example, an environmental enrichment programme at age 3-5 years has been shown to reduce schizotypal traits in early adulthood (Raine *et al.*, 2003).

CONCLUSION

We must work, across disciplinary boundaries, to build on these beginnings of a truly integrated bio-psycho-social model. This will avoid wasting more resources on unproductive research that could be better spent on focusing on what has gone on in the lives of people diagnosed 'schizophrenic' and what will best assist them with the distress and confusion that often results. This more genuinely evidence-based approach will, however, require us to question how we adopted such a narrow view in the first place, and to free our professional organizations, research journals and teaching institutions from the pervasive influence of the pharmaceutical industry (Mosher *et al.*, 2004; Read, 2008; Shooter, 2005). The President of the American Psychiatric Association recently warned: "If we are seen as mere pill pushers and employees of the pharmaceutical industry, our credibility as a profession is compromised. As we address these Big Pharma issues, we must examine the fact that as a profession, we have allowed the bio-psycho-social model to become the bio-bio-bio model" (Sharfstein, 2005, p. 3).

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