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Introduction

Good morning, Chairman Deal, Chairman Barton, and members of the Subcommittee. Thank you for inviting me here today to provide testimony on the biological basis of schizophrenia. My name is Diane Gooding, Associate Professor of Psychology and Psychiatry at the University of Wisconsin-Madison. My primary areas of research are: identifying and validating indicators of heightened risk for schizophrenia and related conditions and identifying and studying individuals putatively at heightened risk for the disorder.

Defining schizophrenia

Schizophrenia is one of the most severe forms of psychopathology. It is a disorder that affects one's thoughts, feelings, goal-directed behaviors, social functioning, and even one's self-care. Since the early observations of Kraepelin [1896] and Bleuler [1911], schizophrenia has been regarded as a primarily cognitive disorder of neurobiological origin. It is an equal opportunity disorder, affecting individuals of all races, ethnicities, and socioeconomic strata. Although its prevalence is relatively low (1.1% of population aged 18 and older; APA, 2000), clinicians and researchers often regard schizophrenia as the "cancer of the mental illnesses" due to its severity, chronicity, societal costs, and personal costs to affected individuals and their loved ones. Clearly, schizophrenia is an important public health concern. Although there are some palliative treatments for schizophrenia, the mechanisms underlying the disorder remain

unknown. If the long term goal is to prevent schizophrenia, then an intermediate goal would be to identify the pathophysiology and etiology of the disorder.

Diagnosing schizophrenia

There is no direct measure of the neuropathology of schizophrenia at present. Currently, the diagnosis of schizophrenia is made on the basis of symptoms, which are inferred based on the individuals' language and behaviors. There are symptoms which represent an exaggeration of normal functions, such as hallucinations, the false perception of sensory experiences (such as hearing voices, or seeing things that aren't there) and delusions, which are false beliefs that are persistent, unusual, and unshakable. Although most of the general public is aware of the florid symptoms of delusions and hallucinations, they have less aware of the symptoms of schizophrenia which represent the absence of normal functions and behaviors. These symptoms include amotivation/avolition (loss of motivation), anhedonia (loss of pleasure), alogia (reduced speech), affective impairments (such as loss or restriction of emotional display) and attentional impairment. The clinical picture of schizophrenia varies from patient to patient. Not all individuals with schizophrenia have the same constellation of symptoms and not all have the same severity of impairment. Despite the apparent heterogeneity of schizophrenia, there is a core underlying deficit; the core deficit in schizophrenia is a cognitive one.

The genetic basis of schizophrenia

Schizophrenia is not the result of the way in which a person is raised, nor is it the result of a personal weakness or failure on behalf of the affected person. Contrary to earlier notions about the causes of schizophrenia (e.g., the schizophrenogenic, ambivalent mother) schizophrenia is a genetically-based brain disorder. Family studies indicate that individuals who are biologically related to a person with schizophrenia are at much higher risk for developing

schizophrenia. The risk of developing schizophrenia for a person who is related to someone with schizophrenia increases as a function of how many genes they share in common.

The role of genes in schizophrenia has been demonstrated by twin and adoption studies. In order to estimate the extent of the genetic component of any trait or disease, twin studies compare the concordance rate, or the likelihood of both twins having the same illness, between monozygotic (identical) and dizygotic (fraternal) twins. The greater the monozygotic twin concordance compared to the dizygotic concordance, the greater the inherited component. The risk for schizophrenia for a co-twin of a schizophrenia patient is significantly higher (46 - 58%) for an identical (monozygotic) twin than for fraternal (dizygotic) twins (15%). Adoption studies demonstrate that a shared genetic component, rather than shared familial environment, contributes to susceptibility for schizophrenia. Adoption studies indicate that adopted-away biological offspring of schizophrenia patients are also at heightened risk for schizophrenia. These studies indicate that it's shared genes, not shared environments, that underlie the increased risk of schizophrenia in relatives of individuals with schizophrenia.

Genes account for approximately 68 to 85% of the underlying risk for schizophrenia (McGuffin et al., 1995). The consensus is that genetic factors that cause schizophrenia are necessary but not sufficient for the development of schizophrenia. One doesn't inherit schizophrenia; one inherits susceptibility to schizophrenia. Environmental risk factors are also important, and the genetic and environmental factors may interact. Nearly all of the theories of the genetic basis of schizophrenia are based on what we call a diathesis-stress model. In a diathesis-stress model there's a diathesis (or susceptibility) which is biological in nature. The manifestation of that diathesis is triggered by a stressor, which may be environmental (pregnancy and birth complications, early childhood brain damage such as ischemic

attacks/hypoxia, early exposure to viral agents, use of psychoactive substances such as cannabis or amphetamines, or psychosocial stress).

In a complex disorder such as schizophrenia, there are likely to be many genes that are involved in predisposing people to the disorder. The genes may affect brain development, they may affect neurotransmitter systems, or they may affect individuals at both these levels.

Investigators and theorists differ in terms of the number of genes that they believe are likely to be implicated in the underlying diathesis for schizophrenia.

While we can conclude that there's a strong genetic basis for schizophrenia, we have not yet identified the genes that are implicated. We are hopeful that new molecular techniques and modern statistical analyses can allow us to focus in on particular genes that confer risk to schizophrenia. The more genes that are associated with the disorder, the harder it will be to replicate associations between the disease and a given gene. However the search for "schizophrenia risk genes" has been made more difficult by the fact that at present most researchers rely upon the presence of symptoms (disease phenotype) to identify individuals who are most likely to possess the genetic diathesis (genotype). Indeed, progress in this area is stymied by the phenotypic heterogeneity of the disorder, i.e., the diversity in clinical presentation of the disorder, as well as the likely existence of etiological heterogeneity. It remains very possible that there are different causes for schizophrenia, all of which can lead to the same outcome (Gooding & Iacono, 1995).

Endophenotypes

The identification and use of heritable neurocognitive markers (known as endophenotypes; Gottesman & Gould, 2003) can be an invaluable aid in the genetic dissection of schizophrenia. Here are characteristics of these biobehavioral markers of liability: low

prevalence among the normal population; genetic transmission; significantly higher proportion among affected individuals; stability over time; independence from clinical status (i.e., symptom remission vs. acute symptoms), and presence in unaffected relatives of affected individuals.

There are several advantages to the application of endophenotypes to the search for the biological basis of schizophrenia. First, endophenotypes may assist genetic studies of schizophrenia because they can provide a way to identify individuals carrying the genetic risk. Endophenotypes are believed to be closer in the etiological chain to underlying genetic factors than the symptoms of the disorder. Moreover, endophenotypes have associated brain regions and circuits that may provide further clues about the areas that are dysfunctional in the schizophrenic brain.

Examples of some promising markers of genetic liability for schizophrenia include: oculomotor deficits such as smooth pursuit eye tracking dysfunction and saccadic inhibition deficits; working memory impairments; and sensory gating abnormalities such as P50 nonsuppression. The occurrence of oculomotor impairments, such as smooth pursuit eye tracking abnormalities has been a consistent research finding since the 1970s. Individuals with schizophrenia have marked difficulty matching their eye velocity to the velocity of a slowly moving target, which results in abnormal smooth pursuit eye tracking. Indeed during smooth pursuit eye tracking, individuals with schizophrenia show insufficient inhibition of small fast eye movements, which tends to take their eyes further away from the target they're trying to visually follow. These deficits are observed in a disproportionate number of schizophrenic individuals even during their first episode of illness.. Some of my early work indicated that this abnormality is stable over time, regardless of chronicity, medication status, or clinical status.

Another potential marker of a schizophrenia liability is a deficit in antisaccade task performance, in which individuals are instructed to look immediately to the opposite side of a laterally displaced visual target. The neural basis of eye movements is well understood, so this remarkably consistent finding in individuals with schizophrenia and their first degree relatives (siblings, parents, and offspring) supports the notion that schizophrenia is a brain disorder.

Working memory is defined as the ability to hold information in temporary storage, manipulate that information, and use it to guide subsequent behavior. Spatial working memory impairments in schizophrenia were first demonstrated in the early 1990s (Park & Holzman, 1992). Since then, several investigators have shown the following: spatial working memory impairments in schizophrenia are common, they're seen in unaffected first-degree relatives such as parents and siblings, and they're stable over time. Schizophrenia patients have these deficits whether they're acutely psychotic or in remission, whether they're medicated or not, whether they're hospitalized or fully functioning in the community.

In the P50 paradigm, two auditory stimuli are presented in quick succession. Normally, a person's neuronal response to the second stimulus will be smaller (lower amplitude) than the response to the first stimulus. P50 suppression is an indicator of information processing, or sensory gating. Individuals with schizophrenia fail to show this P50 suppression. Decreased P50 inhibition is found in approx. 50% of patients and in 10% of healthy subjects. P50 nonsuppression is also frequently observed in the first-degree relatives of schizophrenia patients.

Who is at risk for schizophrenia?

There's increasing evidence that suggests that we may be able to identify the underlying diathesis, or liability to schizophrenia, before the risk condition progresses to full-blown

schizophrenia. There are several ways of identifying individuals at heightened risk for the later manifestation of schizophrenia: they can be identified on the basis of genetic, psychometric (questionnaire/inventory), biobehavioral, or clinical risk factors. Much of the knowledge gleaned about the study of individuals at genetic risk for schizophrenia has been based on studies of the offspring of schizophrenia patient (Erlenmeyer-Kimling, 2000). The presence of clinical risk factors can also be used to identify individuals at heightened risk for the development of schizophrenia. One example of the clinical high-risk strategy would be to study individuals who have clinical disorders that are genetically related to, but less severe than schizophrenia, such as schizotypal personality disorder.

In the psychometric high-risk method, at-risk individuals are identified on the basis of their psychometric profiles using questionnaires or instruments such as the MMPI. Much of my research at the University of Wisconsin-Madison focuses on elucidating the developmental trajectory from risk status to clinical disorder, whether schizophrenia, or a related, but less severe condition such as schizotypal personality disorder. This is done by following at-risk individuals over time, and comparing them with typically-developing, age-matched individuals. Using a set of well-validated instruments known as the Chapman psychosis-proneness scales, investigators (Chapman et al., 1994) observed that individuals who report the experience of strange perceptual experiences are at heightened risk for schizophrenia and other psychotic disorders such as psychotic mood disorders. Individuals who report social anhedonia, or the reduced ability to experience pleasure and/or a deficit in the ability to seek and experience pleasurable activities, are at heightened risk for the specific development of schizophrenia and schizophrenia-related conditions (Gooding et al., 2005). These findings are consistent with data from the genetic high-risk studies that indicate that attentional deviance in early childhood (a

risk factor for the later development of schizophrenia) was associated with poor social skills, anhedonia in adolescence and social deficits in early adulthood (cf. Erlenmeyer-Kimling et al., 2000).

Predicting the development of schizophrenia in at-risk individuals

Studies indicate that offspring of schizophrenia patients who later develop schizophrenia and schizophrenia-related disorders displayed attentional deficits, verbal memory deficits and gross motor impairments even as children. However, among the offspring of schizophrenic patients, only a subset of the at-risk individuals were later diagnosed with a schizophrenia-related illness. A composite index of risk was a better predictor of a schizophrenia-related outcome than reliance upon a single indication of deviance. Because not all good predictors of schizophrenia outcome, such as lower IQ or motor impairments, are indicators of a genetic liability towards schizophrenia, searching for the presence of the endophenotypes in the genetically at-risk population is especially beneficial. At present, we cannot predict who, among the individuals at risk for schizophrenia, will later manifest the disorder or one of its spectrum disorders, such as schizotypal personality disorder, or schizoaffective disorder.

Can we intervene in the case of at-risk individuals before they develop psychotic symptoms?

A newer research strategy concerns the study of individuals at the prodromal stages of schizophrenia, before they have an outbreak of manifest psychosis. So clinical researchers attempt to treat individuals who are showing functional deficits like those seen in schizophrenia, but who are not yet experiencing the psychotic symptoms of delusions and hallucinations. This research strategy is based on the premise that the premorbid and prodromal phases of schizophrenia are windows of opportunity to intervene, in order to maximize the likelihood of a better disease outcome. These early intervention programs are preventive in the sense that part

of the goal is to prevent further psychosocial decline, and/or to delay the onset of severe psychosis. The risks and benefits of these early intervention programs are currently investigated and debated. The preventive treatment of individuals who show an accumulation of risk factors is based upon a statistical risk-oriented approach to treatment. The study of biologically-based markers, in conjunction with other screens, e.g. clinical signs and behavioral symptoms, can be useful in terms of further identifying who the target population should be, which risk factors are most valid as screening tools for the entry into the study, and what prodromal deficits should be targets for intervention. Endophenotypes are increasingly being integrated into some of these prodromal studies.

Current status of schizophrenia research

The consensus is that schizophrenia is a genetically-mediated neurodevelopmental disease that is typically developed during late adolescence and early adulthood. We don't know which genes are involved, how many need to be present, and how they affect brain development.

Schizophrenia is associated with neurobehavioral impairments. We know that as a group, people with schizophrenia differ from healthy people in terms of neurocognitive and psychophysiological performance. A disproportionate number of biological relatives of schizophrenia patients also display these deficits, albeit to a lesser degree. Research indicates that these biobehavioral deficits are stable over time. We can conclude that several of these neurocognitive impairments are potential markers of increased susceptibility of risk for schizophrenia. The study of these putative markers can be useful in terms of refining the diagnosis and classification of schizophrenia and schizophrenia-related disorders. These markers also have the potential to enhance our current research strategies for identifying

individuals at heightened risk for schizophrenia. We know that not everyone at heightened risk for schizophrenia goes on to develop the disorder. However, it appears that even prior to the onset of the disorder, individuals who later develop schizophrenia deviate on a range of functions, including attention and information processing, motor development, language difficulties, and social behavior. We don't know how schizophrenia develops from risk to manifest disorder. We are at the very beginning of discerning the ways in which the at-risk individuals who later develop schizophrenia differ from those at-risk individuals who remain clinically compensated. We are still investigating whether indicators and predictors which have validity at the population level have predictive validity at the individual level as well. Prodromal studies of schizophrenia are underway.

Summary

My hope is that the scientific community will have adequate resources to continue the research, so that can we further the progress of unlocking this epigenetic puzzle that we call schizophrenia. I'm proud of the work that we are doing in Wisconsin to help demonstrate the ways in which schizophrenia is a genetically-mediated neurodevelopmental disorder. At the University of Wisconsin, many of the researchers like myself have partnered with mental health professionals, mental health consumer organizations and community advocates such as NAMI (which originated in Madison, WI) to educate the local community as well as the community at large about schizophrenia. It is especially gratifying to participate in dispelling myths and correcting misconceptions about schizophrenia and schizophrenia-related disorders through education, research, and advocacy.

Thank you for the opportunity to offer testimony on this important health issue. At this time, I would be happy to answer any questions.

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