

# Prenatal Factors in Schizophrenia

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## Abstract

The purpose of this review is to summarize the current state of knowledge on how nongenetic factors occurring before, during, or soon after birth are related to schizophrenia. Schizophrenia is a complex psychiatric illness with a varied clinical presentation that has both environmental and genetic origins and that may result from insults to the nervous system that occur throughout development. In line with this, several endogenous (internal) and exogenous (external) nongenetic factors of pregnancy and birth have been related to an increased risk for schizophrenia in later life. These factors include maternal diabetes, low birth weight, older paternal age, winter birth, and prenatal maternal stress, among others. Although each of these nongenetic factors alone slightly increases the risk for schizophrenia, risk increases when these factors combine with each other and with other risk factors. The mechanisms that link each specific risk factor with the occurrence of schizophrenia remain largely unknown. In order to build better models of the illness, researchers will have to address the question of how environmental and genetic risk factors work together in increasing risk and explore to what extent certain underlying risk factors may explain different aspects of the disease.

## Keywords

neurodevelopment, schizophrenia, risk factors, obstetric complications, prenatal maternal stress

Schizophrenia is a complex psychiatric disorder affecting approximately 1% of the population. Much of the variability in neurobiology, childhood adjustment, symptom profile, onset, course, treatment response, and long-term outcome may well be explained by variability in causes of schizophrenia. There is a clear genetic component to schizophrenia, but despite decades of research, the “schizophrenia gene” remains elusive (Nöthen, Nieratschker, Cichon, & Rietschel, 2010). Some researchers have therefore suggested that schizophrenia may arise from alterations in how some genes are “turned on or off” due to exposure to nongenetic (or environmental) factors (Rutten & Mill, 2009). Exposure to certain environmental factors could also contribute to spontaneous genetic mutations that give rise to vulnerability for the illness. Strong support for the role of environmental factors in the etiology of schizophrenia comes from the finding that in identical twin pairs, in which the twins share about 100% of their DNA, if one twin develops schizophrenia the other twin has only a 50:50 chance of developing it.

Neurodevelopmental models of schizophrenia (Murray, 1994) suggest that schizophrenia results from some combination of genetic and/or environmental insults to the developing nervous system. Some of these insults may occur before birth, lying dormant until later life when normal changes in the brain should occur. Physical markers for which the prenatal developmental processes are known and that are seen more frequently in

individuals with schizophrenia than in community controls (e.g., minor physical anomalies and asymmetric fingerprints) suggest that an insult occurring at a particular time in gestation could affect neurodevelopment and leave behind these physical clues. “Static” neurodevelopmental models implicate events occurring prenatally or perinatally (i.e., around the time of birth), while “progressive” neurodevelopmental models include insults that may occur until the final stages of brain development are complete early in a person’s twenties (Woods, 1998)—insults such as childhood maltreatment, head trauma, or adolescent cannabis use. Genetic and environmental risk factors may combine in additive or multiplicative ways to increase an individual’s risk to a point beyond some threshold for illness (Malaspina, Sohler, & Susser, 1999).

Here, we describe those environmental factors occurring during pregnancy and birth that are associated with increased risk for schizophrenia. We make a distinction, albeit imperfect, between endogenous (internal) factors that have their origins within the mother’s body, the uterus, and the fetus, and exogenous factors with external origins.

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## Prenatal Factors in Schizophrenia

### Endogenous factors

**Pregnancy and birth complications.** The risk of developing schizophrenia is increased approximately twofold (thus, to 2%) in individuals who were exposed to various complications during pregnancy (Cannon, Jones, & Murray, 2002). There are three major categories of complications: (a) complications of pregnancy, (b) abnormal fetal growth and development, and (c) delivery complications. Many of these obstetric complications may compromise neurodevelopment.

In a meta-analysis (combining the results of studies that address the same research question), several obstetric factors were associated with risk for schizophrenia (Cannon et al., 2002). During pregnancy, preeclampsia (i.e., hypertension), bleeding, and diabetes have been most consistently associated with schizophrenia (Cannon et al., 2002). Preeclampsia and bleeding might lead to deficient supply of oxygen to the fetus and may impair the developing nervous system. However, how exactly maternal diabetes influences the fetal brain is unknown.

Of the factors that are related to growth and development of the fetus, low birth weight of the child has been most consistently linked to schizophrenia, with birth weight below 2000 grams increasing schizophrenia risk nearly four times (Cannon et al., 2002). However, low birth weight is often due to prior adverse influences on the fetus, whether of environmental or genetic origin.

The complications of delivery that appear to be linked to schizophrenia are asphyxia (i.e., severely deficient supply of oxygen), uterine atony (i.e., loss of tone in the uterine musculature), and emergency caesarean section (Cannon et al., 2002). Some researchers have proposed that complications of delivery might be the consequence of prior abnormalities in the fetus, but findings that neurological abnormalities were even lower in fetuses with more complications of delivery contradicted this hypothesis (McNeil & Cantor-Graae, 1999).

**Parental age.** Parental age, specifically the biological father's age, has also been found to be associated with schizophrenia. The results of a recent meta-analysis (Wohl & Gorwood, 2007) suggest that late fatherhood increases a child's risk of developing schizophrenia, with the risk increasing approximately from 0.2% in children of 35-year-old fathers to 5% in children of 55-year-old fathers. This may be explained by the number of mutations in a man's germ cell (sperm) that increase throughout the life span. These cells will have undergone about 660 divisions by the age of 40. In contrast, female germ cells (eggs) only divide 24 times, mostly before a woman is even born. Every division increases the risk of new mutations, and such mutations have been implicated in various genetic (i.e., autosomal dominant) diseases such as Huntington's disease and dwarfism.

### Exogenous factors

**Season of birth.** First reported in 1929, winter birth is one of the most firmly established nongenetic risk factors for schizophrenia. Compared to the monthly birth rates in the general population, there is a 5% to 8% excess of births in winter and early spring months in those who later develop schizophrenia (Torrey, Miller, Rawlings, & Yolken, 1997). The season-of-birth effect has been observed in the northern hemisphere and, although less consistently, in the southern hemisphere; no season-of-birth effect has been found in equatorial regions where there is little variation in seasonal temperatures. Studies conducted in the northern hemisphere have generally reported an excess of births among individuals with schizophrenia for the months of December through March, with a maximum peak in January and February.

Researchers are still trying to understand how season of birth might increase risk for developing schizophrenia. There may be seasonal patterns of procreation in the parents of individuals with schizophrenia. Exposure to seasonally fluctuating factors that could potentially interfere with the development of the central nervous system in utero has also been suggested as a mechanism—factors including nutrition, hormones, maternal exposure to viral infections, and certain meteorological factors (e.g., sunlight exposure and vitamin D, temperature, or severe weather; Tochigi, Okazaki, Kato, & Sasaki, 2004).

**Maternal infections.** Much research suggests that prenatal maternal infection can increase the risk for schizophrenia (Brown & Derkits, 2010). Initial studies examining the relationship between maternal infectious disease and subsequent schizophrenia were epidemiological in nature, linking influenza epidemics to increases in population levels of schizophrenia, for example. Given the limitations of this methodology (i.e., no validation of maternal exposure), researchers have since relied on other sources of information such as maternal recall, hospital records, and national registry records of documented infection. However, the strongest line of evidence comes from studies with maternal exposure to infection that has been documented serologically (i.e., from blood samples). These studies suggest there is an increased risk for schizophrenia in people prenatally exposed to toxoplasmosis (2.6-fold increase), influenza (3-fold increase), or genital or reproductive infection (5-fold increase; Brown & Derkits, 2010).

It is hypothesized that maternal infection in the early to mid-stages of pregnancy damages the developing nervous system of the fetus, which subsequently leads to the development of schizophrenia. Proposed mechanisms include the direct effects of the pathogen on the fetal brain, maternal immune reaction to infection, fever, stress, and use of analgesics and anti-inflammatory drugs (Boksa, 2008).

**Urbanicity and toxins.** The prenatal infection hypothesis gains support by the finding that birth in an urban area is associated with a 2.4-fold increased risk of schizophrenia

(Tandon, Keshavan, & Nasrallah, 2008). This effect may be due to crowding in urban areas and the subsequent increase in risk for infection, although this remains a topic of debate. In a similar vein, urbanicity may be associated with an increased exposure to toxic substances (e.g., lead). Current findings suggest that elevated prenatal levels of lead are in turn associated with an almost twofold increase in the risk of schizophrenia and related disorders (Opler & Susser, 2005).

**Nutritional factors.** Maternal nutrition in pregnancy is also believed to influence risk for schizophrenia in offspring (Brown & Susser, 2008). Support comes from two epidemiological studies that found a twofold increase in risk for schizophrenia among individuals who were in their first trimester of gestation at the height of a severe, sudden-onset famine. Additionally, some studies have reported that high maternal prepregnancy and early pregnancy body mass index (BMI) is associated with a 2.8-fold increase in risk for schizophrenia in offspring (e.g., Schaefer et al., 2000). Thus, both under-eating and overeating during pregnancy may increase schizophrenia risk in the offspring.

There are several hypothesized mechanisms by which maternal nutritional factors may increase the risk for schizophrenia. Regarding maternal undernutrition, it has been suggested that nutritional insufficiencies (e.g., folic acid, essential fatty acids, iron, vitamin A) increase the risk of spontaneous genetic mutations and/or disrupt proper neurodevelopment, ultimately resulting in schizophrenia. The effects of high maternal BMI on schizophrenia risk may be explained by metabolic problems (e.g., diabetes), dietary restrictions, or poor maternal care, all of which may affect neurodevelopment and/or increase the risk of obstetric complications.

**Prenatal maternal stress.** A few studies show that a stressful event occurring outside of the pregnant woman's control (referred to as an independent life event) can result in increased risk for severe psychopathology for her unborn child in adulthood. The stressors studied to date have ranged from population threats of human origin (e.g., invasion) or from Mother Nature (e.g., tornados), to personal loss (e.g., death or fatal diagnosis of a close relative). Most studies compare rates of psychiatric illness in the population that was exposed to the stressor with rates for people born in the same geographic region in different years. However, a few studies can make direct links between life events in individual mothers and risk in their children. The first study of prenatal stress and schizophrenia is an example. In Finland, Huttenen and Niskanen (1978) found one case of schizophrenia among 168 individuals whose fathers had died during their first year of life, compared to six cases among 167 people whose fathers died while they were in utero, a significant increase in risk. This and other population studies suggest that exposure to stress in the late first or early second trimesters, or possibly at the very end of pregnancy, increases risk for schizophrenia more than does exposure at other times in the pregnancy. Another example is a study by Khashan et al. (2008), who used population registries

in 1.4 million Danes to link birth dates to, on one hand, the dates of life-threatening diagnoses or death in close relatives of pregnant women and, on the other hand, to mental illnesses in their children as recorded in the national psychiatric registry. The researchers concluded that the death of a close relative during the first trimester of pregnancy increases risk for schizophrenia in the child by 67%. Huizink and her colleagues (Huizink, Mulder, & Buitelaar, 2004) review studies of prenatal maternal stress and risk for schizophrenia and other mental illnesses and describe the physiological mechanisms responsible for "schizophrenia-like" effects in animals.

Exogenous sources of stress ultimately have endogenous mechanisms. Animal studies demonstrate that an externally generated stressor to the pregnant female—such as loud noise, social isolation, or pain—results in a surge of stress hormones passing through the placenta to the fetus (Beydoun & Saftlas, 2008). These changes in maternal hormones result in permanent changes to parts of the fetal brain that are associated with schizophrenia (e.g., the hippocampus). Prenatal stress and its effects on the brain are then associated with a number of behaviors in the offspring, including altered stress reactions and learning. Maternal nutritional factors and maternal and fetal immune function may also be important mechanisms of prenatal stress.

The mechanisms of prenatal stress are difficult to study in humans since researchers cannot randomly assign stressors to pregnant women. The human stress experience involves the objective degree of exposure to the stressor, the individual's subjective distress, and the hormonal response, with several psychological and social factors complicating the process. Prenatal stress may increase risk for schizophrenia directly, by influencing brain development, or indirectly, by increasing the likelihood of other risk factors such as obstetric complications (Beydoun & Saftlas, 2008).

In an attempt to clarify how the objective, subjective, and hormonal aspects of prenatal stress might increase risk for potential precursors of schizophrenia, such as obstetric complications, behavioral problems, cognitive delays, and physical features, we launched Project Ice Storm (King et al., 2009). In this ongoing study, we recruited pregnant women shortly after a natural disaster in 1998 and continue to follow their offspring prospectively. The results of this study may shed light on the mechanisms by which prenatal stress increases risk for schizophrenia. Thus far, results show that greater severity of the mother's objective exposure to the stressor (the ice storm), but not greater subjective distress, predicts significantly lower cognitive and language performance of her offspring throughout early childhood. Subjective maternal distress predicts more asymmetrical fingerprints, as are found in people with schizophrenia, in the children whose mothers were exposed to the ice storm in mid-pregnancy, when fingerprints develop. Maternal cortisol (a stress hormone) following the ice storm also predicts fingerprint asymmetry in the children. Thus, each aspect of the stress experience (objective, subjective, and hormonal) is associated with one or more risk factors or precursors of schizophrenia. The timing of the stressor at different points in

pregnancy is associated with different schizophrenia-related outcomes.

## Discussion

In this brief overview of prenatal and perinatal risk factors for schizophrenia, we have covered risk factors that seem far removed from the illness, like season of birth and severe weather events, and those with more obvious connections to the developing fetus, like birth complications. One point worth mentioning is that these prenatal risk factors are highly nonspecific—that is, they are associated not only with schizophrenia but with a wide variety of other mental illnesses (Huizink et al., 2004). For instance, prenatal maternal stress may increase risk for depression, anxiety, or aggression in children and adolescents (Beydoun & Saftlas, 2008); the type of difficulty that arises from prenatal stress may be a function of the genetic “weak link” in the fetus. Another point worth stressing is that most of the risk factors we have discussed explain a small, but significant, increase in risk for schizophrenia. For example, while bleeding in pregnancy raises risk an additional 69% above the 1% to 1.69%, an emergency C-section increases risk 300% and diabetes in pregnancy increases risk 700% (Cannon et al., 2002). However, even a sevenfold (700%) risk above 1% is only 7 in 100 cases of maternal diabetes. Hence, as argued below, moving toward the simultaneous examination of multiple risk factors for schizophrenia may prove to be more helpful in understanding the etiology of schizophrenia.

Increasingly, schizophrenia research is moving away from studying single risk factors toward studies that consider how risk factors work together to increase risk. Because gene-by-environment (GxE) interactions are likely in schizophrenia, environmental and genetic factors studied alone may yield negative results until they are paired with each other (Rutter, Moffitt, & Caspi, 2006). The GxE approach may ultimately show how an environmental factor, when paired with different genes, may result in different forms of psychopathology. For example, van Os and colleagues (2004) concluded that between 20% and 35% of individuals exposed to both an urban birth and a family history of schizophrenia could be ill because of this GxE interaction (van Os, Pedersen, & Mortensen, 2004). As the field of “epigenetics” advances, we may also see how environmental factors change how genes are expressed—or turned on and off—which may be another way that environment and genes interact to increase risk.

Although researchers have been mostly interested in uncovering risk factors for the diagnosis of schizophrenia, little research to date has focused on discovering associations between risk factors and specific signs, symptoms, or other features of schizophrenia. Yet the power of using such an approach should be greater than that of studies predicting the diagnosis (King, Laplante, & Jooper, 2005).

In summary, decades of epidemiological research have uncovered a wide variety of prenatal and perinatal risk factors for schizophrenia, most with small effects. Our next challenge is to capitalize on the clues provided by the variability in the

causes of schizophrenia and in the patterns of symptoms in people diagnosed with schizophrenia to build better models of the development of this illness.

## Recommended Reading

- Beydoun, H., & Saftlas, A.F. (2008). (See References). An excellent literature review on prenatal maternal stress and its association with both physical outcomes (including brain development) and health outcomes (including mental health).
- Kinney, D.K., Teixeira, P., Hsu, D., Napoleon, S.C., Crowley, D.J., Miller, A., et al. (2009). Relation of schizophrenia prevalence to latitude, climate, fish consumption, infant mortality, and skin color: A role for prenatal vitamin D deficiency and infections? *Schizophrenia Bulletin*, *35*, 582–595. An interesting study that pitted the associations found in 49 epidemiological studies between latitude of birth and schizophrenia against demographic data for each region—including population rates of fish consumption, and measures of quality of health care—to rigorously test the season-of-birth effect.
- Kraemer, H.C., Stice, E., Kazdin, A., Offord, D., & Kupfer, D. (2001). How do risk factors work together? Mediators, moderators, and independent, overlapping, and proxy risk factors. *American Journal of Psychiatry*, *158*, 848–856. A nicely written paper presenting a very clear overview of how risk factors for psychopathology might work together from a statistical perspective, and how to test whether two risk factors for the same outcome are independent, overlapping, proxy, mediating, or moderating.
- Murray, R.M., Jones, P.B., Susser, E., van Os, J., & Cannon, M. (Eds.). (2003). *The epidemiology of schizophrenia*. Cambridge, England: Cambridge University Press. Includes chapters reviewing the literature on the social, developmental, and genetic epidemiology of schizophrenia, including prenatal factors.
- Susser, E.S., Brown, A.S., & Gorman, J.M. (Eds.). (1999). *Prenatal exposures in schizophrenia*. Washington, DC: American Psychiatric Press. An excellent overview of how prenatal factors in schizophrenia work, including sections on schizophrenia and brain development and on schizophrenia and prenatal nutritional, immunological, and infectious exposures written by leaders in the field.

## Declaration of Conflicting Interests

The authors declared that they had no conflicts of interest with respect to their authorship or the publication of this article.

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# Current Research on the Genetic Contributors to Schizophrenia

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## Abstract

In this article, we review genetic research on schizophrenia to illustrate current strategies, findings, challenges, and future directions in the study of a relatively common, severe psychopathological phenotype. Family, twin, and adoption studies indicate that overall genetic effects on schizophrenia are both important and complex. Although efforts to identify specific causal genetic variants have utilized the full range of molecular and analytic techniques, results have been modest. Several putative common genetic variants of small effect appear to be implicated along with some extremely rare variants of potentially large effect. It seems clear that most of the genetic contributors to the liability to schizophrenia, as well as nongenetic ones, remain to be identified. New strategies give reason for optimism that our understanding of the causes of this tragic disorder will continue to increase.

## Keywords

schizophrenia, genetics, GWAS, linkage

Schizophrenia is a psychopathological diagnosis whose current definition includes hallucinations, delusions, disorganized speech, emotional flattening, and bizarre behavior. This definition has a long and evolving history: Kraepelin proposed an influential definition of the disorder as far back as 1896, and revisions for the new fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders (DSM-V)* are being debated today. Not only is the syndrome usually clinically severe and persistent, it is also relatively common and widespread, with a 1% lifetime risk in the general population worldwide.

Our aim here is to briefly review research on the genetic contributors to schizophrenia. Such research is not only important for schizophrenia but may also offer valuable insights into the complexities that lie in wait in the study of genetic causes of many other common psychopathologies, as well as of psychological individual differences in the normal range. Our focus on genetic contributors to schizophrenia does not imply that their effects are specific to that disorder—rather, numerous findings suggest some shared genetic effects with other psychopathologies.

effects contributes to causing the diagnosis. For example, if monozygotic (MZ) co-twins of schizophrenic patients who have been reared apart (and thus who share 100% of the patient's genotype but not his or her environment) were not at increased risk for schizophrenia compared to the general population, then studies seeking to identify specific genetic variants for schizophrenia would be an exercise in futility because there would be no genetic effects to be found. The usual methods used to answer this question (i.e., family, twin, and adoption designs) have a long history in schizophrenia research (e.g., Pogue-Geile & Gottesman, 2006), and only final conclusions will be outlined here. Based on the familial risk data outlined in Table 1, aggregated genetic effects have been estimated to account for approximately 83% of the total variation in liability to schizophrenia (Cardno & Gottesman, 2000). Thus genetic effects appear to be the dominant overall cause of schizophrenia. It is also estimated from the pattern of risk across relatives that variation in multiple genes contributes to schizophrenia. In addition, because MZ co-twins of patients do not all have schizophrenia (i.e., MZ concordance rate of 48%) it seems clear that environmental effects that are largely

## Total Aggregated Genetic Effects on Schizophrenia

Logically, the first question to be asked concerning the causes of schizophrenia (or any phenotype—that is, measurable characteristic of interest) is the degree to which the total sum of all genetic

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**Table 1.** Risk of Definite or Probable Schizophrenia Among Relatives of Schizophrenic Patients Aggregated Across Studies

Relationship to schizophrenic patient	% genes shared with schizophrenic patient	Observed lifetime risk (%) <sup>1</sup>
MZ co-twins	100	48
DZ co-twins	50	17
Siblings	50	9
Offspring (1 parent affected)	50	13
Parents	50	6
Second degree <sup>2</sup>	25	3–4
General population	0	1

Note. After Gottesman (1991).

<sup>1</sup> Estimate of the probability of receiving a diagnosis of schizophrenia at some time during one's life (all risks age-corrected, except twins).

<sup>2</sup> Includes half siblings, uncles/aunts, nephews/nieces, and grandchildren.

not shared among relatives also play an important role (Gottesman & Bertelsen, 1989).

A general etiological hypothesis, the multifactorial threshold (MFT) model, provides an excellent overall fit to the risk data from twin and family studies. First proposed for schizophrenia by Gottesman and Shields in 1967, the MFT model includes independent, additive, equal-sized effects from many genetic variants along with environmental effects that are assumed to add together to form a continuous distribution of risk for schizophrenia, with a categorical threshold beyond which a clinical diagnosis of schizophrenia is produced. For example, if four genetic variants and two environmental experiences each independently and equally increased the risk for schizophrenia and the threshold for diagnosis was a total of three risk factors, then individuals who inherited and/or were exposed to *any* combination of three, four, five, or six of the six risk factors would be diagnosed with schizophrenia and those with any combination of zero, one, or two risk factors would not be diagnosed. This zero-to-six scale would reflect a continuous distribution of risk or liability to schizophrenia in the population. A model allowing for rare, large-effect genetic variants in some families (i.e., a mixed model) further improves the predictions of observed data on risk among relatives of patients. We would expect such a complex etiological situation for schizophrenia and probably for most other common psychological phenotypes. And we should not be surprised that common psychological phenotypes whose definitions were initially developed based on clinical considerations and without reference to genetic criteria may turn out to be genetically complex.

## Where Are Schizophrenia Liability Genes Located?

Composed of approximately 3.5 billion nucleotide base pairs, the human DNA sequence (i.e., genome) is a dauntingly large haystack in which to be looking for these numerous small needles. Therefore, initial attempts to screen for the general locations (loci) of genetic risk variants can be useful in narrowing areas to particular chromosomal “neighborhoods” that can then be searched more intensively. Initial studies attempting to discover the chromosomal locations of liability genes for

schizophrenia employed some sort of *linkage study*. Utilizing polymorphic genetic markers (i.e., DNA sequences that vary among individuals) whose chromosomal locations are known, linkage studies seek to correlate the resemblance between relatives for genetic markers at a particular chromosomal location inherited identically by descent from a common ancestor with their phenotypic resemblance. That is, are relatives who resemble each other at a particular chromosomal location also similar phenotypically (e.g., both have schizophrenia)? If they are, then it is likely that near to that particular chromosomal location is genetic variation that contributes to causing schizophrenia. Genetic markers used in linkage studies do not actually cause schizophrenia but rather serve as signposts that may indicate the presence nearby of a schizophrenia risk gene. DNA sequences close to each other on a chromosome tend to be transmitted together from parents to offspring, because it is less likely that crossing-over (an exchange of paternal and maternal homologous chromosomal sections) occurred between their locations during meiosis, compared to sequences that are farther apart. Thus, relatives who share the same genetic markers at those chromosomal locations physically near to causal genetic variants should resemble each other phenotypically as well (e.g., both have schizophrenia) and vice versa.

Methodological developments now allow screening of the entire genome (using 300–400 genetic markers equally spaced across all chromosomes) in order to identify multiple locations harboring gene variants with modest effects. Meta-analyses of dozens of large, genome-wide studies have produced generally (although not unanimously) agreed-upon linkages at regions on chromosomes 1, 2, 6, 8, 13, and 22, as well as others (Lewis et al., 2003) that can become foci of more fine-grained efforts. However, even with quite large samples, linkage studies still have relatively little power to detect gene variants with small effects, and the chromosomal regions identified are quite large, often containing hundreds of genes.

## Which Specific Genetic Variants Contribute to Schizophrenia Liability?

Identification of specific causal gene variants typically require *allelic association studies*, in which correlations between

particular DNA-sequence variants that differ among individuals (i.e., alleles) and the schizophrenia phenotype are examined. For example, at a particular polymorphic chromosomal location, is allele “A” or “B” more common among schizophrenia patients compared to controls? Valid phenotype–allele associations may arise either because the allele contributes causally to schizophrenia or because it is in linkage disequilibrium with an allele at a very nearby locus that does. Linkage disequilibrium denotes the situation in which alleles at different but very close loci tend to remain together on the same chromosome even across many generations, due to their lower likelihood of being reshuffled in the crossing over that occurs during meiosis. Because of linkage disequilibrium, allelic association studies have the advantage of being more statistically powerful for detecting small effects than are linkage studies, with the corresponding feature that they are sensitive to effects from loci only a very small distance on either side of the genetic marker. Association studies typically utilize single nucleotide polymorphisms (SNPs) whose chromosomal locations are known as genetic markers. SNPs are DNA sequences at a particular chromosomal location that differ across individuals by only a single nucleotide base pair at a single location. Millions of such SNPs spread throughout the human genome have been identified. Because the less-frequent allele of any particular SNP is by definition relatively common in the population (greater than 1% and ranging up to 50%), such techniques are best suited for detecting causal alleles that are also relatively common in the population.

Because they are only sensitive to effects from loci that are extremely close to the genetic markers, a very large number of SNPs are needed to screen any particular chromosomal region for associations with a phenotype. In order to reduce genotyping expense, until recently allelic association studies have typically employed some sort of *candidate* strategy to narrow the search to a manageable number of markers. Candidate strategies have been based either on hypotheses drawn from models of pathology or on chromosomal location information (positional candidates) provided by linkage studies. (As mentioned above, linkage studies are most useful for identifying a general chromosomal neighborhood that might harbor a risk locus—for example, regions of Chromosome 6). There have been hundreds of such association studies using SNPs located within candidate genes chosen because they might be relevant to schizophrenia’s hypothesized pathophysiology (e.g., genes coding for aspects of dopamine neurotransmission). However, to date, many such pathology candidate association results have been negative, and positive findings have been small and difficult to replicate, suggesting that our current models of schizophrenia pathology may not be very accurate or that the causes of the pathology lay elsewhere. In contrast, positional candidate strategies that use a large number of SNPs to screen genes in those chromosomal regions suggested by linkage studies have produced some promising associations with schizophrenia. Although by no means unanimous, variants in the following genes initially suggested by linkage studies have all had a number of positive replications (along with some negative):

Regulator of G Protein Signaling 4 (*RGS4*, on chromosome 1), Disrupted in Schizophrenia 1 (*DISC1*, on chromosome 1), Dystrobrevin-Binding Protein 1 (*DTNBP1/Dysbindin*, on chromosome 6), and Neuregulin 1 (*NRG1*, on chromosome 8; Williams, Owen, & O’Donovan, 2009). It is important to note that even the most positive studies find only small associations between SNP alleles in these genes and schizophrenia, accounting for 1% to 2% of the liability to schizophrenia.

In contrast to candidate approaches, *genome-wide* association (GWA) studies have become practical only recently, as about 1 million SNP markers are needed to screen the entire genome for associations (Sullivan, 2009). However, new technologies using microchips that allow relatively inexpensive genotyping have now made such strategies realistic, although the statistical issues surrounding performing hundreds of thousands of tests are notable. These SNP-based GWA studies combine the statistical power and chromosomal precision of allelic association studies with the genome-wide screening of the earlier linkage studies and have successfully revealed several novel gene variants of small to moderate effects for other conditions. After much anticipation, in the past year results from several large GWA studies, including tens of thousands of schizophrenia cases and controls and hundreds of thousands of SNPs, have been reported (The International Schizophrenia Consortium, 2009; Shi et al., 2009; Stefansson et al., 2009). There were some points of agreement among the GWA studies with previous linkage results and with positional candidate association findings. For example, SNPs on Chromosome 6 in genes of the major histocompatibility complex (MHC), which controls immune functions, were consistent across some of the GWA studies and with prior linkage results. However, few of the favorite positional candidate genes discussed above were significant in the GWA studies, and replication across the GWA studies was far from complete, with only a few (and often not the same) SNPs in each study reaching genome-wide significance. Importantly, even the most significant SNPs only accounted for 1% to 2% of the liability for schizophrenia. Such results imply both that only small genetic effects contribute to schizophrenia risk and that most of the genetic liability is still unidentified, despite the fact that researchers have apparently looked everywhere! This latter phenomenon has been termed “missing” or “dark” heritability, analogous to the presumably common but undetectable “dark matter” of astronomy (Manolio et al., 2009), although recent GWA analyses suggest that perhaps, at least for schizophrenia and height, much of this “dark heritability” may be due to the accumulated impact of tens of thousands of very-small-effect polymorphisms along with possibly lower-than-expected correlations between the SNP markers and putative risk variants (the International Schizophrenia Consortium, 2009; Yang et al., 2010). In any case, this initial wave of GWA studies of schizophrenia has implicated some new gene variants of small effect and suggested that many of the genetic effects are quite small and are very numerous and perhaps that much causal genetic variation remains to be identified (see the Schizophrenia Research Forum, [www.schizophreniaforum.org](http://www.schizophreniaforum.org), for weekly updates).

## Other Genetic Effects

As noted earlier, SNP-based association studies are most sensitive to relatively common risk alleles, which is appropriate if liability largely arises according to the “common disease-common variant” hypothesis, which, like the MFT model, states that schizophrenia results from combinations of common risk alleles, each with a small main effect. In the presence of evolutionarily negative selection effects (i.e., reduced reproductive rates among patients over time), main effects of common alleles should be small, whereas large effects should be rare because they are being selected out. A recent approach has focused on one class of such rare *structural* variants. Structural variants include copy number variants (CNVs)—that is, variation in the number of copies of certain DNA sequences—and micro-deletions—that is, small missing bits of DNA sequence at particular locations. Recent studies that have searched for such structural variants have produced some intriguing findings that suggest the total number of such variants is increased in individuals with schizophrenia compared to controls. Although each particular variant is still extremely rare among schizophrenia patients (i.e., much less than 1%), altogether they may occur in 1% to 3% of schizophrenia patients compared to almost 0% in controls (St. Clair, 2009). Although not accounting for a large percent of cases, such rare but large genetic effects appear to be part of the overall genetic architecture of schizophrenia.

## Future Directions

Although research will certainly continue to follow up leads discussed above, there are also several other approaches that may improve on the modest results to date.

### Improving the phenotype

Although the diagnosis of schizophrenia is useful clinically, it has certainly not mapped simply onto genetic effects. This suggests that “improvements” in the phenotype—that is, developing a definition or measurement of the phenotype that better reflects genetic causes—might clarify matters. Two general and potentially related approaches have been taken to this question. One strategy aims to resolve phenotypic variation among patients with schizophrenia and perhaps identify subgroups or dimensions that correlate better with genetic effects. Subtyping of schizophrenia to reduce heterogeneity has a long history, but so far, results from recent candidate allele studies have not been dramatic. However, using GWA studies to correlate phenotypic variation among schizophrenia patients with measured genetic variation may prove more useful.

A related phenotypic strategy aims to “extend” the schizophrenia phenotype by identifying characteristics that are more sensitive to genetic effects than is the overall diagnosis of schizophrenia itself. For example, although only a small number of individuals with a particular genetic risk allele may develop schizophrenia (e.g., 2% compared to 1% among those without

it) perhaps almost all of those with the risk allele have attentional problems even if they are not schizophrenic. Measuring attentional problems in this situation would make identifying the schizophrenia risk allele much easier than focusing on the diagnosis alone. There is an important literature attempting to identify such “endophenotypes” (Gottesman & Gould, 2003) using risk for schizophrenia as the criterion for determining the potential usefulness of the endophenotype, with many promising suggestions, ranging from schizotypal (mild schizophrenia-like symptoms) personality traits (Pogue-Geile, 2003), neuropsychological deficits (Snitz, MacDonald, & Carter, 2006), and neural differences revealed by brain imaging (MacDonald, Thermenos, Barch, & Seidman, 2009), that are more common among nonschizophrenic relatives of patients than among controls. It is only recently, however, that such potential endophenotypes have been incorporated within multivariate, genome-wide linkage studies, with some early positive results suggesting novel potential risk loci with pleiotropic (joint) effects on both schizophrenia and cognitive function (e.g., Almasy et al., 2008). There have also been a number of studies investigating phenotypic correlates of putative schizophrenia risk alleles in the general population or among relatives of patients. Although having the potential to elaborate the pathological effects of putative risk alleles, such studies must rely on risk alleles being identified in the first place.

### “Proximal” measures of pathophysiology

Although many strategies are being used to improve understanding of schizophrenia pathophysiology that could be used to “improve the phenotype,” as described above, there are some approaches that emphasize aspects of pathology very close to the genotype. Perhaps the most exciting are techniques to measure gene expression—that is, the extent to which genes are “turned on” and are producing their RNA transcripts. These techniques may be applied to hypothesized pathological tissue (e.g., brain tissue studied post-mortem) or even to blood cells in order to identify genes that are under- or over-expressed among patients compared to controls. Because gene expression can be environmentally modulated, such measures also reflect environmental effects. Although most efforts to date have relied on expression levels of candidate genes, genome-wide expression studies of virtually all human genes (over 20,000) can now be performed (Cookson, Liang, Abecasis, Moffatt, & Lathrop, 2009). This emerging technology opens numerous possibilities for identifying candidate genes for allelic association studies, although access to appropriate tissue for the expression study is a theoretical and practical challenge. A related strategy attempts to identify risk-associated variation in the “epigenome” (i.e., epigenetic effects). Environmental exposures may affect histones and DNA methylation patterns that in turn affect gene expression. Histones are chemical structures that surround DNA and whose configuration affects whether genes can be expressed or “turned on”; DNA methylation patterns similarly affect gene expression. Assays of

histone or methylation patterns in appropriate tissue may thus identify abnormalities in the epigenome of schizophrenia.

### Searching for dark heritability

Although perhaps much of this dark heritability is due to the accumulated effects of tens of thousands of polymorphisms, each with very small effect, along with imprecision of SNP measurement, other approaches have also attempted to explain the small (1%–2% of liability) main and aggregate effects of most putative genetic variants suggested to date. One hypothesis is that genetic main effects are small because genes interact with other genes (called epistasis) and that it is the interactions, not the main or average effects, that are large. For example, perhaps only individuals with risk alleles at two (or more) loci develop schizophrenia but those with only one or the other do not. Although intuitively plausible, investigations to identify important interactions among a large number of alleles, such as are produced in a GWA study, suffer from enormous statistical complexities. In addition, statistical modeling of familial risk does not usually detect such non-additive epistatic effects. Nevertheless these approaches may hold promise if the problems of high dimensionality can be resolved either statistically or through the use of improved candidate hypotheses that are perhaps based on identification of interactions within gene networks.

A similar hypothesis concerns interactions between gene variants and environmental experiences. For example, it may be that a genetic effect is small on average but that among individuals with a particular environmental exposure, such as a viral infection, many more would develop schizophrenia. Again, this is a plausible scenario for which there are some early suggestive leads.

A final approach to illuminating the dark heritability of schizophrenia is *whole-genome sequencing*. Although they are massive, SNP-based GWA and CNV studies still detect only particular kinds of polymorphisms. Only by complete sequencing of individuals' genomes will all the variation present be measurable. Although currently such whole-genome sequencing is too expensive, it is anticipated that within the relatively near future, costs will approach \$1,000 per genome (Metzker, 2010). Of course, the statistical issues of comparing DNA sequences of approximately 3.5 billion nucleotides will be daunting.

### In Conclusion

Genetic research on schizophrenia has grown exponentially in recent years and has exploited the rush of new molecular technologies and analytic techniques. In many ways it represents a prototype of modern genetic research on a psychological phenotype—a model for application of new techniques and of the resulting challenges. Although it is clear that molecular genetic and analytic techniques will continue to advance, it is equally clear that research on improving the phenotype and identifying environmental contributors will be needed to improve our

understanding of the tragic problems associated with the disorder. Similarly, although atheoretical genome-wide explorations may lead us to undiscovered causes, innovative hypotheses of pathophysiology have the potential to suggest both candidate phenotypes and genotypes that may lead us more directly to at least some of the needles in this large and important haystack.

### Recommended Reading

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- Schizophrenia Research Forum. (2010). [www.schizophreniaforum.org](http://www.schizophreniaforum.org). An important Web resource for up-to-date information about schizophrenia.

### Declaration of Conflicting Interests

The authors declared that they had no conflicts of interest with respect to their authorship or the publication of this article.

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# Neurodevelopment and Schizophrenia: Broadening the Focus

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## Abstract

Developmental changes in the brain are now a central feature of most etiological theories of schizophrenia. From the fetal period, in which vulnerability is presumed to originate, to the emergence of clinical illness in adolescence, brain changes are setting the stage for the first episode of psychosis. A host of factors that have the ability to alter fetal brain development have been linked with schizophrenia. Heritable genetic factors may increase risk for aberrant fetal brain development, and molecular genetic studies are now revealing mutations and epigenetic events that can also derail normal developmental processes. Prenatal complications also are now known to be associated with vulnerability. Later, adolescence and early adulthood are the critical periods for the onset of the prodrome, the period of decline before illness onset, and then the clinical syndrome. Here we summarize hypothesized elements of the neurodevelopmental process in schizophrenia in a model that spans both the prenatal and adolescent/young-adult periods. It is likely that future models will be much more complex as epigenetic processes and gene-environment interactions are incorporated.

## Keywords

schizophrenia, neurodevelopment, prenatal, adolescent

The idea that *neurodevelopment* is associated with risk for schizophrenia has become widely accepted among researchers in the field. Over the past three decades, however, conceptualizations of neurodevelopmental mechanisms in schizophrenia have been broadened to encompass a larger portion of the life span. Neurodevelopmental models have also become increasingly complex as theorists incorporate findings from the burgeoning fields of neuroscience and molecular genetics.

The term *neurodevelopment* emerged in the literature on schizophrenia in conjunction with scientific evidence that prenatal complications were linked with risk for the disorder. Thus the term was initially used to refer to abnormalities in fetal brain development that were presumed to set the stage for vulnerability (Murray, Jones, & O'Callaghan, 1991). In fact, a Medline search revealed no publications containing the terms *neurodevelopment* and *schizophrenia* prior to 1989 but showed a steady increase in subsequent years. In 1989 there was only one such publication (Green, Satz, Smith, & Nelson, 1989), while in 2009 more than 30 were documented.

In the late 1990s, a short-lived controversy arose between researchers arguing that schizophrenia has a neurodevelopmental origin and those arguing that the disorder is "neurodegenerative" in nature (Lieberman, 1999). However, it is now

generally accepted that these are not mutually exclusive and that both may characterize schizophrenia (Ikeda et al., 2008; Velakoulis, Wood, McGorry, & Pantelis, 2000). This conceptual shift was associated with a broadening of the notion of neurodevelopmental models to include brain development in adolescence and young adulthood (Walker, 1994). This broadening was partly a consequence of advances in neuroimaging technology. Prior to the advent of neuroimaging, it was generally assumed that the development of the human brain primarily occurred during the prenatal period. While it is certainly true that all of the regions of the human brain are formed prenatally, we now know that neurodevelopment extends throughout the life span (Walker, Mittal & Tessner, 2008), and this knowledge has served as the impetus for researchers to modify their conceptual frameworks.

There are three general sources of evidence suggesting that the development of the nervous system is linked with

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schizophrenia. These are bodies of research indicating that risk for the disorder (a) appears to be linked with genes that play a role in the development of the central nervous system (Arnold, Talbot, & Hahn, 2005); (b) is associated with prenatal complications (Clarke, Harley, & Cannon, 2006); and (c) is characterized by changes in brain structure prior to the onset of illness, typically in adolescence/young adulthood (Pantelis et al., 2005).

## Neurodevelopmental Mechanisms in the Origins of Vulnerability

### Heritable genetic risk factors

During the 1960s and extending through the 1980s, behavioral genetic paradigms provided clear evidence that vulnerability to schizophrenia could be inherited. Although the magnitude of the heritability estimates varied, findings from family, twin, and adoption studies all yielded support for the hypothesis that genes that confer risk for schizophrenia could be passed from one generation to the next. While some researchers were optimistic that one or a few genes would be identified as major risk factors, subsequent studies using sophisticated molecular genetic techniques failed to provide consistent support for the influences of any single gene or even subgroup of genes as major risk factors. Instead, the findings from genome-wide association studies (GWASs) have led to the conclusions that (a) there are likely many genes, perhaps thousands, that are capable of contributing to risk; and that (b) risk genes act in additive or interactive ways to set the stage for schizophrenia (International Schizophrenia Consortium et al., 2009; St. Clair, 2009). Moreover, among the genes that have been implicated in multiple studies, such as *DISC1*, *dysbindin*, and *neuregulin 1*, many play a role in brain development and neuronal connectivity. Thus, risk genes may be disrupting the complex process of fetal brain development (Arnold et al., 2005).

### Mutations

Within the past few years, GWASs have revealed another likely source of vulnerability. There are now numerous reports showing that, when compared to healthy controls, schizophrenia patients manifest significantly more abnormalities in their DNA—abnormalities that entail mutations in the form of deletions or duplications of DNA sequences (referred to as “micro-deletions” and “copy number variations”; St. Clair, 2009). Again, the affected genes tend to be those that are involved in the development of the nervous system, although any single mutation likely contributes only slightly to risk for schizophrenia. Further, differences in such mutations are even observed in monozygotic twins who are discordant for schizophrenia, with the discordant twin manifesting more of them (Singh & O’Reilly, 2009). Thus, while mutations can be inherited, these findings indicate that de novo (noninherited) changes in DNA can also contribute to vulnerability.

## Epigenetics

The term *epigenetic* (i.e., in addition to genetic) refers to changes in the expression of genes that can affect the biological and behavioral phenotype (i.e., manifest characteristics) of an organism—that is, genes, located in the nucleus of cells, can be turned off or on depending on the cellular milieu. When this occurs, the RNA message encoded by the genes is altered but there is no change in the DNA. A discussion of the complexities of this process is beyond the scope of this paper. Nonetheless, the field of epigenetics is revolutionizing our view of the origins of vulnerability for schizophrenia and other diseases. Recent molecular genetic studies have shown that the profiles of gene expression patterns differ in members of monozygotic twin pairs who are discordant for schizophrenia (Tsang, Huang, Holmes, & Bahn, 2006). Thus the member of the twin pair that is affected by psychosis shows a different pattern of gene expression than does his or her healthy twin.

Scientists are only beginning to understand the nature, breadth, and determinants of epigenetic effects (Akbarian & Huang, 2009). It is known, however, that a host of prenatal factors, including maternal exposure to stress, can influence patterns of gene expression in offspring. Thus fetal development is assumed to be a period characterized by a high rate of epigenetic processes. Further, as described later, adolescence may be another critical period for changes in gene expression that trigger the onset of mental illness.

### Prenatal complications

As noted previously, mounting evidence of a relation between prenatal complications and risk for schizophrenia was partially responsible for interest in neurodevelopmental models of schizophrenia. This now-vast literature has linked a range of prenatal factors with heightened risk. Included among these are prenatal exposure to maternal viral infection, nutritional deficiency, psychosocial stress, blood type incompatibility, and a host of complications that can lead to the fetus receiving insufficient oxygen (hypoxia; Clarke et al., 2006). All of these factors are known to have the potential to alter fetal brain development.

### Brain structural abnormalities

Early studies of brain abnormalities in patients with schizophrenia revealed that such patients have enlarged ventricles, the areas of the brain that contain cerebrospinal fluid. Numerous subsequent investigations have shown reductions in the volumes of several other brain regions, most notably the temporal lobes, and particularly the hippocampus (located within the temporal lobe), a key region for memory functions. At the cellular level, postmortem studies have revealed abnormalities in the structure and placement of neurons, irregularities that typically arise during the formation of the fetal brain (Connor, Guo, & Akbarian, 2009). Taken together, these findings lend additional support to the notion that schizophrenia is a brain disorder and that at least some of the brain abnormalities originate during fetal development.

## Neurodevelopmental Mechanisms in the Onset of Schizophrenia: Adolescence/Early Adulthood

### The prodrome

Among the most well-established aspects of schizophrenia is its modal age of onset, usually the early 20s. Yet, prior to the onset of clinical symptoms of psychosis, there is a period of functional decline and gradual emergence of more subtle symptoms, a period now referred to as the *prodrome* (Addington et al., 2007). Lasting from months to several years, the prodrome is characterized by a range of signs, including depression, anxiety, and a decrease in social interaction. But the key factors defining the prodrome are attenuated psychotic symptoms—namely, perceptual abnormalities, unusual ideations, disturbances in thought, and suspiciousness. Perceptual abnormalities entail sensory experiences that are perplexing or disturbing but that do not constitute clinical hallucinations because the individual doubts that they are real (e.g., “I seem to keep hearing my mother calling my name before I fall asleep, even when I know she isn’t home. It is strange. I guess I must be hearing the TV in the next apartment.”). Unusual ideations entail ideas that are unlikely to be based in reality but do not meet criteria for delusions because, again, the individual is not convinced of them (e.g., “Every time I turn on the radio the first song I hear is always about a guy who is leaving home, and I keep thinking that the DJ is playing those songs to give me the message that I should leave home. But that could not be true, right?”).

The prodrome usually has its onset during adolescence, leading investigators to conclude that neurodevelopmental processes during this period are playing some role in triggering the expression of latent vulnerability for psychosis. Developmental neuroscientists have documented a host of brain maturational processes that occur in adolescents, and several of these have been implicated in theories about the neural mechanisms underlying the onset of psychosis.

### Adolescent brain development

Scientific data on postnatal brain development, especially from studies using MRI, burgeoned in the past decade, and the findings clearly indicate that maturational changes in the brain extend through adolescence and into early adulthood (Walker, 2002). In particular, it has been discovered that normal neurodevelopmental processes during adolescence are both regressive and progressive. Regressive processes include reductions in gray matter volume and the pruning (reduction) of synapses. Progressive processes include increases in white matter and in volume of the amygdala and hippocampus. Some of these processes continue into at least the early 20s, and all are assumed to enhance brain function and to subserve the acquisition of adult cognitive abilities.

Adolescence is, of course, also characterized by dramatic changes in hormonal levels and activity. Sex hormones, particularly testosterone and estrogen, rise precipitously around

puberty due to activation of the hypothalamic-pituitary-gonadal (HPG) axis. Recently, research has shown that adrenal hormones, in particular hormones involved in the biological response to stress, also increase during the course of adolescence. Notable among these are the hormones governed by the hypothalamic-pituitary-adrenal (HPA) axis, including cortisol (Walker et al., 2008). These findings and others have contributed to the growing view that adolescence is associated with heightened sensitivity to stress. Consistent with long-standing vulnerability–stress models, specifically the notion that stress plays a role in triggering the expression of vulnerability, this further implicates the adolescent stage as a critical period.

Because neurons have receptors for hormones, changes in hormone levels have implications for brain function and development. In binding to receptors on neurons, hormones can affect neurotransmitter function and can trigger changes in the expression of genes in the nuclei of neurons. Recent findings indicate that these hormonal effects may be driving normal developmental changes in brain structure.

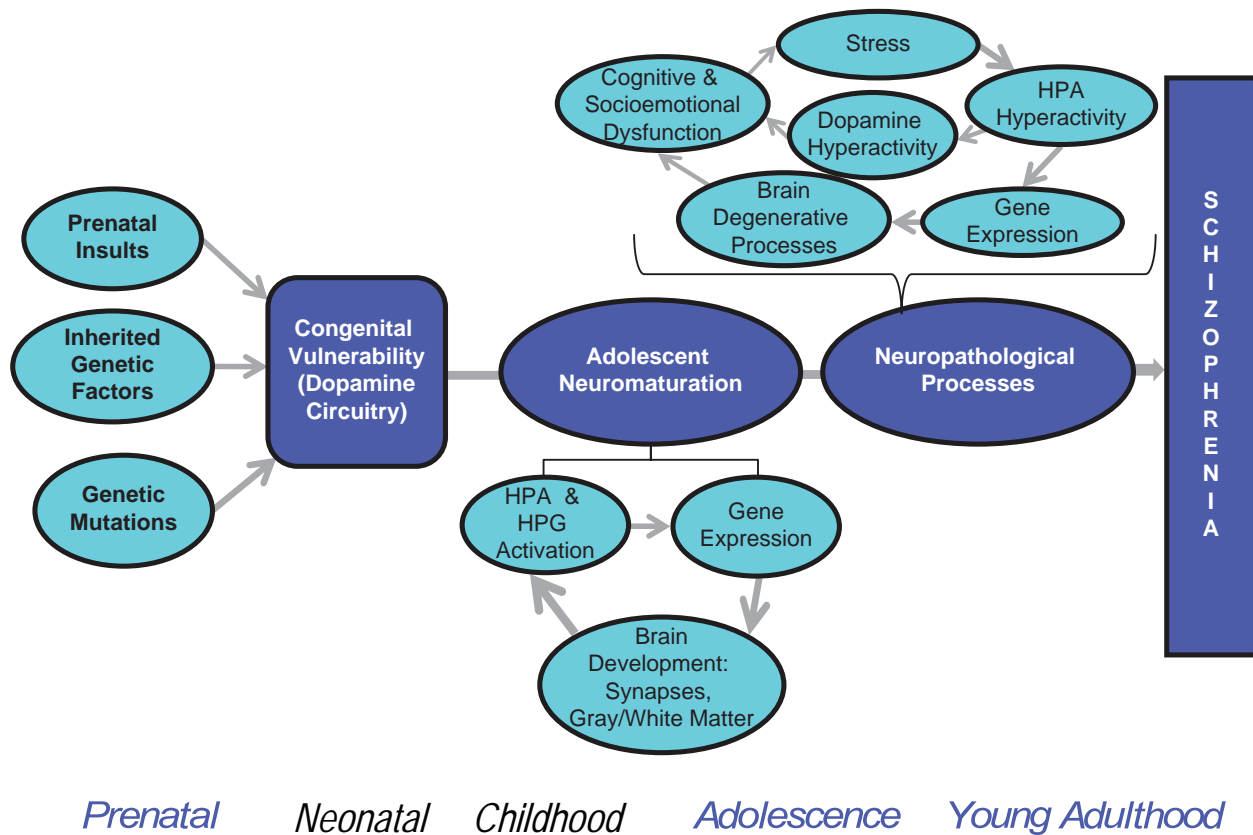
Although much is still unknown about neurotransmitter changes in the developing brain, there is evidence of increasing activity in dopamine systems following the onset of puberty (Walker et al., 2008). This is relevant to theories about the etiology of schizophrenia, because dopamine continues to be the major neurotransmitter implicated in psychotic disorders. It has been hypothesized that abnormal activity of subcortical (below the cortex) brain regions involving dopamine may underlie the onset of psychotic episodes. It should be noted, however, that cortical dopamine activity appears to be reduced in schizophrenia. Further, other neurotransmitters, including glutamate and gamma-Aminobutyric acid, have also been hypothesized to be part of the pathophysiology of schizophrenia.

## The Broad Neurodevelopmental View

Contemporary models of schizophrenia now incorporate changes in brain structure and function that span from the fetal period through young adulthood. Of course, these models are largely based on inferences from research findings, as well as on speculation. Nonetheless, a picture is beginning to emerge. Figure 1 is intended to illustrate the key elements in the neurodevelopmental process.

We begin with the origins of vulnerability at the left of the figure. We know that genetic factors, both heritable and acquired (e.g., mutations), are linked with risk for schizophrenia. In addition, exposure to prenatal complications enhances risk. The adverse effects of prenatal complications may be restricted to fetuses characterized by certain genetic risk factors, or they may contribute independently to risk for schizophrenia. This is one of many questions that remain to be answered.

Moving to the right in Figure 1, it is generally assumed that genetic factors and prenatal events confer vulnerability for schizophrenia. In other words, vulnerability is typically congenital (i.e., present at birth) and may entail abnormalities in brain regions where dopamine plays a critical role in



**Fig. 1.** Neurodevelopmental pathogenesis of schizophrenia. Stress-induced and developmental increases in cortisol can augment brain dopamine activity and changes in gene expression. The latter can lead to neurodegenerative brain changes that give rise to impaired cognition and social and emotional functioning. These impairments can increase stress, thereby exacerbating the neuropathological process.

neurotransmission. The striatum, a subcortical region that is part of many important circuits connecting various brain regions, is currently assumed to be a likely candidate.

Continuing to the right in Figure 1, it is not until later in life, following the onset of adolescent maturation, that vulnerability begins to be manifested in the prodromal signs of psychosis. As described earlier, during this age period, the adolescent brain is undergoing normal maturational changes that affect synapses as well as gray and white matter volumes. There is a gradually building consensus around the hypothesis that abnormal neurodevelopmental processes during adolescence give rise to the brain dysfunction that leads to schizophrenia. More specifically, there is evidence that the decrease in gray matter (suggesting reduced neuronal interconnections rather than loss of cell bodies) and heightened dopamine activity in the striatum are more marked in at-risk youth who subsequently manifest psychotic disorders. There is also evidence that those who develop psychosis manifest a decline in volume of the hippocampus. These abnormal changes may contribute to abnormalities in connectivity among neurons, thereby interfering with brain function.

As illustrated in Figure 1, this neuropathological process may entail a feedback loop. It has been demonstrated that both

stress exposure and increases in cortisol secretion can augment brain dopamine activity. Thus, the normative increase in HPA activity during adolescence may be a contributing factor in the emergence of prodromal symptoms during this period. The hypothetical model proposes that HPA activity and concomitant cortisol secretion trigger both dopamine activity and gene expression changes that, in turn, contribute to neurodegenerative changes, such as exaggerated gray matter decline, volume reduction in the hippocampus, and reduced connectivity. At the behavioral level, the result is increasing impairment in the domains of cognition and social and emotional functioning. These impairments can contribute to stress that further exacerbates the neuropathological process. The final outcome of these converging events is the first episode of psychosis.

### Conclusions

It is important to emphasize that the neurodevelopmental model depicted in Figure 1 is speculative. It reflects a combination of empirical research findings and hypotheses about causal processes. Other elements and mechanisms are likely involved. Further, schizophrenia is varied in its clinical

presentation, and it is generally assumed that there is variability in how it originates. As noted, genetic research indicates that many genes and genetic mechanisms are involved as are many prenatal complications. Finally, recent findings from genetic studies indicate that schizophrenia shares genetic risk factors with other forms of psychosis, such as bipolar disorder with psychotic features. In sum, the model depicted in Figure 1 is assumed to be highly oversimplified and unlikely to account for all cases. It does, however, incorporate many current views and can serve as a point of departure for future models. For example, future research is likely to reveal that interactions between genetic and environmental factors and dynamic epigenetic processes are key pieces of the puzzle, and these will certainly be elements in future neurodevelopmental models.

We clearly have a long way to go in unraveling the complex etiological pathways to schizophrenia. But there has been significant progress. In part, our progress is our acceptance of two facts about the etiological process: (a) that it is extremely complicated, and (b) that it interacts with the development of the brain at critical periods.

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## Declaration of Conflicting Interests

The authors declared that they had no conflicts of interest with respect to their authorship or the publication of this article.

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# Emotion in Schizophrenia: Where Feeling Meets Thinking

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## Abstract

Our understanding of the nature of emotional difficulties in schizophrenia has been greatly enhanced by translational research over the past two decades. By incorporating methods and theories from affective science, researchers have been able to discover that people with schizophrenia exhibit very few outward displays of emotion but report experiencing strong feelings in the presence of emotionally evocative stimuli or events. Recent behavioral, psychophysiological, and brain imaging research has pointed to the importance of considering the time course of emotion in schizophrenia. This work has shown that people with schizophrenia have the ability to experience emotion in the moment; however, they appear to have difficulties when anticipating future pleasurable experiences, and this perhaps affects their motivation to have such experiences. While advancements in our understanding of emotional experience and expression in individuals with schizophrenia have been made, these developments have led to a new collection of research questions directed at understanding the time course of emotion in schizophrenia, including the role of memory and anticipation in motivated behavior, translating laboratory findings to the development of new assessment tools and new treatments targeting emotional impairments in people with this disorder.

## Keywords

schizophrenia, emotion, anticipation, memory

Schizophrenia is a disorder that impacts many domains. Some of its more recognizable symptoms involve difficulties in thinking (e.g., disorganized thinking, delusions) and perception (e.g., hallucinations). While these symptoms may come and go with episodes, some of the more long-lasting symptoms involve difficulties in emotion. In particular, the so-called negative symptoms of flat affect (lack of outward expression of emotion), anhedonia (diminished experience of pleasure), and avolition (diminished motivation) all involve emotion. These symptoms are often resistant to medication and are associated with poor overall functioning, pointing to the importance of understanding emotion in schizophrenia.

What do we mean by emotion? Most psychological researchers and theorists agree that emotions are responses to events, whether internal or external, that consist of multiple components including outward expression (e.g., a smile), reported experience (e.g., reporting feelings of happiness), physiology (e.g., increased heart rate), appraisal (e.g., labeling one's experience and its probable cause), and brain activation (e.g., activation in certain areas of the prefrontal cortex).

Kring (1999) summarized the state of the field with respect to understanding emotional difficulties in schizophrenia and pointed toward promising future directions. Ten years later, much of this promise has been realized, and exciting

new avenues for the assessment and treatment of emotional difficulties in schizophrenia are now under way. In this paper, we review our current understanding of how emotion does (or does not) go awry among people with schizophrenia and then highlight the ways in which these research findings have been translated into current assessment and treatment strategies.

Our understanding of the nature of emotional difficulties in schizophrenia has become much clearer in the last two decades because of translational research. Specifically, researchers have adopted the methods and theories developed in affective science and neuroscience to study emotion in schizophrenia. These methods include laboratory studies in which emotionally evocative stimuli are presented to people with and without schizophrenia and measures of facial expression, reported experience, physiology, and brain activation are obtained. A remarkably consistent pattern of findings has emerged from these studies (see Kring & Moran, 2008, for review): In the presence of emotionally evocative stimuli—whether they be

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films, pictures, foods, odors, or sounds—people with schizophrenia are less outwardly expressive of positive and negative emotion than are people without schizophrenia. However, people with schizophrenia report feeling emotions as strongly as, if not stronger than, people without schizophrenia. Additionally, studies of emotion in the context of daily life find the same pattern of results: People with schizophrenia experience strong feelings in their day-to-day lives even though the contexts in which they experience these feelings are different from those without the disorder.

## A Closer Look at Emotional Experience

Over the past 10 years, researchers have taken a closer look at emotional experience in schizophrenia. Many question whether people with schizophrenia can complete a self-report rating scale about their feelings given concurrent problems with disorganized thinking that may accompany the disorder. However, people with schizophrenia draw upon the same knowledge structures of emotion when reporting on their experiences as do people without schizophrenia (Kring, Barrett, & Gard, 2003), bolstering our confidence in these reports of emotion experience. Further, reports of emotional experience are stable across time and medication status (Kring & Earnst, 1999). This is not to say that symptoms may not impact reports of emotional experience, in the same way that any type of context may influence people's reports of emotional experience, regardless of whether an illness like schizophrenia is involved. Yet, the emotion reports of people with schizophrenia are just as reliable and valid as those of people without the disorder.

Results of studies using physiological measures of emotion (e.g., skin conductance, facial muscle activity, startle modulation) support the findings of comparable reports of emotional experience between people with and without schizophrenia, thus rendering less likely the possibility that people with schizophrenia are reporting feelings according to the demands of the experimental situation. For example, an indirect physiological measure of emotional response is the magnitude of an eyeblink in response to a startling noise. If a person is in a negative emotional state when hearing the startling noise, the blink response will be larger than it will be if the person is in a neutral state or a positive emotional state. Four studies have now shown that people with schizophrenia show the same pattern of blink response (or emotion-modulated startle) as do people without schizophrenia (Kring & Moran, 2008).

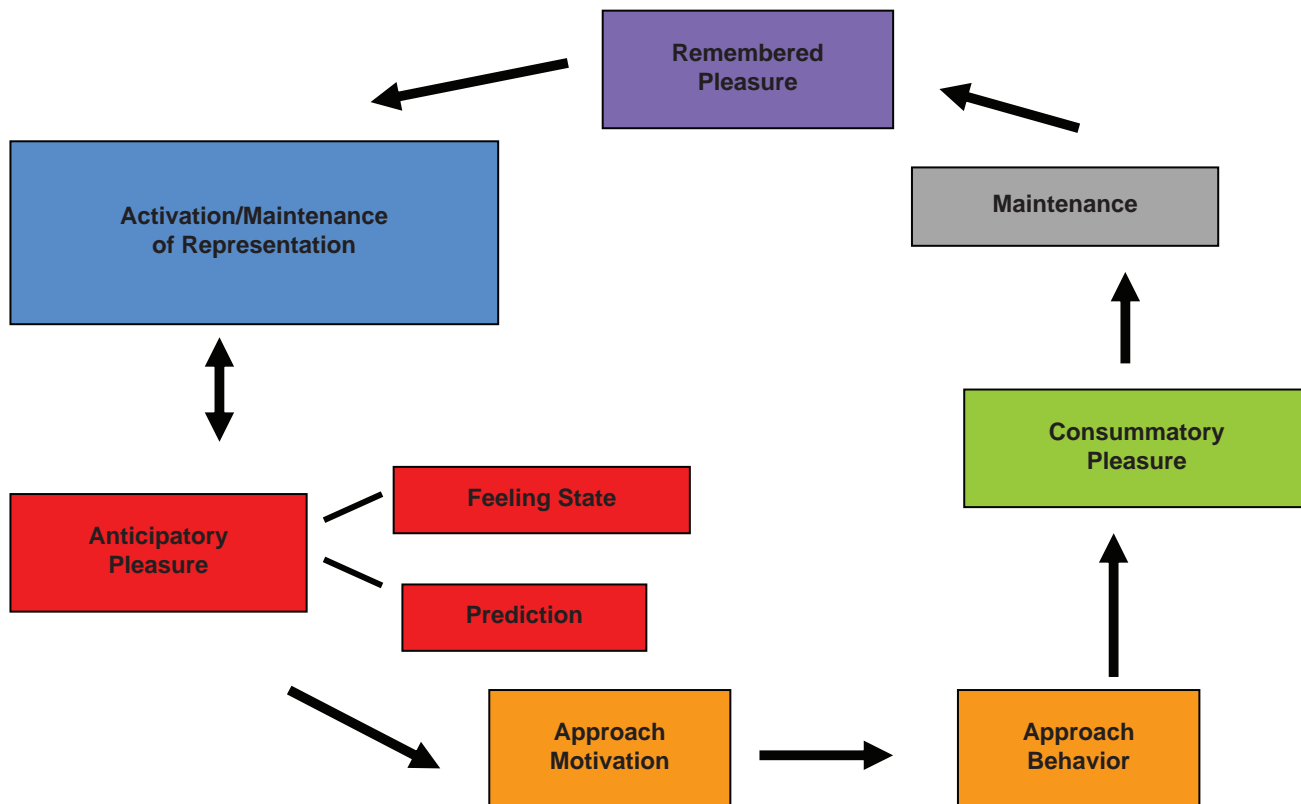
Findings from brain activation studies using functional magnetic resonance imaging (fMRI) or positron emission tomography (PET) during the presentation of emotionally evocative stimuli are more mixed. Several studies have found that, compared to people without schizophrenia, those with the disorder show less activation of the amygdala (an area of the brain linked to the salience of stimuli, including emotional intensity) in response to positive and negative stimuli (see Aleman & Kahn, 2005, for review), but other studies find comparable or even greater amygdala activation among people with schizophrenia; some studies have found decreased activation

in areas of the prefrontal cortex as well, whereas others have not. The reasons for the mixed findings likely have to do with the fact that, to date, there are relatively few brain activation studies in which emotionally evocative stimuli have been presented to people with schizophrenia. Furthermore, differences in scanning methods, in emotional stimuli used and task instructions, and in participant characteristics (e.g., differences in medication, years of illness, severity of symptoms) contribute to the differences across studies. For example, studies often examine the difference between brain activation in response to an emotional stimulus (e.g., picture of puppies) compared to brain activation in response to a neutral stimulus (e.g., picture of a chair) by subtracting brain activation to the neutral stimulus from brain activation to the emotional stimulus. However, some studies find that people with schizophrenia show greater activation to neutral stimuli compared to people without schizophrenia; thus the results of such subtractions might suggest under-recruitment of a particular brain region (e.g., the amygdala) when in fact activity in response to emotional stimuli is comparable or even greater among people with schizophrenia.

Studies with healthy participants may be particularly relevant when interpreting these mixed findings. For example, studies of the perception of facial expressions find relatively more robust brain activation in areas such as the amygdala, parahippocampal cortex, pregenual cingulate, and dorsal portions of the inferior frontal gyrus. By contrast, studies that present evocative stimuli and ask participants to report on their feelings find relatively greater activation in other areas such as the prefrontal cortex (ventromedial, orbitofrontal, dorsolateral), anterior insula, medial temporal lobe, ventral inferior frontal gyrus, and temporal pole (Wager et al., 2008). Making the picture even more complicated, studies suggest that reporting on feelings is associated with activation in more dorsal/rostral areas of the medial prefrontal cortex, whereas reporting on the affective properties of a stimulus (e.g., identifying something as positive or an expression as angry) is associated with activation in more ventral portions of the medial prefrontal cortex (e.g., Ochsner, 2008). Thus, when interpreting brain activation findings in schizophrenia, it is important to consider the type of stimuli presented (e.g., faces, other evocative stimuli) and the type of task instruction (e.g., rating feelings vs. rating stimuli).

Despite these complexities and differences between studies, the findings of comparable physiology and reported experience among people with and without schizophrenia despite possible differences in brain activation raises the intriguing possibility that people with schizophrenia are recruiting the brain differently to end up with the same behavioral result (i.e., comparable reports of emotional experience). The upsurge of interest in linkages among emotion, motivation, and cognition in schizophrenia alongside technological advances in imaging will promote further collaborations between affective and cognitive neuroscientists. Thus we will know a great deal more about how the brain supports emotional experience among people with schizophrenia in the very near future.

## Temporal Experience of Pleasure



**Fig. 1.** A model of the temporal experience of pleasure. A pleasurable experience may involve activating a cognitive representation of a past, related experience that will then trigger a process of predicting or anticipating what the new experience will feel like as well as a feeling of pleasure knowing that the experience is going to be happening in the future. These anticipatory processes will activate the motivation and behavior to go after or approach the experience. In the moment of “consuming” the experience, pleasure is experienced and savored or maintained so that it will be remembered at a later time.

### Linking Emotion and Cognition

One of the paradoxes that emerged from the findings on emotional experience in schizophrenia is a discrepancy between laboratory studies and clinical ratings. Specifically, many people with schizophrenia receive a clinical rating of anhedonia, indicating that they have diminished experience of positive emotion. Yet in the presence of emotionally pleasant things, such as films, pictures, tastes, or just day-to-day life, people with schizophrenia report experiencing as much pleasure as do people without schizophrenia. Drawing upon research on the reward system in humans and animals, Kring (1999) argued for the importance of considering the temporal course of pleasure to distinguish anticipatory from in-the-moment pleasure. When people with schizophrenia are presented with pleasurable stimuli either in a lab or in daily life, they can and do derive pleasure from these experiences. However, evidence now supports the contention that people with schizophrenia appear less likely to anticipate that future events will be pleasurable, are less likely to experience pleasure in anticipation

of things to come, and thus may be less likely to seek out pleasurable experiences (Gard, Kring, Germans Gard, Horan, & Green, 2007). Other behavioral and fMRI studies also find that people with schizophrenia have difficulties in what we call *anticipatory pleasure*. This term encompasses both the anticipation of future pleasurable experiences as well as the experience of pleasure in anticipation of future events.

The ability to anticipate whether something in the future will be pleasurable requires complex cognitive skills, such as imagination, reflection, drawing upon past experiences, and maintaining an image or emotional state. Thus, the latest wave of research on emotion in schizophrenia explicitly integrates emotion and cognition, or feeling and thinking. What do we mean by cognition? Broadly, cognition refers to a set of mental or thought processes, such as attending, thinking, remembering, perceiving, and deciding. In Figure 1, we point to several emotion–cognition interactions that come into play in the temporal experience of pleasure. For example, consider the problem of what to have for dinner. You consider pizza, which

may then lead you to summon a past experience of eating pizza from the neighborhood pizzeria (activating a representation and holding this in working memory), which prompts you to predict that the pizza will be very enjoyable; indeed you experience pleasure now, knowing you will soon be eating tasty pizza (i.e., anticipatory pleasure). These processes will support your motivational system such that you will order and pick up the pizza (approach motivation and behavior), and once you eat it, you will experience in-the-moment or consummatory pleasure. You will savor (maintain) the pleasure from the pizza, and this experience will be encoded into memory. Thus, the next time you contemplate dinner, this memory may be called upon to kick-start the process all over again.

Cognitive and affective neuroscience research with healthy people has clearly demonstrated that the brain is not simply divided into regions specific to our psychological concepts, such as cognition and emotion. Instead, overlapping brain regions support thinking and feeling in interesting and complex ways (e.g., Barrett, 2009). Understanding cognition–emotion interactions is also at the forefront of research on mental illness (Taylor & Liberzon, 2007).

Cognitive neuroscience findings in healthy people suggest that our ability to forecast relies on our ability to remember the past (e.g., Schacter, Addis, & Buckner, 2007), with a core network of brain regions, including areas of the medial prefrontal and medial temporal cortex, supporting both abilities. Thus, when we imagine what it will be like to have a tasty dinner with friends, we likely draw on our past experiences with dinners and friends to help imagine this future experience. Maintaining and processing emotional experiences as they occur no doubt facilitates the development of memories for these experiences, and evidence from psychophysiological and fMRI studies finds that people with schizophrenia appear to have difficulty holding on to these experiences (Horan, Wynn, Kring, Simons, & Green, 2010; Kring, Germans Gard, & Gard, 2009; Ursu et al., 2010).

Only a few studies to date have examined whether people with schizophrenia can retrieve memories of their emotional experiences, and even fewer have examined the relationship between memory and anticipation. One study found that people with schizophrenia were able to recall their feelings about positive films and foods 4 hours later (Horan, Green, Kring, & Nuechterlein, 2006). However, the majority of the work in this area focuses on recalling emotional stimuli (which is distinguishable from remembering feelings). For example, one study found that people with schizophrenia had difficulty recalling positive emotional stimuli 24 hours later (Herberner, Rosen, Khine, & Sweeney, 2007). Research with healthy people has found that emotionally arousing events and stimuli are remembered better than neutral ones. However, individuals with schizophrenia may not exhibit this enhancement for remembering emotional stimuli (Hall, Harris, McKirdy, Johnstone, & Lawrie, 2007).

A study that investigated the link between memory and anticipation in schizophrenia found that people with schizophrenia recalled fewer specific memories and generated fewer specific anticipated future events than did people without

the disorder (D'Argembeau, Raffard, & van der Linden, 2008). It will be particularly important to explicitly examine the linkage between envisioning the future and remembering the past, particularly for emotional events among people with schizophrenia, at both the behavioral and neural levels.

Other investigators have begun to examine how cognitive control, which refers to a broad array of processes including direction of attention to relevant information, maintenance of contextual information to guide behavior, and monitoring of novel information for its relevance to current goals, can influence emotional experience. For example, Dichter, Bellion, Casp, and Belger (2009) examined how, among people with and without schizophrenia, attention and emotion interact. The daily-life analog to this type of experiment might be paying attention to road signs on your way to a destination despite a screaming toddler in the backseat of your car. Findings indicated that healthy individuals activated different brain regions to facilitate attention to the demands of a task (e.g., more dorsal regions of the prefrontal cortex) while at the same time inhibiting attention to emotionally distracting information (e.g., more ventral areas of the prefrontal cortex), whereas people with schizophrenia did not. Ursu et al. (2010) found that people with and without schizophrenia exhibited comparable activations in the ventromedial prefrontal cortex while viewing emotionally evocative pictures. However, healthy controls continued to show activation in the dorsolateral and ventromedial prefrontal cortex during a 12-second delay between picture viewing and reporting emotional experience, presumably reflecting the active maintenance and control of their feelings, whereas people with schizophrenia did not show this persistent activation.

### **Toward the Next Step of Translation: Assessment and Treatment**

The next step of translational research on emotion and schizophrenia—that is, research translating laboratory findings to the development of new assessment and treatments—is well under way. For example, the Collaboration to Advance Negative Symptom Assessment (CANSAS) is a currently ongoing multisite study developing and validating a new clinical measure of negative symptoms (CAINS). The CAINS includes items to assess the five consensus negative symptoms: flat affect, alogia, anhedonia, asociality, and avolition. Importantly, the measure includes questions to distinguish anticipatory and in-the-moment pleasure to better assess the nature of anhedonia in schizophrenia. Once the 3-year CANSAS study is completed, the new measure will be ready for dissemination for use in treatment trials and other research pertinent to elucidating negative symptoms.

Translational research over the past decade has also informed the development of psychosocial treatments that target not just symptoms but also specific emotional and cognitive difficulties. For example, cognitive behavior therapy has been successfully used as an adjunctive treatment to medications for symptoms such as disorganized thinking, delusions, and

hallucinations (Wykes, Steel, Everitt, & Tarrier, 2008). More recently, it has been modified to more explicitly target the negative symptoms in schizophrenia. Preliminary data on an emotion-focused meditation treatment targeting anticipatory pleasure and motivation difficulties in schizophrenia are also promising (e.g., Johnson et al., 2009). In the next 10 years, additional efforts to develop treatments that selectively target the specific emotional difficulties in schizophrenia will likely yield much promise, thus fully realizing the potential of translational research. That is, efforts to better uncover specific deficits in schizophrenia (e.g., links between anticipation and remembering salient emotional experiences) along with the causes of these deficits (e.g., disrupted connections between brain areas supporting emotion and anticipation/memory) will allow us to develop more targeted interventions, whether pharmacological or psychosocial, for these mechanisms rather than for broad categories like negative symptoms.

## Recommended Reading

- Gard, D.E., Kring, A.M., Germans Gard, M., Horan, W.P., & Green, M.F. (2007). (See References). A recent paper illustrating the deficits in anticipatory pleasure among people with schizophrenia.
- Kring, A.M., & Moran, E.K. (2008). (See References). A recent and more comprehensive narrative review of the literature on emotional responding in schizophrenia.

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## Declaration of Conflicting Interests

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# Psychosocial Treatments for Schizophrenia

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## Abstract

This article focuses on the importance of psychosocial interventions for individuals with schizophrenia. We present recent research in the areas of cognitive behavior therapy, social skills training, family interventions, supported employment, and cognitive remediation. We consider issues within those domains of treatment, such as symptom remission versus functional recovery, the limitations of pharmacotherapy, and the potential for psychosocial interventions to address both family and patient issues.

## Keywords

schizophrenia, psychosis, psychosocial treatment

For individuals with schizophrenia, recovery from psychotic symptoms is common after the first episode, with 75% to 90% achieving remission from the positive psychotic symptoms—that is, hallucinations, thought disorder, and delusions—1 year after treatment. Even when best practices are adhered to, there are limitations to the effectiveness of medications. Rates of compliance with taking medication are low even in those who are sick for the first time. Some patients are characterized as “slow responders”—that is, medications take longer than expected to have an effect for these individuals. Others are at risk of experiencing limited effect of the medications even when they adhere to the treatment. Even with ideal pharmacotherapy, relapse rates are very high after the first year of follow-up. In addition, functional recovery remains a major challenge. By functional recovery, we are referring to social relationships and the ability to socialize, make friends, finish school, or attend work. The illness remains disabling and problematic for patients and their families as so often symptom improvement is not always matched with functional improvement. Thus, to help achieve improved outcomes, it is critical that we develop treatment approaches to complement pharmacotherapy. Progress in the research and development of such interventions for schizophrenia can easily be overshadowed by progress in psychopharmacology. Empirical testing of such interventions takes time and money, is labor intensive, and does not lead to a highly profitable product. There are fewer data available to assess the efficacy of such interventions, and they are not widely tested beyond the settings in which they were developed.

## Goals of Psychosocial Interventions

To achieve the goals of the psychosocial treatments used in schizophrenia, it is necessary to take into account not only the

symptoms of the illness but also the impact of the illness on an individual. This includes isolation from families and friends; damage to social and working relationships; depression and demoralization; and an increased risk of self-harm, aggression, and substance abuse. Persistent symptoms that remain after the early recovery phase are an additional problem and add to the already disrupted developmental trajectory, particularly for young people who are experiencing their first episode of psychosis. Since the overall goal is to enhance both symptomatic and functional recovery, these interventions should be available to everyone and especially to those who are recovering from their first episode. Psychosocial interventions have a very important place in the treatment of schizophrenia. In fact, most schizophrenia treatment guidelines now have specific recommendations about including psychosocial and psychological interventions.

## What Psychosocial Interventions Are Available?

The terms *psychological interventions* and *psychosocial interventions* tend to be used interchangeably. In schizophrenia, psychological interventions—for example, cognitive behavior therapy (CBT)—sometimes used for schizophrenia have usually been developed to target the positive symptoms and include psychological strategies such as reattribution, which involves having the individual consider alternatives to his or her current belief system. Psychosocial interventions target

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areas not directly linked to symptoms but may include some psychological strategies. In this article, we will use the term *psychosocial* as a general term to describe the treatments that may aim at improving symptoms but to some degree focus on functional outcome. A range of psychosocial interventions is available. The major ones are CBT, social skills training (SST), family interventions, cognitive remediation, and supported employment. We will present the most recent and relevant research on each of these interventions—in many cases, a recent review or meta-analysis (i.e., combining the results of several studies) that contains the most up-to-date information.

## CBT

Traditionally, CBT has been used to treat depression and anxiety, and it has more recently been adapted to treat psychosis. CBT is now gaining recognition as an effective treatment in schizophrenia. Delusional thought processes have been traditionally thought of as being qualitatively different from nondelusional processes, although some features of these delusions appear to be consistent across both psychotic and nonpsychotic conditions. These features of delusions include conviction, significance, intensity, and inflexibility—features that are the focus of CBT interventions. CBT conceptualizes symptoms within a stress-diathesis framework, in which behavior is viewed as the product of biological factors, such as genetics, and potentially stressful life experiences or other stressors such as substance abuse.

To date, more than 30 randomized controlled trials of CBT for schizophrenia have been published, demonstrating moderate effect sizes on average ( $d = 0.37$ ; Wykes, Steel, Everitt, & Tarrier, 2008). Although this is promising, outcome in most CBT studies has been limited to positive symptoms (delusions, hallucinations, thought disorder, bizarre behavior) and occasionally negative symptoms (for example, apathy, avolition, poverty of content and thought, flat affect), despite the fact that CBT for psychosis can potentially affect other domains such as depression or anxiety. Several studies in the meta-analysis by Wykes et al. have begun to address functional outcome but only as a secondary outcome to outcome of symptoms. Some excellent work has demonstrated a successful use of CBT to prevent relapse (Gumley et al., 2003) and to reduce command hallucinations, which are among the most distressing and high-risk symptoms (Trower et al., 2004).

CBT is used for those experiencing their first episode of psychosis. To help with the many concerns of these young patients, a modular approach has been described (Addington & Gleason, 2005). This is a hierarchical patient-oriented approach to treatment that draws on a diverse array of texts and treatment protocols using empirically supported intervention strategies that have been written up as manuals. The modules in this approach utilize CBT techniques to address such factors as engagement, education, adaptation, comorbid anxiety and/or depression, coping strategies, relapse prevention, and reduction of positive and negative symptoms.

Thus, research appears to support the implementation of CBT as an excellent addition to pharmacotherapy, as it may

improve symptoms, reduce relapse, and potentially enhance functional capacity and overall life quality. This is a rapidly expanding area of research and has proved to be a promising and dynamic treatment modality.

## SST

Deficits in social skills are a significant characteristic of schizophrenia, and this is one of the most salient problems addressed through psychosocial intervention in this population. SST is a promising treatment strategy that has grown tremendously over the last few decades. This strategy, which began with the social skills model of Robert Liberman (see Liberman et al., 1986) incorporates three elements seen as the defining features of social competence or interactions: receiving skills (social perception), processing skills (social cognition), and finally how the individual responds (behavioral responding or expression). Within this framework, social skills are a set of learned abilities and therefore provide opportunity for modification through SST. Current SST protocols target these elements through goal setting, modeling, role playing, positive reinforcement, corrective feedback, and community-based homework assignments (Bellack, Mueser, Gingerich, & Agresta, 2004; Corrigan, Mackain, & Liberman, 1994). A recent meta-analysis by Kurtz and Mueser that reviewed many high-quality randomized controlled trials suggests much more positive results. Significant effect sizes for improvements in skill acquisition ( $d = 1.20$ ), assertiveness ( $d = 0.92$ ), social interaction ( $d = 0.52$ ), and reducing general psychopathology ( $d = 1.08$ ) have been noted (Kurtz & Mueser, 2008).

The stress-vulnerability model of schizophrenia suggests that coping skills such as social skills and associated social support could reduce the contribution of stress to psychotic symptomatology. Treatment that increases one's ability to cope by increasing social skills has therefore been investigated as a means to improve functional outcome with this population. Kurtz and Mueser (2008) identified content mastery—defined as the integration of factual information with procedural and analytic skills—and skill acquisition as those aspects of social skill most associated with improvement in functioning after SST. They found measures of social performance and activities of daily living (such as interacting appropriately with others at the supermarket or balancing one's checkbook) to be more moderately associated with improvement. There was a moderate to small effect size in reductions in negative symptoms ( $d = 0.40$ ) and a small effect size in the risk of relapse (0.23). Overall, SST provides the foundation for further social competence (Kopelowicz, Liberman, & Zarate, 2006), which increases functional capacity in those with schizophrenia and improves their ability to cope with stressful life events.

## Family Interventions

A diagnosis of schizophrenia can have devastating consequences for family members, who may feel burdened and

experience significant distress, anxiety, depression, and economic strain. In fact, taking on responsibilities over and above pre-existing family roles often results in increased psychiatric morbidity among family caregivers. Traditionally, family interventions were specifically designed to address the problems observed in patients with a chronic course of schizophrenia and their families during the post-hospitalization period. These programs consisted mostly of psychoeducation, were often inadequately designed, were fitted more for those who had been chronically ill for many years, and reflected at times limited understanding of the course of schizophrenia. More recently, family interventions for individuals with schizophrenia have been assessed either for their benefit in reducing relapse for the individual or for their effectiveness at reducing family members' stress. A meta-analysis conducted by Pilling et al. (2002) highlights the benefits of family interventions over other treatments such as basic pharmacology in reducing relapses, re-admissions to hospital, and symptoms. Important elements that should be part of family interventions include (a) illness education, (b) crisis intervention, (c) emotional support, and (d) training how to cope with symptoms associated with the illness (Lehman et al., 2004).

More recently, working with the family at the start of the illness has been advocated. The goals of early intervention with the family are to maximize the family's adaptive functioning to the illness; minimize any disruption to family life caused by the onset of schizophrenia; and minimize the risk of long-term grief, stress, and burden experienced by the family. What is also important is to help the family understand the impact of psychosis on the family system and on individual family members, and help them understand the interaction between the family and the course of psychosis. Using this model, Addington, McCleery, and Addington (2005) observed, over the course of 2 to 3 years, a significant reduction in the distress of the families. Although the support was available for up to 3 years, families required minimal sessions, suggesting that what families need is not necessarily an intensive intervention but one that is long term. Interestingly, it was the family's appraisal of how the illness impacted everyone, not the severity of the illness, that had most impact on family outcome.

A recent innovative approach with families addressed the problem of substance abuse in schizophrenia. This trial examined the effectiveness of an integrated treatment of CBT and motivational interviewing. Motivational interviewing involves evaluating all family members' desire to change and trying to increase their actual motivation to change. Results showed significantly greater improvement in patients' general functioning and the number of days they were abstinent from substances (Barrowclough, et al., 2001).

These findings and recommendations emphasize the fact that family intervention is a proven-effective evidence-based treatment for reducing relapse and symptoms in schizophrenia. Family work can be with individual families or in groups of families, and there is no evidence that one is necessarily more effective than the other.

## Supported Employment

The onset of schizophrenia often occurs at critical times of development and thus can have a major impact on a young person's future education and vocational development. Thus, employment is pivotal for the process of recovery in schizophrenia and for improved social and economic functioning. The most empirically validated approach to vocational rehabilitation is supported employment combined with skills training. This approach is based on a "place then train" philosophy guided by the following six principles: (a) eligibility is based on the consumer's choice, (b) supported employment is incorporated with other treatments, (c) competitive employment is the goal, (d) a job search begins almost immediately after interest in employment, (e) follow-up support systems are continuous, and (f) the preferences of the consumer are essential. Thus with individuals with schizophrenia, the individual placement and support model has been shown to be more effective than the use of regular community employment agencies. Overall, supported employment has been shown to improve the employment outcomes of persons with severe mental illness, although many clients who receive this service still fail to achieve their vocational goals (McGurk & Mueser, 2004).

## Cognitive Remediation

Impairments in cognitive function are a core feature of schizophrenia. A range of studies strongly supports the association between cognitive deficits and functional outcomes such as work, social relationships, and independent living. To address the problem of cognitive impairment in schizophrenia, a range of cognitive remediation initiatives (i.e., cognition-enhancing and compensatory) developed for treatment of traumatic brain injury has been adapted and evaluated in patients with schizophrenia. These training initiatives involve either paper-and-pencil tests or individual computerized exercises that target specific cognitive skills (e.g., attention, memory, psychomotor speed) and require continuous training over a number of weeks and months. Whereas cognition-enhancing approaches train subjects with laboratory tasks in order to improve specific abilities in different cognitive domains (e.g., learning, attention, memory), compensatory approaches attempt to bypass cognitive deficits and teach strategies to compensate for them by relying on aids or similar processes. In a recent meta-analysis of cognitive remediation in schizophrenia, McGurk and colleagues (McGurk, Twamley, Sitzer, McHugo, & Mueser, 2007) reported moderate improvements ( $d = 0.41$ ) in some aspects of cognition, improvements that were consistent across reviewed studies. In contrast, there was considerable variability between studies on effects of cognitive remediation on social functioning. In other words, studies that implemented cognitive remediation alone did not report significant effects on social functioning ( $d = 0.05$ ), whereas studies that provided adjunctive rehabilitation programs did ( $d = 0.47$ ). What is most interesting is that, although improvement in cognitive functioning

in schizophrenia does not spontaneously improve functional outcomes, the empirical evidence suggests that it may improve response to psychiatric rehabilitation and vocational training.

## Summary

Results in areas of SST, CBT, family interventions, supported employment, and cognitive remediation are all promising. Outcomes in psychosocial treatment studies in schizophrenia are, as in pharmacotherapy research, highly variable. However, it needs to be emphasized that there is evidence that psychosocial treatments do enhance functioning beyond the improvements that result from medication alone. Much of the research has involved individuals with a more chronic course of schizophrenia, but many of these treatments are now being assessed with individuals at the first episode of schizophrenia. Future work will involve further testing of these interventions in early stages of schizophrenia to determine if they will improve the longer-term outcome of the disorder. Additionally, these treatments need to be assessed in combination to determine the cumulative effects. Finally, further research will begin to determine which treatments may be more effective for which people.

## Recommended Reading

- Addington, J. (2008). The promise of early intervention. *Early Intervention in Psychiatry, 1*, 294–307. A comprehensive review of current research in early psychosis, including current treatments and outcomes.
- Gumley, A.I., & Schwannauer, M. (2006). *Staying well after psychosis: A cognitive interpersonal approach to recovery and relapse prevention*. Chichester, England: John Wiley & Sons. A textbook describing CBT methods to treat individuals with psychosis and including approaches to prevent relapse.
- Kingdon, D.G., & Turkington, D. (2005). *Cognitive therapy of schizophrenia*. New York, NY: Guilford. A review of treatments used at the first episode of schizophrenia.

## Declaration of Conflicting Interests

The authors declared that they had no conflicts of interest with respect to their authorship or the publication of this article.

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# Ventral Hippocampus, Interneurons, and Schizophrenia: A New Understanding of the Pathophysiology of Schizophrenia and Its Implications for Treatment and Prevention

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## Abstract

Dysfunction within the dopamine system has been the predominant hypothesized cause of schizophrenia for some time; however, there is little anatomical or postmortem evidence showing that the roots of this disorder are to be found within the dopaminergic neurons. Instead, the dopamine system appears to be dysregulated due to pathological influences from other structures. Recent postmortem and imaging studies have looked to the hippocampus as a potential site of this pathology. Our studies using a developmental animal model of schizophrenia found hyperactivity in the hippocampus likely drives the disruption in dopamine system function. This overactivity appears to be due to the functional loss of short axon interneurons that control the activity of the primary output neurons of the hippocampus. These data suggest that a more effective treatment of schizophrenia may be to normalize hippocampal function rather than block dopamine receptors. Moreover, given the high sensitivity of the hippocampus to stress-induced damage and the fact that stress is a risk factor for schizophrenia, controlling stress in the pre-morbid state may be an effective preventative measure to circumvent the transition to psychosis.

## Keywords

dopamine, hippocampus, glutamate, schizophrenia, GABA, stress

Schizophrenia is a devastating disorder that affects more than 1% of the population, striking teenagers and young adults and causing severe impairment in cognitive and social functioning. For more than 40 years, the predominant model of schizophrenia has been based on dysfunctions of the dopamine system. This model was drawn from data showing that drugs that increase dopamine transmission tended to mimic psychosis in normal individuals and exacerbate psychosis in schizophrenia subjects; accordingly, the primary mode of treatment of schizophrenia was and continues to be the use of dopamine-receptor-blocking drugs (Grace, Bunney, Moore, & Todd, 1997). However, despite substantial efforts, a significant deficit in the dopamine system itself that was sufficient to cause such a widespread disruption of brain function has not been found. This led to the hypothesis that the disorder does not lie directly within the dopamine system but instead is due to an abnormal regulation of the dopamine system by other transmitters. The theory that function of the dopamine system is disrupted is reinforced by recent findings that, although baseline dopamine levels are not strongly elevated, amphetamine-induced dopamine release in humans (as determined by measuring the ability of

amphetamine-induced release of dopamine to compete with the dopamine antagonist raclopride for dopamine receptors) is significantly greater in schizophrenia patients than in individuals without the disorder, and the increased release is proportional to the ability of the amphetamine to exacerbate psychosis (Laruelle & Abi-Dargham, 1999). Nonetheless, the source of this dysregulatory event has remained in dispute.

## Glutamate, the Hippocampus, and Schizophrenia

Over the past decade or longer, interest in the role of glutamatergic systems in the pathophysiology of schizophrenia has grown. This interest has arisen because of several important findings. Although dopaminergic agents will exacerbate

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primarily the psychotic symptoms of schizophrenia, drugs that affect the glutamatergic system, such as phencyclidine, will evoke a more complete pathophysiological change, including negative symptoms (i.e., factors missing from a normal personality, such as social interactions and hygiene) and cognitive dysfunction. Moreover, administration of phencyclidine or ketamine to schizophrenia patients has been reported to evoke a condition that the patient cannot distinguish from a relapse (Javitt & Zukin, 1991). Thus, attention has been directed at the involvement of glutamatergic systems, with a strong emphasis on the prefrontal cortex. The prefrontal cortex attracted attention due to its role in executive function—a cognitive process in which schizophrenia patients exhibit substantial deficits (Goldman-Rakic, Castner, Svensson, Siever, & Williams, 2004). Thus, a role for the prefrontal cortex with respect to the cognitive deficits of schizophrenia has been established. However, the psychosis appears to involve a different system, and studies have identified correlates of hippocampal dysfunction in schizophrenia patients. Postmortem studies describe decreases in hippocampal volume in people with this disorder (Suddath, Christison, Torrey, Casanova, & Weinberger, 1990), and this initially led to the suggestion of a hippocampal deficit in schizophrenia. However, this perception was strongly altered by a series of metabolic imaging studies, in which investigators found hyperactivity in the anterior hippocampus (Malaspina et al., 1999) that appeared to correlate with psychosis. However, how this subcomponent of the hippocampus could relate to a disruption of the dopamine system was not clear, since this area does not project directly to the dopaminergic neuron group.

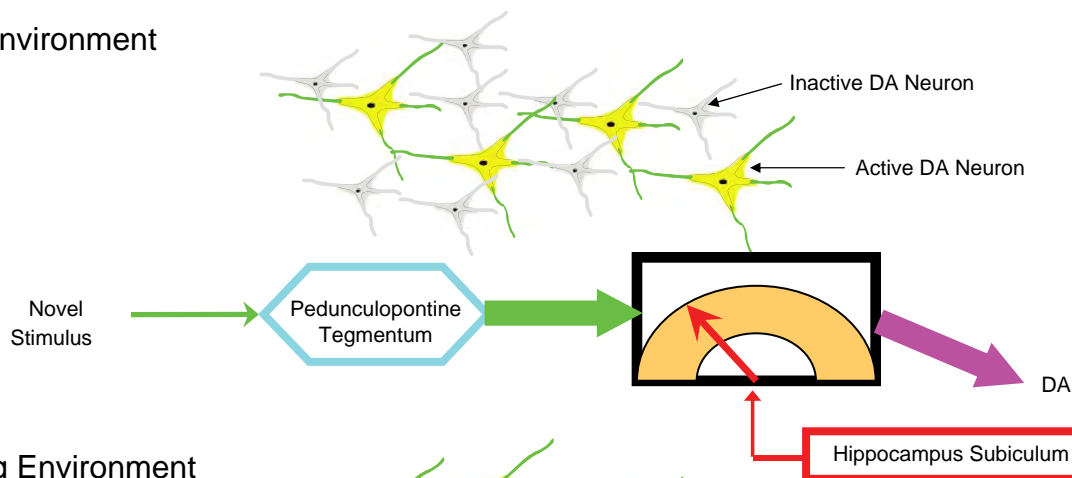
The mechanism by which the hippocampus can affect circuitry related to schizophrenia was uncovered using animal models. Schizophrenia is a genetically linked disease that, along with other risk factors, will lead to the onset of a psychotic break in the young adult. Therefore, the brain of the schizophrenia patient changes during the premorbid state to predispose the individual to psychosis. This was first modeled in animals by Lipska and Weinberger (Lipska, Khaing, & Weinberger, 1999). Using evidence of decreased hippocampal volume in schizophrenia patients, these investigators performed a ventral hippocampal lesion in a neonatal rat and found that, as an adult, the rat demonstrated behavioral disruptions consistent with what one would predict for a rodent model of this disorder. Using this lead, our lab developed another type of developmental disruption based in interference with DNA function. Thus, we injected the DNA methylating agent methyl-azoxymethanol acetate (MAM) into pregnant rats during gestational day 17 and examined the offspring as adults (Grace & Moore, 1998). Gestational day 17 was chosen because in the rat this would approximate the second trimester of humans—a developmental time point at which disruption can predispose the offspring to schizophrenia (Murray & Fearon, 1999). The adult offspring of the MAM-injected dams demonstrated a number of characteristics consistent with what one would expect for an animal model of schizophrenia, including thinning of limbic cortices with an increased cell

packing density (as reported in schizophrenia patients), disruption of prepulse inhibition of startle reflex (a measure of sensory gating), disruption of latent inhibition, altered executive function, and hyper-responsivity to both phencyclidine and to amphetamine (Lodge & Grace, 2007; Moore, Jentsch, Ghajarnia, Geyer, & Grace, 2006). Therefore, this model was consistent with schizophrenia in terms of both the genetic disruption and developmental origin and as validated by the anatomical disruptions, the behavioral alterations, and the pharmacological responses. This provided us with an effective animal model with which to examine the physiological properties of the neurons in this disorder.

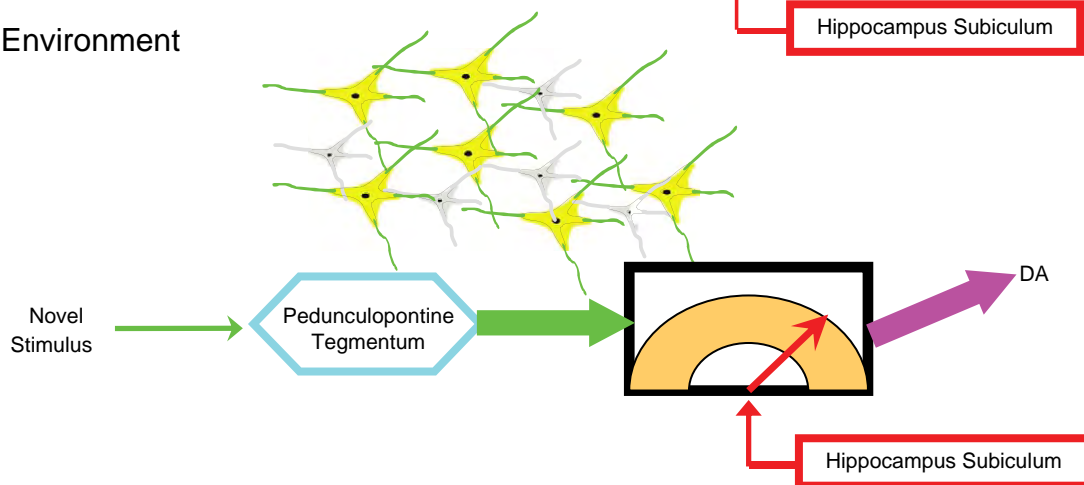
### **The Hippocampus Overdrives the Dopamine System in Schizophrenia**

As mentioned earlier, a consistent observation in schizophrenia patients is increased limbic hippocampal activity. Recordings in the ventral subiculum of MAM-treated rats (the rat limbic hippocampus that is analogous to the anterior hippocampal region in humans) revealed that the neurons were indeed hyperactive compared to controls. However, how this activity would translate into increased dopamine neuron responsiveness was unclear. Experiments found that activating the hippocampus subiculum using drugs produces a unique activity state of the dopamine system. The dopamine system has three activity states: The neurons can be firing or nonfiring (termed population activity), the neurons can be firing at different firing rates, or they can fire in a bursting or nonbursting pattern (Grace & Bunney, 1984). The burst pattern is considered to be the functionally relevant output of the dopamine neuron, since DA neurons will fire in bursts whenever an organism is presented with a behaviorally activating stimulus. Burst firing is driven by inputs from a brain stem region known as the pedunculopontine tegmentum—an area that is activated by various salient events. However, in order for a dopamine neuron to fire in bursts, it must first be spontaneously active; if it is not active, it cannot burst. Whether a neuron is active or not is dependent on its inhibitory input. The ventral pallidum is a brain region that has a potent and prominent GABAergic inhibitory influence over dopamine neuron firing; when it is active, dopamine neurons are in a nonfiring state (Grace, Floresco, Goto, & Lodge, 2007). When the hippocampus subiculum is activated using drugs, it drives firing in the ventral striatum, which in turn inhibits the ventral pallidum, thereby increasing the number of dopamine neurons firing spontaneously (Floresco, West, Ash, Moore, & Grace, 2003). Therefore, dopamine neuron activity is regulated by two processes: (a) a behaviorally salient signal that causes spontaneously firing dopamine neurons to burst fire; and (b) a modulatory “gain,” (i.e., how much the signal is amplified) whereby the hippocampus subiculum controls the number of dopamine neurons firing, and thereby controls the number of dopamine neurons that can be driven to burst fire by the behaviorally salient input from the pedunculopontine tegmentum (Lodge & Grace, 2006; Fig. 1).

## a. Benign Environment



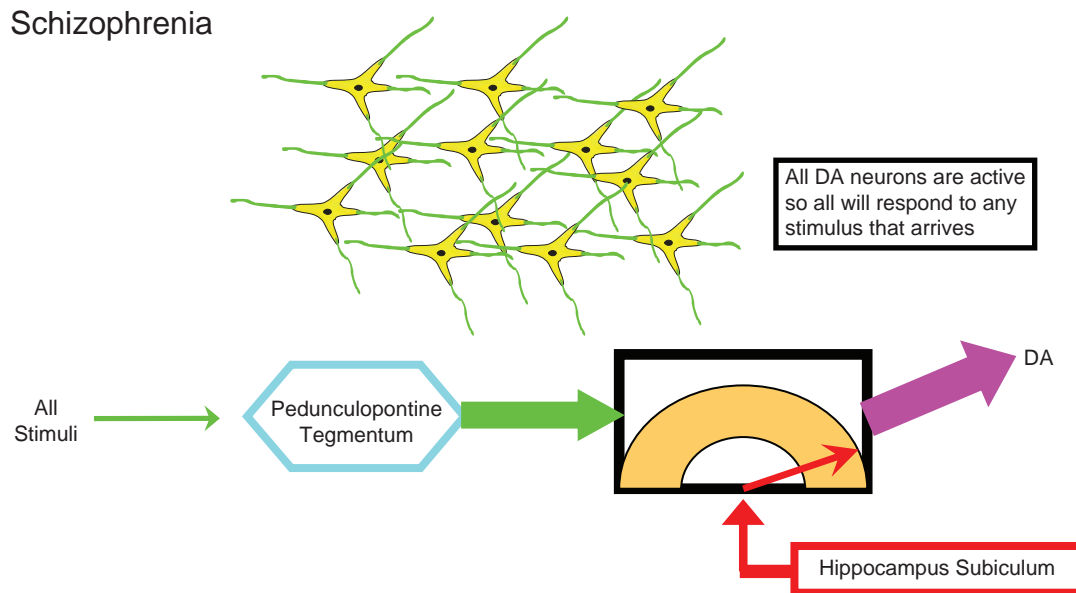
## b. Activating Environment



**Fig. 1.** Role of the hippocampus subiculum in controlling the relative amplitude of the dopamine (DA) response to a stimulus, depending on the environmental context. In a benign environment (a)—one in which a substantial threatening stimulus is unlikely to be encountered or in which the opportunity for a substantial reward is minimal—the hippocampus subiculum maintains a low level of DA neuron activation; that is, a small percentage of DA neurons are active. As a result, when a novel stimulus is encountered, the signal from the pedunclopontine can only signal an event (i.e., generate a burst of spikes) from the small number of DA neurons that are already active. As a result, the stimulus does not have a strong attribution of salience and does not require a vigorous response. But if the individual is in an environment that is highly threatening (b)—one in which failing to respond could have lethal consequences—or alternately is in an environment in which stimuli are likely to signal a strong reward (e.g., a casino or hunting for food), the hippocampal subiculum maintains the DA system in a highly active state. Now, when a novel stimulus is encountered, the system is positioned to assign a high level of behavioral salience and is prepared to respond appropriately.

What is the function of the ventral subiculum of the hippocampus, and how does the regulation of dopamine neuron gain contribute to this function? Various studies have shown that the subiculum plays a prominent role in context-dependent behaviors. The response that an organism makes in response to a stimulus depends greatly on the context in which the stimulus is presented. Thus, a stimulus (e.g., someone pointing at you) can have a very different interpretation in a rewarding context (e.g., a game show) or a threatening context (a courtroom). Moreover, context dependency plays an important role in responses to stress and in relapse to drug abuse, both of which are context-dependent phenomena. The ability of the subiculum to regulate dopamine system responsivity would therefore be consistent with its involvement in context-dependent information processing. Thus, in a benign environment in which

stimuli would not be predicted to have substantial salience, the subiculum would be less active, causing a smaller proportion of dopamine neurons to be spontaneously firing. If a stimulus is detected, the number of dopamine neurons that the brain stem pedunclopontine tegmentum will cause to burst fire would be smaller, and the dopamine response—and hence the attentional state—would be minimal. However, if the individual is in a highly threatening environment in which great attention must be directed toward any event, or alternately in a highly rewarding environment in which stimuli could indicate the presence of food source or a mate, the subiculum would be strongly activated, causing a large proportion of dopamine neurons to be firing spontaneously. Now if a salient stimulus is detected, there is a massive dopamine release and strong attention is directed toward the stimulus (Fig. 1).



**Fig. 2.** Overdrive of the dopamine system in schizophrenia. Due to failure of inhibition within the hippocampus subiculum, the subiculum keeps the dopamine (DA) neuron population in a constant active state independently of the environmental context. As a result, the DA system is positioned to respond maximally to any stimulus that arrives; when a stimulus is encountered, whether it is novel or even common in the environment, the massive DA signal generated tells the system that the stimulus has maximal behavioral salience and must be responded to immediately to ensure survival. This would result in inappropriate attributions being made to what normal individuals would consider irrelevant events (e.g., noise from the radio, random headlines, strangers talking to each other). The individual would be incapable of filtering truly salient events from those that have no significance.

What is the state of the dopamine system in the MAM model of schizophrenia? Recordings made in the dopamine neuron group reveal that, just as in the case of pharmacological activation of the ventral subiculum, there are more than twice as many dopamine neurons firing in the MAM-treated rat as in the control animal (Lodge & Grace, 2007). Therefore, the hyperactive ventral subiculum would cause the dopamine system to be in a hyper-responsive state (Fig. 2). Consequently, any stimulus that arrives, whether it is strongly salient or even nonsalient, could drive the dopamine system maximally. This would cause the individual to attend to all stimuli indiscriminately, with little ability to select between important and irrelevant stimuli, and thus with all events demanding maximal attention. Because the dopamine system is tagging all stimuli as highly relevant and of immediate overriding importance, the individual could be expected to interpret the stimulus in a manner that is consistent with this tagging. Such a condition could lead the patient to attribute to the signal excessive motivational salience (i.e., level of importance as it relates to the individual's well-being, which is suggested by Kapur to lead to psychosis (Kapur, 2003).

Therefore, hyperactivity in the limbic hippocampal regions could lead to the aberrant overdrive of the dopamine system, causing the individual to inappropriately attribute maximal salience to nonrelevant situations and events. But what is the source of this hyperactivity? Postmortem studies in humans have shown that the hippocampus and the prefrontal cortex are missing a critical neuronal component, the inhibitory interneurons that contain the peptide parvalbumin

(Zhang & Reynolds, 2002). Parvalbumin interneurons contain and release the inhibitory neurotransmitter gamma aminobutyric acid (GABA) that inhibits, or limits, the activity of pyramidal neurons, the neurons that provide the output of the hippocampus and prefrontal cortex. This class of parvalbumin interneurons is essential for the normal functioning of cortical structures; if these neurons are damaged, rhythmic activity in cortical structures is disrupted. In particular, there is a loss of evoked gamma rhythms, electroencephalogram rhythms measured over the cortex that are associated with stimulus recognition and higher cognitive functions. Gamma rhythms are known to be disrupted in schizophrenia. Indeed, our studies revealed that MAM rats also show a selective loss of parvalbumin-containing interneurons in both the hippocampus and the prefrontal cortex (Lodge, Behrens, & Grace, 2009). As a consequence of this loss, these brain regions in the MAM rats also show a disrupted gamma rhythm response to conditioned stimuli: A tone paired with a foot shock will evoke gamma rhythms in the ventral hippocampus and prefrontal cortex in normal rats, but in the MAM-treated rats the same conditioned tone fails to evoke gamma rhythms in the regions in which a loss of parvalbumin interneurons was found. This interneuron component is clearly critical for the normal rhythmic function of these circuits; if these neurons are damaged, then the normal gated rhythmic activity may be replaced by a nonspecific higher-frequency output, disrupting cognitive functions mediated by these regions and overdriving the dopamine system.

## Stress-Induced Hippocampal Damage: Insights Into Potential Methods for Schizophrenia Prevention

Among the risk factors that can lead to a transition to schizophrenia is stress. Exposure to stress is known to lead to relapse, and environmental or social stressors can be a precipitating factor in schizophrenia (Murray & Fearon, 1999). Our studies show that stress will cause an activation of the hippocampus and an overdrive of the dopamine system (Valenti & Grace, 2008). Thus, in a susceptible individual, stressors may reveal an underlying premorbid psychotic state. But more than this, stress in itself may lead to the pathophysiological changes in the brain that engender a psychotic break. Indeed, studies have shown a strong link between stress and hippocampal pathology, in that stressors are known to precipitate damage in the hippocampus. We have shown that the prefrontal cortex is an important area regulating stress responses. Activation of the prefrontal cortex will attenuate stress responses via inhibition of the amygdala (Rosenkranz & Grace, 2002), which we propose will enable an individual to regulate responses to stressors. However, if the prefrontal cortex is not sufficiently engaged, as may occur in schizophrenia, then the stress response would be unregulated. This could lead to a cascade of events whereby an underlying prefrontal dysfunction produces a pathologically large stress response to stimuli, which then could lead to hippocampal damage. The hippocampal damage would, in turn, lead to dysregulation of the dopamine system, which in itself would exacerbate the stressful condition (Thompson, Pogue-Geile, & Grace, 2004). It may be that the hippocampal damage caused by unregulated stressors is a primary pathophysiological factor leading to disruption of hippocampal interneuron function and consequently overdrive of the dopamine system. Indeed, studies by Johnstone (Johnstone, Lawrie, & Cosway, 2002) show that, among children at risk for schizophrenia, those showing the highest stress responses tended to be the ones that transitioned to schizophrenia. If this is indeed the case, then it is possible that transition to psychosis in susceptible individuals could be diminished by controlling this proposed unregulated stress response. This was tested in our animal model. Preliminary data show that, in rats that had been treated prenatally with MAM, administration of the anti-anxiety drug diazepam around puberty actually prevented the hyperdopaminergic state in adult animals (Fox & Grace, 2009).

### Summary

These data provide a pathophysiological basis for schizophrenia in humans: hippocampal damage leading to dysregulation of the dopamine system. In addition, it provides a potential explanation for hippocampal damage arising from a pre-existing pathology within the prefrontal cortex that may predispose an individual to stress-induced hippocampal damage. An extension of these studies would suggest that a more effective treatment for schizophrenia than the current dopamine-blocking antipsychotic drugs would be one that involves restoring inhibitory

function within the limbic hippocampus. On the other hand, if susceptible individuals can be identified—for example, based on abnormal stress responses in the genetically at-risk population—we may be able to circumvent the transition to schizophrenia merely by treating the stress condition that is already present (Thompson et al., 2004).

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- Grace, A.A., Floresco, S.B., Goto, Y., & Lodge, D.J. (2007). (See References). This paper provides an overview of the gain model and how it is related to regulation of behavior.
- Grace, A.A., & Sesack, S. (2010). The cortico-basal ganglia reward network: Microcircuitry. *Neuropsychopharmacology*, *35*, 4–26. This paper provides an overview of the circuitry of the cortex and basal ganglia as they relate to reward and affect, and how they affect behavior.
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### Declaration of Conflicting Interests

The author declared that he had no conflicts of interest with respect to his authorship or the publication of this article.

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# Social Factors in Schizophrenia

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## Abstract

One of the defining characteristics of schizophrenia is impaired social functioning. This was recognized a century ago in the earliest clinical descriptions of the disorder. Today, deterioration of social relations remains a hallmark of schizophrenia, with social isolation and withdrawal forming part of its clinical profile in the *Diagnostic and Statistical Manual of Mental Disorders*. But what kind of social problems do patients with schizophrenia have? When do they become apparent? Who is most affected? In this article, I present a brief review of what is currently known and highlight issues that still require attention from researchers. In addition to describing the social deficits associated with schizophrenia, I also consider some of the social consequences that may arise from these deficits. These consequences include social rejection, stigma, and problematic family relationships. I also consider the role of social-skills training in improving patients' general social functioning and the clinical course of their disease.

## Keywords

schizophrenia, social competence, social skill, stigma, expressed emotion

Navigating a complex social world is not easy. Perhaps we struggle to make small talk at a party, or to be appropriately assertive when we need to be. All of us make social errors from time to time. But the problems experienced by patients with schizophrenia go far beyond this. For many people with this disorder, understanding and functioning in the social world seems to demand skills that do not come naturally.

In this article I provide a brief review of social functioning in schizophrenia. *Social functioning* is a global term that reflects a person's ability to interact appropriately and effectively in the social world. This term is often used interchangeably with terms such as *social adjustment* and *social competence*. Within the literature, there is no standard use of these terms, and they will all be used interchangeably in this article. At a conceptual level, however, it may be helpful to think of social functioning as being dependent on social competence (or the ability to affect favorably one's social environment), which is itself dependent on such things as social knowledge and social skills, as well as on social judgment. As should be readily apparent, problems or deficits in any of these areas will have implications for social functioning more broadly.

The impairments in social functioning that influence the lives of patients with schizophrenia are well captured by one simple observation. The majority of patients with this disorder do not marry: Compared to people in the general population, patients with schizophrenia are more than six times more likely to remain unmarried (MacCabe, Koupil, & Leon, 2009). They are also much less likely to enter into meaningful long-term

relationships even when compared to people with other forms of severe mental illness such as affective psychosis.

*Social competence* is a term used by researchers to refer to how well a person is doing in day-to-day social situations. On measures of social competence, patients with schizophrenia fare poorly. Studies show that patients diagnosed with schizophrenia typically score lower than healthy controls or patients with other clinical disorders. Impaired social functioning relative to healthy controls is also found in patients who are experiencing their first episodes of the illness (Ballon, Kaur, Marks, & Cadenhead, 2007) or who are only beginning to show very early (premorbid) signs of the disorder. Interpersonal deficits have even been found to characterize individuals who are simply at heightened risk for developing the disorder but who are not in any way ill (Hans, Auerbach, Asarnow, Styr, & Marcus, 2000).

Global difficulties in social competence thus seem to be characteristic of those diagnosed with schizophrenia at all stages of the illness. Such difficulties may also predate any signs of illness, often by many years. Moreover, the social difficulties and deficits that are apparent early on resemble the difficulties and deficits that are characteristic of patients in the later stages of the illness.

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The fact that social problems predate the clinical onset of schizophrenia is important. It suggests that the problems in social functioning that are associated with schizophrenia are unlikely to be explained solely by the symptoms of the disorder or by the effects of medications and hospitalization. Were the latter the case, we would not expect social deficits to be apparent prior to the onset of the illness. Longitudinal research also suggests that these social impairments are stable over time. This further suggests that they are not a simple result of symptoms. On the contrary, Cornblatt et al. (2007) found that social impairments measured in the prodromal period (the period prior to the onset of psychosis) actually predicted the presence of psychosis 1 year later. This raises the possibility that impaired social functioning could be an early marker for schizophrenia.

### Social Skill Deficits

Underlying socially competent behavior are social skills. Social skills are the specific behavioral components or abilities that we need in order to communicate effectively or to be successful in social situations. They include verbal and nonverbal behaviors (such as body position or voice tone). Social skills include the ability to obtain or provide information and to express and exchange attitudes, opinions, and feelings. These skills, which people routinely use in their everyday conversations, encounters, and relationships, are thought to be critical to social competence.

The typical way to measure social skills in a research setting is via role-play. This might involve the patient interacting with a research assistant to simulate a situation such as buying an item in a store. Specific behaviors are then rated by trained assessors. Despite its "staged" nature, role-play appears to be a valid method for the study of interpersonal behavior. Behavior during role-play is strongly correlated with more global measures of social competence (see Mueser & Bellack, 1998).

Social-skills research, relying heavily on role-playing tasks, has provided useful information about specific deficiencies in the social functioning of schizophrenia patients. For example, in conversation, patients with schizophrenia show weaker verbal (e.g., clarity, negotiation, and persistence) and nonverbal skills (e.g., interest, fluency, and affect) than do nonpatient controls (Bellack, Sayers, Mueser, & Bennett, 1994). Compared with mood disordered or nonpatient controls they also tend to be less assertive when challenged. Moreover, although healthy and psychiatric controls tend to apologize or try to explain when they are criticized, people who suffer from schizophrenia are more inclined to deny making errors or simply to lie when challenged (Bellack, Mueser, Wade, Sayers, & Morrison, 1992). However, it is important to recognize that the overall social performance of people with schizophrenia is compromised more by mild impairments across a broad range of skill areas rather than by severe problems in one specific domain (see Mueser, Bellack, Douglas, & Morrison, 1991).

### Social Problem Solving and Social Understanding

In addition to having problems with specific social skills, patients with schizophrenia also show deficiencies in their social problem solving. When presented with a hypothetical interpersonal problem situation they are less able to conceptualize and generate effective solutions than are control participants. However, social problem-solving deficits, although characteristic of schizophrenia, are also found in patients with other disorders (e.g., bipolar disorder). In other words, social problem-solving deficits are not specific to schizophrenia (Bellack et al., 1994). It is very likely, however, that the factors underlying poor social problem solving in patients with schizophrenia (such as cognitive impairments) differ from those underlying impaired social functioning in patients with bipolar disorder, in which acute symptoms may play more of a role.

Schizophrenia patients also perform poorly on other social-cognitive tasks (Hooker & Park, 2002; Pinkham & Penn, 2006). They have difficulties recognizing faces they have seen before and have problems correctly identifying the emotional expressions of others. They are also impaired relative to controls when it comes to recognizing emotion conveyed in speech. Patients with schizophrenia also do less well on tests that tap social knowledge. Compared to healthy controls and to patients with other forms of severe mental illness they fail to spot subtle (or not so subtle) social hints. They also are less able to recognize when someone has made a social error or faux pas (Zhu et al., 2007). Stated simply, patients with schizophrenia seem relatively less aware of the rules that govern social situations and that facilitate smooth and effective interpersonal exchanges.

### Gender and Social Functioning

No review of social functioning in schizophrenia would be complete without consideration of gender issues. A wealth of evidence shows that female schizophrenia patients have a milder range of interpersonal problems and are characterized by better social functioning than are males with the disorder (see Hass & Garratt, 1998). In a representative study, Andia et al. (1995) found that, compared to men, women with schizophrenia were more likely to have been married, to be able to live independently, and to be employed, despite having similar symptom profiles. Moreover, females in this study had higher levels of social functioning even though they were being maintained on lower doses of antipsychotic medication than the male patients.

Role-play studies assessing social skills reveal similar findings. Mueser and his colleagues (Mueser, Bellack, Morrison, & Wade, 1990) reported a clear advantage for female patients across a range of different measures. Although they did not differ from male patients with respect to their symptomatology, females with schizophrenia were more skilled in how appropriate the duration of their speech was (very short or very long responses were rated less favorably), their turn-taking abilities

during conversations, aspects of their verbal content in specific role-play scenarios, and their overall social skills. There is also evidence that gender differences in social skill may be specific to schizophrenia. In the study just described, gender was unrelated to social skill in both the affective control group (people with mood disorders) and the healthy control group.

### **Social Skills, Stigma, and Rejection**

People with schizophrenia are often stigmatized and avoided by others. Societal misinformation about schizophrenia undoubtedly plays a role in contributing to this. However, it is also reasonable to expect that some of the social deficits that characterize people with this disorder create difficulties for them and for the people with whom they interact. Over time, this may lead to increased negativity, social distance, and rejection by others.

In an empirical demonstration of this, Nisenson, Berenbaum, and Good (2001) asked student research assistants (all of whom had been selected because they had pleasant dispositions) to form brief friendships with patients who suffered from schizophrenia. Over the course of the study, which lasted 2 weeks, the behavior of the research assistants changed. Most notable was that the amount of negativity that the students showed toward the patients increased considerably.

But do poor social skills explain why people tend not to want to marry, befriend, or employ someone who has schizophrenia? At least in part, the answer appears to be yes. Penn, Kohlmaier, and Corrigan (2000) videotaped clinically stable outpatients with schizophrenia during a 3-minute role-play conversation with a confederate. Trained research assistants then rated the patients' social skills, noting such things as how well they made eye contact, how clearly they spoke, and whether their conversation was interrupted by pauses or stutters. The videotaped role-plays were then shown to 41 undergraduates, who were asked how much social distance they would want to have from each of the patients they had seen. The best predictor of the students expressing a desire to avoid interacting with the patient in the videotape was how "strange" the patient was rated as being. This, in turn, was predicted by the patient's overall social skills. In short, what this study demonstrates is that people who have poor social skills seem strange to us; and when we regard people as strange we tend to want to avoid them.

### **Families Coping With Schizophrenia**

If brief interactions with schizophrenia patients present challenges for student research assistants, what is it like to live with someone who suffers from this disorder? Many family members of patients confront the symptoms of schizophrenia and the social deficits associated with it on a daily basis. Although some relatives seem able to respond quite well to the inevitable challenges that this creates, high levels of family tension are much more typical.

Expressed emotion (EE) is a relational variable. It provides a measure of the family environment and reflects high levels of criticism, hostility, or emotional overinvolvement (intrusive or overprotective behaviors and attitudes) toward the patient. Many studies have demonstrated that patients with schizophrenia are more than twice as likely to experience a symptomatic relapse if they live in a high-family-EE environment (see Hooley, 2007). But why do high-EE attitudes develop? In many cases, high levels of EE may be a natural response to the stress of prolonged caretaking and continued exposure to the social or behavioral disturbances of the patients themselves (Hooley & Gotlib, 2000). EE levels do seem to increase in families in which patients have been ill for longer periods of time (McFarlane & Cook, 2007). Nisenson et al.'s (2001) findings of increased negativity in the students who visited schizophrenia inpatients also lends credence to this notion that criticism and hostility might develop, at least in part, as a consequence of continued interaction with a disturbed patient.

### **Does Social-Skills Training Improve Social Functioning?**

There is reason to believe that the social-skill deficits of patients with schizophrenia compromise their overall social competence, make them appear strange to others, and contribute to the social rejection and stigma associated with the disorder. To the extent that this is true, social-skills training might be expected to provide a variety of benefits.

Social-skills training programs are designed to teach new skills and improve overall interpersonal functioning. Complex sequences of social behaviors (such as starting a conversation with a new person or interviewing for a job) are reduced to their component parts. These parts are further broken down into even more basic elements (such as eye contact, rate of speech, or turn taking). Patients then learn to combine skills in a smooth and fluid manner into more elaborate sequences of behaviors such as those involved in being assertive. All of this is accomplished through goal setting, instruction, rehearsal, corrective feedback, and practice homework assignments.

A recent meta-analysis suggests that social-skills training significantly improves the social functioning of patients with schizophrenia in a number of important ways (Kurtz & Mueser, 2009). As would be expected, patients who receive social-skills training demonstrate considerable gains in such skills. Patients also show improvements on measures of overall social functioning and independent living. Social-skills training also has a modest effect on reducing rates of relapse. This could be because social-skills training improves patients' abilities to cope with stress. It is also possible that social-skills training reduces the overall level of stress in the family and reduces potential targets for criticism.

### **Summary and Future Directions**

Difficulties in social functioning characterize patients with schizophrenia at all stages of the illness. Social difficulties

frequently predate the onset of the illness and remain even during periods of symptom remission. They can also be observed in those who are at potential risk for developing schizophrenia. Although there is considerable individual variation in the nature and extent of social difficulties, males are especially likely to experience problems.

The symptoms of schizophrenia no doubt compromise social functioning to some degree. However, there is reason to believe that the difficulties in relating that are experienced by many schizophrenia patients are important in their own right. We do not know yet why they are such a central feature of the illness. They may, at least in part, be related to neurocognitive deficits associated with schizophrenia, particularly those involving attention/vigilance and aspects of memory. Neurocognitive difficulties may also underlie problems in social cognition. Understanding how social and nonsocial cognition are related is now an important new area of research. We also need to learn more about how the pattern of associations between these domains and social functioning is influenced by such factors as gender and symptoms.

The challenges that schizophrenia patients experience when it comes to relating to and understanding the social world likely limit the extent to which they can develop supportive interpersonal relationships. People with schizophrenia do not pick up on the kind of social hints that are obvious to most people. They also tend to be emotionally unexpressive and hard for others to "read." Together, these and other characteristics may conspire to make interactions with schizophrenia patients less rewarding for those who live or work with them. This contributes to stigma. The fact that interactions with patients with schizophrenia are difficult and less rewarding for others is also problematic because schizophrenia patients, like many other patients, are at higher risk of relapse when they live in emotionally stressful home environments. Helping patients improve their social skills and helping families cope with the stress of living with a person with schizophrenia is therefore important. Although treatment developments are needed in many areas, research suggests that older patients benefit less from social-skills treatments than do younger patients (Kurtz & Mueser, 2009). Refining treatments to improve clinical outcomes for older patients is thus a high priority.

We also need to learn more about the social difficulties that are specific to schizophrenia. Marked difficulties in interpersonal relating are characteristic of other clinical conditions such as Asperger's syndrome. Comparing patients with these disorders would be informative because, like schizophrenia, Asperger's syndrome has its origins in neurodevelopment. The two disorders are also believed to have certain candidate genes in common. Understanding more about the similarities and differences between patients with these clinical conditions may advance knowledge about factors that might underlie deficits in social skills and social understanding more broadly. Finally, although research is now moving in this direction, the neuroanatomical correlates of social-skill and social-competence deficits in schizophrenia remain essentially unexplored. Although we have come a long way, answers to some of the

most pressing questions in the area of interpersonal functioning and schizophrenia still await future systematic investigation.

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## Declaration of Conflicting Interests

The author declared that she has no conflicts of interest with respect to her authorship or the publication of this article.

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# Schizophrenia Course, Long-Term Outcome, Recovery, and Prognosis

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## Abstract

Our 26-year longitudinal study and other longitudinal studies confirm older views that outcome for schizophrenia, while showing some variation for different schizophrenia patients, is still significantly poorer than that for other psychiatric disorders, with the exception of the dementias. Our research leads us to propose that risk factors, either stress related or those related to vulnerability to psychosis, account for the episodic course of periods of recovery followed by periods of recurrence that is experienced by most schizophrenia patients. These risk factors interact with personality, temperament, and cognitive traits that, while not causing psychosis, influence its course. It is these interactions that account for the heterogeneous outcome trajectories of different subgroups of people with this condition. Our research and that of others has focused on the contributions of these risk factors, such as vulnerability to trait anxiety, poor developmental achievements before the illness, personality traits such as locus of control, cognitive styles, neurocognitive impairments, length of untreated psychosis, and several others. Despite the proven efficacy of antipsychotic medications over the short term, there is a subgroup of schizophrenia patients who, a few years after the acute phase, function adequately or experience periods of recovery for a number of years, without treatment.

## Keywords

schizophrenia, prognosis, longitudinal research, outcome, recovery

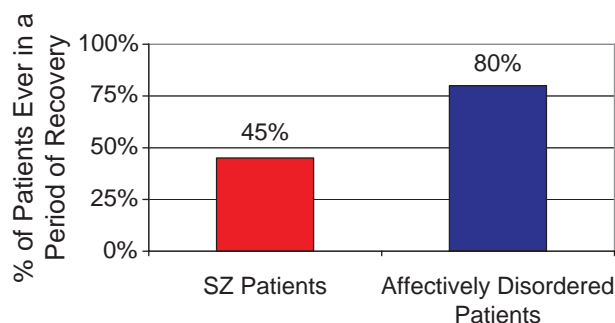
Long-term outcome in schizophrenia and whether recovery is possible have long been central issues in theoretical views of the nature of the disorder (Lieberman & Kopelowicz, 2002; Harrow, Grossman, Jobe, & Herbener, 2005; Jobe & Harrow, 2005; McGlashan, 1988, Silverstein & Bellack, 2008). Central to ideas about the nature of schizophrenia and about its definitional boundaries is its very poor long-term course. Emil Kraepelin originally viewed this disorder as involving a progressive downhill course like forms of dementia (e.g., Alzheimer's) but beginning in late adolescence or young adulthood; he thus called it *dementia praecox* ("premature dementia"). Eugen Bleuler was slightly more optimistic. Although he recognized that some of the symptoms in the disorder are chronic, he did not believe that patients always show a downward course; he noted that chronic symptoms are often less severe after the initial acute phase. Bleuler renamed the disorder *schizophrenia* to reflect his observations that connections between ideas are often "split" (i.e., loose associations). A series of modern follow-up studies, including our own longitudinal research and that of others, has suggested that despite the advent of the modern era of psychopharmacological treatment and psychosocial rehabilitation, schizophrenia is still a diagnosis with a relatively poor outcome (Harrow, Sands, Silverstein, & Goldberg, 1997; Harrow, Jobe, & Astrachan-Fletcher, 2008; Harrow, McDonald, Sands, & Silverstein, 1995; McGlashan, 1988; Tsuang, Woolson, &

Fleming, 1979); however, some recent studies show that modern treatment methods may produce some limited improvement in disease course, as well as periods of complete recovery for a number of patients with schizophrenia (Jobe & Harrow, 2005; Harrow et al., 2005; Lieberman & Kopelowicz, 2002; Silverstein & Bellack, 2008).

Thus, when we look at the recent literature, we find both promising and disappointing features associated with outcome and recovery in schizophrenia. On the negative side, our longitudinal research from the Chicago Followup Study (Harrow et al., 2005; Jobe & Harrow, 2005) and the research of Tsuang et al. (1979), McGlashan (1988), and the World Health Organization Study (Harrison et al., 2001), as well as others who also use control groups of other severely disturbed patients, provide very strong evidence that, despite modern treatment, the course and outcome for schizophrenia patients are poorer than those for other psychotic and nonpsychotic patients. A consistent feature during early phases (the first 10 to 15 years) is more recurrent psychopathology for many patients. Even after the first 10 years,

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**Fig. 1.** Cumulative percent of patients with schizophrenia (SZ) versus those with affective disorder ever experiencing a period of recovery (seven follow-ups over 26 years). Recovery is defined as a period of 1 or more years with no positive symptoms or negative symptoms, no psychiatric hospitalizations, adequate socialization, and at least half-time instrumental work functioning.

outcome and the potential for periods of complete recovery are poorer for schizophrenia than they are for other psychotic and nonpsychotic disorders. The majority of patients with schizophrenia are vulnerable to recurring positive symptoms, such as psychosis and/or disorganized thinking/thought disorder and also to negative symptoms (i.e., reduced or flattened affect, reduced or impoverished speech, and reduced or retarded motor movements), with more persistent symptomatic and functional impairment over time than is found in other types of psychotic patients (Harrow et al., 2004; Harrow et al., 2008; Herbener & Harrow, 2004). The functional impairment—particularly work disability (in regard to obtaining or maintaining employment)—is considerable (Harrow et al., 2004; Harrow et al., 2005; Herbener & Harrow, 2004).

On the positive side, with modern-day treatment during the acute phase, over 40% of patients with schizophrenia will later show one or more periods of global recovery (defining recovery as a period of 1 or more years with no positive symptoms or negative symptoms, no psychiatric hospitalizations, adequate socialization, and at least half-time instrumental work functioning). Rather than viewing recovery as a static state, one should view it in terms of periods of recovery; partly depending on the extent of a particular patient's underlying biological vulnerability to psychosis, these periods may last for a relatively short period, or they may last over 10 years or even for a lifetime.

Figure 1 shows results on periods of recovery in patients hospitalized with schizophrenia and mood disorders whom we have followed up seven times over 26 years. For many of the more resilient and less vulnerable schizophrenia patients, the disorder is not chronic and continuous but, rather, is episodic, although episodes are still generally more frequent, more severe, and last longer than those of other major disorders.

We have looked at our longitudinal data in terms of a stress-diathesis model in which the internal biological diathesis component plays a dominant role in vulnerability to future potential psychopathology. In this model, stress is viewed as external or environmental factors that can create

anxiety in the particular person; a diathesis is a constitutional or biological predisposition to certain types of psychopathology, and vulnerability is viewed in terms of areas of greater internal and/or external susceptibility to various types of psychopathology. Using this model, patients with schizophrenia (a) have an underlying biological vulnerability to psychosis, negative symptoms, and poor outcome; and (b) this vulnerability is accentuated by a large group of internal and external risk factors (e.g., vulnerability to anxiety, external locus of control, low self-esteem). The combination of these risk factors with other unfavorable cognitive biases and deficits (e.g., jumping to conclusions, externalizing attributional biases, poor understanding of the intentions of other people) emphasized by Garety and Freeman (Garety, Kuipers, Fowler, Freeman, & Bebbington, 2001), and by Bentall and others can dramatically increase these patients' chances of expressing overtly their underlying biological/genetic vulnerability to psychosis. A combination of some of the above factors, in a patient with greater vulnerability to psychosis, can sometimes result in new acute episodes.

Other aspects of a model of course and outcome in schizophrenia involve a neurodevelopmental view in which poor pre-morbid developmental achievements, poor prognostic features, and neurocognitive impairment strongly increase the recurrence and persistence of later positive and negative symptoms and produce poorer global course, poorer outcome, and lower chance of periods of recovery years later (Harrow et al., 2005; Zigler & Glick, 2001).

### Model of Outcome in Schizophrenia

On the basis of our data and other data reported previously, one could propose a model in which, with modern-day antipsychotic medications to shorten periods of extreme psychosis, virtually all patients with schizophrenia improve some after the original acute phase of hospitalization. After the acute phase, a small- to moderate-sized subsample of schizophrenia patients (25%–35%) show chronic or continuous psychotic symptoms and/or show other chronic symptoms that last for many years (Harrow et al., 1997, Harrow et al., 2008). However, for a moderate to large percentage of schizophrenia patients (over 50%), the disorder is not chronic but, rather, is characterized by episodic periods of symptoms, often with continual or chronic malfunctioning, adjustment difficulties, and some impairment in functioning between episodes (Harrow & Jobe, 2010).

### Antipsychotic Medications: A Subgroup of Patients With Schizophrenia Who Leave Treatment

At this point, another important subgroup of schizophrenia patients that is often ignored in treatment studies should be mentioned. Our longitudinal studies have found evidence of a subgroup of 20% to 35% of patients with schizophrenia who, after showing signs of better functioning and partial or global recovery for a period of time, have gone off or been taken off

antipsychotics or have left treatment (Harrow & Jobe, 2007). Many schizophrenia patients from this subgroup continue to function well for a number of years without treatment. This would suggest that not all schizophrenia patients need to be on antipsychotic medications throughout their lives (Harrow et al., 2005; Harrow & Jobe, 2007; Bleuler, 1978). Since many patients from this subgroup of patients are not in treatment, this subgroup, many of whom are experiencing periods of recovery, are almost never included in double-blind drug–placebo studies. Findings by our group, by M. Bleuler (1978), and by Fenton and McGlashan (1987) agree that some unmedicated schizophrenia patients are doing well. Also, data from the longitudinal studies of the World Health Organization (WHO; Harrison et al., 2001) and of R. Bland would support the conclusion that not all schizophrenia patients need to be treated with antipsychotics throughout their lives. This in no way detracts from the strong evidence of some improvements with both psychopharmacological, psychological, and psychosocial treatment of schizophrenia over the short term of months to a few years.

### Other Aspects of Outcome in Schizophrenia

Many long-term follow-up studies in both the United States and Europe suggest that after about 5 years, the symptom picture in schizophrenia becomes stable and does not worsen. Other data suggest that the overall picture for some schizophrenia patients could improve as they get older, although this latter possibility still awaits solid research on those patients' longitudinal course. Despite the fact that a plateau or stabilization process appears to occur, this does not imply a single trajectory for the later course of the illness. Rather, as with many other disorders, there can be a high degree of divergence or heterogeneity among individuals. Also, this stabilization process does not protect against a relatively high mortality rate for schizophrenia (Jobe & Harrow, 2005).

Overall, the lifespan for schizophrenia patients is shortened by 9 years or more. Some, but not all, of this is accounted for by a high suicide rate during the first 10 years of the disorder for middle-socioeconomic-class male schizophrenia patients (Harrison et al., 2001). People with other major mental disorders and with substance abuse also have a shorter life expectancy.

Cultural variables also affect long-term follow-up. The WHO study followed a large sample of culturally diverse subjects for up to 15 and 25 years (Harrison et al., 2001). Surprisingly, outcome for the patients with schizophrenia was better in developing countries than it was in developed countries. This finding could be influenced, in part, by greater acceptance of schizophrenia by patients' families in developing countries; the mechanism could be less anxiety and stress, although many other as-yet-unknown factors are probably involved.

### Risk and Protective Factors for Course and Outcome in Schizophrenia

In addition to genetic/biological factors that contribute to a poor outcome, there are many other patient-centered factors

that contribute substantially. These include poorer cognitive skills, longer duration of untreated psychosis, less continuity of treatment, substance abuse, family overinvolvement with high expressed emotion, higher vulnerability to trait anxiety (Harrow et al., 2008; Walker, McMillan, & Mittal, 2009), poorer developmental achievements prior to becoming ill (Zigler & Glick, 2001; Harrow & Jobe, 2007), and other important developmental variables, as well as unexpected, unpredictable life events.

In addition, older research by Vaillant (1978) and by J. Stephens, our own group, and others produced empirical evidence that an important series of variables predict subsequent poor prognosis in schizophrenia. These variables include indicators such as lack of acute onset, no precipitating stress at index hospitalization (index refers to early hospitalization, when patients first begin to be studied), poor work and social adjustment before index, absence of depressive symptoms, no preoccupation with death, no guilt, no confusion, being unmarried, and having blunted affect. Modern, narrow definitions of schizophrenia (e.g., *DSM-III-R* and *DSM-IV*) have already incorporated in the diagnostic criteria for schizophrenia some of these prognostic variables that predict unfavorable outcome. However, despite this, some of these classical prognostic variables that have not been incorporated into modern narrow criteria for schizophrenia still have negative prognostic significance.

### The Role of Anxiety

We view the issue of risk and protective factors in terms of the stress-diathesis vulnerability model. One example is a combination of high internal vulnerability to psychosis and vulnerability to anxiety (as part of the diathesis) coupled with the experience of external stress. Stress-related anxiety as a factor presents some complexity since the difficulty is a function of both external stress and a person's biological vulnerability to anxiety. Thus some people get "anxious" much more quickly than others, because of a higher vulnerability to anxiety, and also the biological system (the hypothalamic-pituitary-adrenal [HPA] axis) of some patients with schizophrenia may produce more negative effects on other functions when those patients get anxious. The research and reviews of a number of major investigators have emphasized the importance of anxiety and stress as potential factors involved in the genesis and maintenance of psychosis in vulnerable people (Corcoran et al., 2003; Harrow et al., 2008; Docherty et al., 2009; Walker et al., 2009).

Our multiple follow-up research design has allowed us to begin to explore this issue on a longitudinal basis. Our research using standardized anxiety scales suggests that some, but not all, patients with schizophrenia are vulnerable to high anxiety. Our longitudinal data suggest high anxiety is one prominent risk factor increasing the chances for more sustained and chronic pathology in patients who are biologically vulnerable to psychosis and schizophrenia (Harrow et al., 2008).

While our anxiety data suggest that not all patients with schizophrenia are vulnerable to anxiety, our research has indicated that those schizophrenia patients with greater vulnerability to anxiety are more likely to have a poorer or more chronic course. Looked at from this perspective, anxiety is not a specific diathesis for schizophrenia, but it is a nonspecific risk factor that increases vulnerability to psychosis in already-vulnerable patients and that can influence overall course and outcome in schizophrenia in a negative direction.

It has been proposed that the biological response to stress, which is linked to the level of the hormone cortisol and is regulated by the HPA axis, can trigger a downstream cascade of neurochemical events—events that could exacerbate psychosis through several neural circuits as well as lead to hypersensitivity of the D2 dopamine receptor, as noted by P. Seeman and other major investigators (Corcoran et al., 2003; Walker et al., 2009). A high vulnerability to anxiety combined with external stress, high cognitive arousal, and other genetic risk factors can trigger excess HPA axis and neurochemical activity, leading to psychosis in biologically vulnerable patients. The longitudinal data on anxiety also could be consistent with the view, advanced by some, that the release of dopamine (a neurotransmitter that is one factor playing an important role in the emergence of psychosis) is differentially increased by exposure to stress and anxiety in schizophrenia. Our findings are also consistent with other proposed mechanisms that may increase vulnerability to anxiety in schizophrenia patients, such as increased presynaptic striatal dopamine release during stress and increases in aberrant salience, which refers to the attribution of undue importance to insignificant stimuli and/or emotions (Howes & Kapur, 2009). British social psychiatrists have found evidence, replicated many times, that schizophrenia patients tend to have poorer outcomes when living in family environments with high expressed emotion (EE), in which key relatives are critical of or hostile to the patient or are emotionally overinvolved with him or her. Our group and several other groups link the poor outcome to the patients living in a high-anxiety environment in which they sense their family's unhappiness about them and, as a result, continuously feel under pressure and anxious (Docherty et al., 2009; Harrow et al., 2008). Other factors are probably also involved.

### Other Risk and Protective Factors

In our studies of the role of various personality dimensions, we have looked at a number of personality factors, including locus of control (LOC). The concept of LOC, originally proposed as part of Rotter's social learning theory, is assessed by asking people whether they believe that events in their lives result from their own efforts, skills, and internal dispositions (internal control). The alternative to this belief is that events result from external forces such as luck, chance, fate, or powerful others (external control). Our data indicate that external LOC is not specific to schizophrenia (Harrow, Hansford, & Astrachan-Fletcher, 2009). However, patients with psychosis (including schizophrenia patients) and also those with depression tend to

be more external. We also have looked at our longitudinal data to see if being internal predicts recovery (Harrow et al., 2009). Our results indicate that internality is significantly associated with recovery in schizophrenia.

The data could be interpreted as suggesting a possible reciprocal effect between recovery and increased internality on LOC (internal attitudes increase the chances of recovery, and successful recovery encourages a view of positive events such as recovery as due to one's own efforts and skills). This finding would fit within the results of Strauss and Carpenter's concept of an open-linked system (Strauss & Carpenter, 1972). This refers to the linkages between predictor variables and outcome variables in which some predictor variables are more highly correlated with themselves at outcome than with other predictor variables at outcome when outcome is assessed over multiple years. It is an open-linked system in the sense that outcome variables are moderately intercorrelated, and no one variable comes to dominate the others.

Longitudinal research on outcome has challenged some seemingly promising formulations on the background basis of recovery and of psychosis in schizophrenia. Thus, research indicates that a multitude of different complex factors, rather than only one factor, influence the behaviors associated with psychosis, outcome, and recovery.

### Overview

Overall, longitudinal research on outcome has substantially increased our knowledge of schizophrenia and provided new leads concerning issues that need further study. As far as our current knowledge of course and outcome in schizophrenia, the research has provided data showing both negative and positive aspects concerning their outcome. On the negative side, the long-term studies that compare schizophrenia patients with other types of patients have produced data indicating that, even with modern-day treatment, patients with schizophrenia as a group show poorer outcome than patients with other types of psychiatric disorders; in this sense, schizophrenia is a poor-outcome disorder. On the positive side, there is overwhelming evidence that very few patients with schizophrenia show a progressive downhill course and that a moderate-sized subgroup of more resilient schizophrenia patients show intervals or periods of recovery. However, still open to question are the percentage of patients with schizophrenia who have the potential for long-term recovery, the factors involved in facilitating recovery, and how (and whether) those factors fit together (Harrow et al., 2005).

We now have a much better understanding of how the course of schizophrenia differs from that of other disorders, and we have been alerted to the danger of suicide and early death in schizophrenia. We have also been alerted to potential problems in the management and treatment of schizophrenia, as well as to the possibility of intervals or periods of recovery. The heterogeneity that has been found in schizophrenia should alert us to explore in greater detail the internal characteristics that lead to different individuals having different outcomes and to the factors involved in the multiple different variables that can lead to the

poorer outcome of patients with schizophrenia. This level of complexity in outcome of schizophrenia supports the view that therapies need to be varied and evidence based (Silverstein, Spaulding, & Menditto, 2006). Finally, whether antipsychotic medication should be used continuously beyond 2 years from the initial acute episode is also a question that needs to be answered based on the evidence, given the potential of failure of antipsychotic drugs, breakthrough hypersensitivity psychosis (where D2 dopamine receptors become hypersensitive to compensate for their persistent blockade by antipsychotic medications taken by the patient), and rebound psychosis—factors that may contribute to the poorer outcome of schizophrenia patients on antipsychotic medication than of those not on medication over the longer term (Chouinard & Chouinard, 2008).

Have modern-day treatments changed the course or prognosis of schizophrenia in the last 60 years? The data on long-term course and treatment clearly indicate that, largely as a result of antipsychotic medications, the flagrant psychosis that is often present at the acute phase has been shortened for many patients. Partly as a result of antipsychotics and other modern treatments, and partly as a result of changes in social attitudes and outlooks, long-term hospitalization has been discouraged. Outcome during the first 2 years after the acute phase is also probably somewhat better than before. The improvement in outcome provides a more favorable therapeutic framework for starting rehabilitation. Numerous rehabilitative efforts have been attempted (including supported employment), with a number showing some limited promise. However, beyond shortening the acute phase, reducing long-term hospitalization, and reducing the chances of remission during the first few post-hospital years (all important gains), researchers still disagree on the extent to which the long-term outcome of schizophrenia has been improved.

### Recommended Reading

- Harrison, G., Hopper, K., Craig, T., Laska, E., Siegel, C., Wanderling, J., et al. (2001). *British Journal of Psychiatry*, 178, 506–517. A study describing the World Health Organization's longitudinal research on outcome in a large sample of schizophrenia patients from diverse countries, emphasizing different aspects of outcome and mortality.
- Harrow, M., Grossman, L., Jobe, T., & Herbener, E. (2005). (See References). A longitudinal (15 years) study providing data on periods of recovery in schizophrenic patients, comparing those patients to other psychotic and nonpsychotic patients, and also providing data on the issue of recovery in unmedicated patients and on whether schizophrenia is a chronic or continuous disorder.
- Jobe, T., & Harrow, M. (2005). (See References). An article reviewing longitudinal studies of outcome in schizophrenia and discussing the methodological strengths and weaknesses of each study design.
- McGlashan, T. (1988). A selective review of recent North American long-term follow-up studies of schizophrenia. *Schizophrenia Bulletin*, 14, 515–540. A classic paper providing a strong review of the major longitudinal studies from North America prior to 1988 and containing a very good, thoughtful discussion of some of the important issues related to course and outcome in schizophrenia.
- Walker, E., McMillan, A., & Mittal, V. (2009). (See References). A compelling overview of one of the most robust models of stress-induced vulnerability to psychosis in schizophrenia research, with an important discussion of how antipsychotic medication may affect this model, which involves the HPA axis and its effect upon the hippocampus.

### Declaration of Conflicting Interests

The authors declared that they had no conflicts of interest with respect to their authorship or the publication of this article.

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# New Opportunities in the Treatment of Cognitive Impairments Associated With Schizophrenia

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## Abstract

The cognitive deficits so characteristic of patients with schizophrenia are largely responsible for the poor functional outcome apparent in this patient population and are not ameliorated by existing antipsychotic drugs. The critical unmet need for treatments for the cognitive impairments associated with schizophrenia has been addressed in a series of federally funded initiatives, beginning with Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) and continuing with Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia (CNTRICS). As reviewed here, these programs have set the stage for an expansion of basic and clinical cognitive neuroscience research to support the discovery and development of cotreatments to be used in conjunction with antipsychotic medications in the treatment of specific cognitive deficits in patients with schizophrenia.

## Keywords

Schizophrenia, MATRICS, TURNS, CNTRICS, cognition, CIAS

The group of schizophrenias has long been among the most challenging mental disorders to understand and treat. The advent of antipsychotic drugs in the 1950s brought about a revolution in the care and treatment of patients with schizophrenia, profoundly reducing the number of patients who are chronically institutionalized. Nevertheless, the functional outcome of patients treated effectively with antipsychotic medications remains far less than adequate, with few patients achieving successful reintegration into the workplace and society. Cognitive impairments are present at the onset of the illness, persist throughout the lifespan, are strongly associated with poor outcome and functional disability, and are largely refractory to treatment. The focus of the present review is on initiatives that have evolved over the past several years with the goal of rectifying this critically important unmet clinical need. These initiatives have paved the way for psychological and neuroscientific investigations that could revolutionize treatment strategies in the care of patients with schizophrenia.

## MATRICS: Measurement and Treatment Research to Improve Cognition in Schizophrenia

Cognitive deficits have been long recognized as core characteristics of the group of schizophrenia disorders and are largely

responsible for the functional disability apparent in this patient population (Green, 1996). It has become clear that the cognitive deficits so characteristic of patients with schizophrenia have not been ameliorated by existing antipsychotic drugs. Although many antipsychotic treatments have been identified and marketed, the cognitive deficits remain and most individuals with schizophrenia are burdened by significant psychosocial deficits. Only a small percentage of antipsychotic-treated patients with schizophrenia achieve full employment and independent living. Strong evidence that cognitive deficits are critical contributors to the typically poor functional outcome in schizophrenia has emerged (Green, 1996). For several decades, the U.S. Food and Drug Administration (FDA) has licensed drugs for use in schizophrenia only if they reduce the positive symptoms of psychosis (i.e., are antipsychotics). In effect, the FDA has operated from the implicit assumption that a single drug should treat the entire disorder instead of specific compounds treating specific clinical problems. This requirement precluded the development of drugs having therapeutic effects

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that were limited to amelioration of the cognitive impairments associated with schizophrenia (sometimes abbreviated CIAS). Instead, attempts to improve the efficacy of treatments for such impairments focused on combining multiple actions in the same molecule. Thus, industry sought more complex drugs having multiple mechanisms of action in order to treat both the positive symptoms and the cognitive deficits.

This approach forced the field away from specific pharmacological tools that impacted specific molecular targets toward less specific drugs with complex mechanisms and multiple unwanted effects. At a time when the fields of psychology and neuroscience were bringing new levels of sophistication to our understanding of the substrates of separable aspects of cognitive function, our efforts at intervention in the cognitive functions of patients were becoming progressively less specific. Once this critical bottleneck limiting the development of treatments for the cognitive impairments associated with schizophrenia was identified (Fenton, Stover, & Insel, 2003), the United States National Institute of Mental Health (NIMH) initiated the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) program. MATRICS developed a broad consensus as to how cognitive deficits could be assessed and treated (Marder & Fenton, 2004), enabling the FDA to consider registering compounds intended to treat these deficits in schizophrenia, independently of treating psychosis *per se*.

The MATRICS initiative consisted of a systematic series of six conferences designed to build consensus opinions spanning governmental, academic, and industrial sectors. In just 2 years, the MATRICS group established agreement between these different constituencies in critically important areas. In the first meeting, a neurocognition working group determined the domains of cognition deemed most relevant in schizophrenia: working memory, attention/vigilance, verbal learning and memory, visual learning and memory, speed of processing, reasoning and problem solving, and social cognition (see Green & Nuechterlein, 2004; Nuechterlein et al., 2004). It is noteworthy that the domain of social cognition was included in this list not on the basis of an extensive supporting literature, as was the case for the other six domains of cognition, but by virtue of a clear consensus among the MATRICS participants that the psychosocial disabilities so pervasive in schizophrenia patients are powerful impediments to functional recovery and are relatively specific to this disorder compared to other cognitive disorders (see Green, Olivier, Crawley, Penn & Silverstein, 2005). In the second MATRICS meeting, a diverse group of psychopharmacologists identified the most intriguing molecular targets, promising compounds, relevant human test measures, and potentially predictive animal models for use in the discovery of treatments that target basic mechanisms related to complex cognitive operations (Geyer & Tamminga, 2004a, 2004b). In the third meeting, MATRICS established a MATRICS Consensus Cognitive Battery (MCCB) for clinical trials (see [www.matrics.ucla.edu](http://www.matrics.ucla.edu); Green et al., 2004) and described the processes required for assessment of cognition as a clinical endpoint (Buchanan et al., 2005). In follow-up work by the leaders of MATRICS, the

MCCB was refined using empirical comparisons of alternative versions and assessed for its psychometric properties in an additional NIMH-funded program. Subsequently, MATRICS leaders developed a nonprofit entity to make the MCCB, which drew upon a variety of established psychological test instruments, available as a package (see [www.matricsinc.org](http://www.matricsinc.org)). In a fourth meeting, MATRICS published extensive discussions regarding the development of a research agenda that would foster improved methods for the discovery, validation, and assessment of procognitive cotreatments for schizophrenia (see Geyer, 2005; Geyer & Heinssen, 2005). As a result of MATRICS, the FDA appears ready to consider registering drugs for the treatment of cognitive impairments associated with schizophrenia, either as global treatments for cognition or as specific treatments for the separate domains of cognition identified by MATRICS as being affected in those with the disorder. Hence, multiple new indications for use in patients with schizophrenia are now clinical targets for the pharmaceutical industry. A key to the success of the entire MATRICS program was the enlightened willingness of NIMH to provide the leadership and support for the partnership between industry and academia that were essential to the consensus-building process.

It is relevant here to note that the willingness of the FDA and NIMH to consider using a strategy of licensing cotreatments for specific aspects of a diagnostic entity has broad implications for psychiatric drug development and treatment. In part, this approach reflects the considerable complexity of disorders such as schizophrenia, which likely have a variety of etiologies. Although there are always concerns regarding interactions between different drugs when using cotreatment strategies, the reality is that most patients with schizophrenia are treated routinely with multiple psychoactive prescription medications. This movement away from requiring that all aspects of a complex disorder be treated with a single medication may further enable clinicians to personalize treatment by utilizing more specific compounds targeting specific complaints and domains of function. Of course, such optimism assumes that pharmaceutical companies will be successful in identifying and developing specific treatments for the specific cognitive impairments that a particular patient exhibits. It also presumes that clinicians will be able to identify specific profiles of impairments and assess the efficacy of cotreatments. Such changes in drug development and prescribing practices will not evolve rapidly, especially considering the intrinsic complexity of assessing cognitive functions. Nevertheless, the MATRICS model is in keeping with the growing recognition that few psychiatric symptoms are unique to any given diagnostic entity and that more dimensional characterizations of psychiatric patients may provide better guides to treatment strategies. Since many stakeholders are already discussing the potential value of adopting a MATRICS-like approach to revising treatments for other psychiatric disorders, the MATRICS program may have influences far beyond the treatment of schizophrenia.

## **URNS: Treatment Units for Research on Neurocognition in Schizophrenia**

It is important to emphasize that the model developed by MATRICS and approved by the FDA involves the use of cognitive enhancers to be administered as cotreatments in schizophrenia patients who are already on stable regimens of antipsychotic medications. The consensus was that cognitive deficits, and their amelioration, simply could not be assessed accurately in patients experiencing hallucinations and other disruptive psychotic symptoms. Given the novelty of this treatment approach involving the addition of a cognitive enhancer to continuing treatment with an antipsychotic drug, NIMH funded another substantial project called Treatment Units for Research on Neurocognition in Schizophrenia (URNS). This multisite clinical-trials network sought to implement the MATRICS clinical-trial design using the MCCB assessment tools (see [www.turns.ucla.edu](http://www.turns.ucla.edu); Stover, Brady, & Marder, 2007). The URNS Project was charged with selecting potential cognitive-enhancing agents and developed a network of academic sites in order to evaluate potential efficacy of novel agents in proof-of-concept trials (Buchanan, Freedman, Javitt, Abi-Dargham, & Lieberman, 2007). Some of the URNS studies are still ongoing under the auspices of the Treatment and Evaluation Network for Trials in Schizophrenia (TENETS) network, although the clinical network is no longer receiving federal support. To date, no clearly efficacious agent has been identified by URNS, although it should be recognized that this field is still in its infancy.

It can be argued that URNS was an overly ambitious program that underestimated the scope of work required and the complexity of dealing with the intellectual property implications of partnerships between industry, government, and multiple academic institutions. Since federal funding was involved, there were intrinsic constraints against utilizing the more developed expertise of the pharmaceutical industry in guiding the selection of candidate compounds and optimizing the designs of clinical trials. Funding limitations also constrained the sample sizes and therefore the power of the URNS studies. The concern remaining is that some might feel that the failure of URNS to demonstrate the efficacy of a procognitive cotreatment indicates that such treatments will be difficult to discover. Given how little fundamental research has been directed at validating potential treatments for cognitive impairments associated with schizophrenia, it should not be surprising that the few candidate compounds tested to date, mostly in small trials involving relatively few patients, have not met with success. A more protracted effort based on more targeted basic neuroscience research will be required to satisfy this critical unmet need in the treatment of schizophrenia patients.

### **Additional Post-MATRICES Initiatives in the United States**

Another continuing effort spawned from MATRICS is the MATRICS-CT (for co-primary selection and translation of the

MCCB; see [www.matrices.ucla.edu/matrices-ct](http://www.matrices.ucla.edu/matrices-ct)). MATRICS-CT is supported by a partnership of pharmaceutical companies to address the need for measures of functioning and functional capacity (Stover et al., 2007). In MATRICS meetings, the FDA indicated that improvement on neuropsychological tests alone would be insufficient for approval of a treatment for cognitive impairments in schizophrenia. Rather, measured cognitive improvement should be accompanied by improvement on a measure of functioning or at least the patient's perception of improved cognition. The FDA did not require confirmation of improvement in community functioning but indicated the need for improvement in a measure that had more face validity (i.e., improvement on a measure that appears to be relevant to function) than a neuropsychological task. Given the lack of consensus regarding instruments for measuring functioning that can be used in relatively brief clinical trials, MATRICS-CT is working to develop such a consensus. This emphasis on a demonstration of treatment-induced improvement in functional outcome reflects the fundamental rationale for MATRICS, insofar as the focus on ameliorating cognitive deficits was driven by the evidence indicating that psychosocial disabilities were attributable in large part to impaired cognition. In addition, MATRICS-CT is translating and validating the MCCB for use with additional languages, in recognition of the international nature of drug discovery and development in psychiatric disorders. Another initiative (the NIMH Initiative Regarding Treatment for Negative Symptoms) is using the MATRICS consensus-building model to address the inadequate treatment of negative symptoms in schizophrenia (i.e., those symptoms that reflect an absence of normal behavior, such as apathy, lack of pleasure, or social withdrawal), with the aim of developing more sensitive instruments for measuring this symptom domain (see Stover et al., 2007).

### **European Initiatives**

In Europe, the European Commission has approved funding to be provided by a combination of governmental and pharmaceutical industry funds and directed specifically to the improvement of preclinical-clinical translation via partnerships between industry and academia under a program called Novel Methods leading to New Medications in Depression and Schizophrenia (NewMeds) as part of Europe's Innovative Medicines Initiative (see [imi.europa.eu/documents\\_en.html](http://imi.europa.eu/documents_en.html)). Approximately €10 million will involve projects focusing on psychiatric drug discovery, including a substantial focus on drugs to treat the cognitive impairments associated with schizophrenia. Included within this effort are plans to assess empirically the possible interactions between pharmacological treatment of cognitive deficits and the application of cognitive training programs. One concern raised during MATRICS was that the effects of pharmacological cognitive enhancers might not yield changes in functional outcome, or even surrogate (i.e., laboratory-based) measures of outcome, in the absence of some form of concomitant cognitive training. Another practical issue being addressed in this initiative, as well as by

independent groups, is the development of formal comparisons between the MCCB and other cognitive-test batteries. Although currently considered the standard that the FDA will expect for licensing compounds for treating cognitive impairments, the MCCB is seen by some to be limited by the fact that it takes a substantial amount of time, is not computerized, and is not particularly conducive to cross-species comparisons. Clinical assessment tools that cannot be predicted by or translated from preclinical tests in animals considerably constrain the drug discovery process. As with the original MATRICS effort in the United States, an encouraging and critically important aspect of this initiative is the openness of European governments to support, and the pharmaceutical companies to participate in, cooperative efforts involving multiple companies and multiple academic institutions.

### **CNTRICS: Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia**

A subsequent program that is still ongoing, Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia (CNTRICS), is designed to bring the modern tools and concepts of cognitive neuroscience to bear upon the assessment of cognitive impairments in schizophrenia and the efficacy of pharmacotherapeutics in ameliorating them (see [cntrics.ucdavis.edu](http://cntrics.ucdavis.edu)). The CNTRICS initiative was born of discussions during MATRICS about the desirability of utilizing tasks and tools derived from cognitive neuroscience to supplement the MCCB (Carter & Barch, 2007; Carter et al., 2008; Stover et al., 2007). This supplementation could involve the use of additional physiological and behavioral measures, such as event-related potentials (i.e., changes in brain waves elicited by sensory stimuli), prepulse inhibition of startle (i.e., a simple laboratory measure of sensory filtering that reflects the difficulties in inhibiting irrelevant responses), or functional imaging technologies (Green et al., 2009). The goal of CNTRICS is to integrate the tools and constructs of cognitive neuroscience to enhance our ability to translate basic research in animals into clinical studies in patients in order to facilitate the discovery and development of treatments that target cognitive impairments in schizophrenia.

As is true in all psychiatric drug discovery (Geyer & Markou, 2002), an emphasis on understanding the neurobiology underlying cognitive constructs is required for the development of novel treatments for cognitive impairments. Such work will depend on the coordinated use of both animal and human measures to identify and validate novel molecular targets for cognitive deficits (Floresco, Geyer, Gold, & Grace, 2005; Hagan & Jones, 2005). Because MATRICS needed to produce a consensus-based cognitive battery quickly, it necessarily focused on extensively studied tasks having demonstrated reliability, as well as considerations of how faithfully the measures assessed the cognitive domains that are impaired in patients. Measures derived from cognitive neuroscience were considered, but many were not included primarily because their measurement properties

had yet to be established. The CNTRICS project grew out of the final MATRICS meeting, where the potential benefits of using tasks and tools from cognitive neuroscience were broadly acknowledged (see Geyer, 2005). These benefits include: (a) the use of fine-grained tasks that measure discrete cognitive processes; (b) the ability to design tasks that distinguish between specific cognitive deficits and poor performance due to generalized deficits resulting from sedation, low motivation, poor test-taking skills, and so on; and (c) the ability to link cognitive deficits to specific neural systems using animal models, neuropsychological or psychophysiological tests, and functional imaging (Barch et al., 2009). Measuring the function of specific cognitive systems that are linked to specific neural systems using a cognitive neuroscience approach offers unique advantages, especially for translational research (see Carter & Barch, 2008; Carter et al., 2008).

CNTRICS acknowledges the practical realities inherent in clinical trials, such as the need for efficient and standardized tasks having good psychometric properties. The idea is to adapt tasks being used in academic settings, which typically are long and frequently modified, for use in clinical settings. Clearly, some of these tasks will be burdened with technological requirements beyond the scope of larger clinical trials but still may be valuable for Phase II trials that are so critical to a company's decision to make a major investment in costly Phase III trials with a potential new drug. A related reality being addressed in CNTRICS is the value of developing biomarkers reflecting the underlying neural systems in addition to measures of behavior. The use of simultaneous measures of behavior and brain function may help determine when and even why new drugs are or are not working. Further, biomarker measures may eventually provide important information about individual differences in neural function that may determine who will respond in what way to which type of medication, supporting the move toward personalized medicine. CNTRICS has developed an ambitious agenda, to bring new sophisticated tests to bear upon assessments of clinical efficacy. The critical need for tests having construct validity for the cognitive impairments troubling our patients is undeniable. It must be recognized, however, that the process envisioned by CNTRICS is a slow one. CNTRICS is not focused on utilizing tasks that have already been developed and may have some degree of established validity in the context of biomarkers or efficacy signals. The worthy goal of CNTRICS is to foster the development, adaptation, and validation of new tasks being used largely in academic settings and to streamline them for use in the clinic. Since such a process will take years to evolve, it may be difficult for the field to be sufficiently patient, given the pressures for industry to see tangible proof-of-principle studies in order to invest further in treatments for cognitive impairments associated with schizophrenia.

The need to identify and develop cross-species tools with which to predict and evaluate novel treatments of cognitive impairments associated with schizophrenia is evident (Floresco et al., 2005; Hagan & Jones, 2005). Due to the

absence of any treatments known to ameliorate the cognitive deficits in schizophrenia, preclinical drug discovery programs have difficulty assessing the predictive validity of the many cognitive tests available (Floresco et al., 2005). As a result, current efforts are based primarily on our understanding of the theoretical constructs and neurobiology related to cognition. A subgroup of TURNS began to address this need by surveying a number of experts in the field regarding the appropriate approaches to evaluating rodent and primate tests of each of the cognitive domains identified by MATRICS (see [www.turns.ucla.edu](http://www.turns.ucla.edu); Young & Geyer, 2007). Many groups are exploring translational paradigms that have construct validity for the assessment of cognitive impairments in schizophrenia and may be applicable across species. The preclinical models ranked in the TURNS survey are now being used by pharmaceutical companies to guide their preclinical drug discovery and validation programs. More recently, Young and colleagues have provided an extensive critical review of the available animal tasks that best relate specifically to the constructs and tasks assessed by the MCCB (Young, Powell, Risbrough, Marston, & Geyer, 2009). Future meetings of the CNTRICS program will constitute the first formal effort to develop some consensus about what preclinical tests will be optimal for predicting the clinical efficacy of pharmacological treatments for cognitive impairments in schizophrenia.

As discussed briefly at the last of the MATRICS meetings (Floresco et al., 2005), the drug discovery process will depend essentially on the development and validation of preclinical tests having construct and predictive validity across species for the several domains of cognitive impairments associated with schizophrenia. Construct-valid cognitive tests are typically complex and relatively time-consuming and costly to conduct. Hence, the overall task of creating a useful preclinical test battery for cognitive impairments in schizophrenia is enormous. Most of the extant literature relevant to tasks that might be included in a preclinical test battery derives from models related to the cognitive impairments seen in disorders such as Alzheimer's, not schizophrenia. Many believe that the scope of work required to develop useful preclinical screening tests for cognitive enhancers is such that coordinated collaborations among multiple pharmaceutical companies and many academic laboratories will be critically important. Although the development of a collaborative preclinical trials network for cognitive impairments in schizophrenia was suggested by the MATRICS group (Floresco et al., 2005), it is difficult for industry to share data and work openly with academia. Some such collaborative efforts appear to have been initiated successfully by the NewMeds program begun in the European Community (discussed previously). There is not yet a safe harbor in the United States for a similar organized effort to foster data sharing and for cooperation to flourish, even if it is limited to studies of established compounds that are no longer patented. Such an effort would be highly recommended and could have a significant impact.

## Implications for Psychological Science

MATRICES has altered the environment for drug discovery for schizophrenia in substantial ways. The products of MATRICS and CNTRICS have the potential to provide evidence for efficacy in the early phases of clinical drug testing. The availability of validated measures of the specific cognitive deficits seen in schizophrenia could enable Phase II trials to identify the particular cognitive target affected most strongly by selective pharmacological interventions. Hence, Phase III trials targeting specific cognitive functions could be designed with increased confidence, power, and efficiency. Furthermore, CNTRICS' focus on using homologous animal and human paradigms during the drug discovery and validation process should enhance translational predictions of efficacy. Thus, pharmaceutical companies and academic laboratories alike now have the incentive to pursue the development of compounds with specific pharmacological actions on systems known to modulate separable domains of cognition. In concert, cognitive psychologists and behavioral neuroscientists now have renewed enthusiasm to refine our understanding of the neural substrates of particular cognitive processes. Within these academic communities, the most immediate consequence of the MATRICS initiative has been the renewed hope that improvements in our fundamental understanding of the neurobiology of cognition may potentially be translated into improved treatments that could actually be developed and marketed and thereby become available to treat patients with schizophrenia.

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The author declared that he had no conflicts of interest with respect to his authorship or the publication of this article.

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