The research evidence for schizophrenia as a neurodevelopmental disorder
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INTRODUCTION

It is evident that many schizophrenia patients have brains that are not entirely normal, and these give rise to cognitive problems. Schizophrenia is now seen as a neurodevelopmental disorder that starts very early. For instance, we know that there are delays in cognitive and neuro-motor skills in childhood among those who later develop schizophrenia. I will begin this review of the empirical evidence for the neurodevelopmental model by outlining the roots of psychological research that laid the foundation of the model. Thereafter, I will describe cognitive dysfunction observed in schizophrenia, and the course of cognitive functioning in schizophrenia (both after onset and before onset). Then, I will outline research findings that speak for and studies that speak against the view that schizophrenia is a degenerative process. Finally, I will point out some of the factors that may trigger the deviant neurocognitive development which is the topic of this paper.

EARLY RESEARCH

Eugen Bleuler was the first to place weight on cognitive dysfunction in schizophrenia. This is evident from his inclusion of associative disturbance among both the lists of fundamental symptoms and primary symptoms. He described schizophrenia patients as incapable of holding their train of thought in the proper channels (Bleuler, 1911/1950, 1924/1976). To understand the emergence of the neurodevelopmental model it may be of relevance to take a historical look at the research that has influenced the model. In retrospect, I believe there are two roots of decisive importance: experimental psychopathology research and neuropsychological research.

*Experimental psychopathology research*

In the early 1950s, Joseph Zubin established a laboratory for psychology research at Columbia University in New York, and David Shakow another laboratory at the National Institute of Mental Health (NIMH) outside Washington DC. But even before World War II, Shakow had published pioneering works with Eliot Rodnick related to reaction time experiments (Rodnick & Shakow, 1940). Their work has been described as: “.... the closest thing to a north star of
schizophrenia research” (Cancro, Sutton, Kerr, & Sugerman, 1971). Their primary finding was the so-called "cross-over effect." This refers to schizophrenia patients - in contrast to healthy controls - not being able to utilize the regularity between a warning signal, while the imperative stimulus subjects were asked to respond to when the interval between the two signals exceeded approximately five seconds (Rund, 1985). Surprisingly, they found that schizophrenia patients responded faster with irregular- rather than regular intervals. No viable explanation of the mechanisms of the "cross-over effect" has been provided, beyond the fact that it involves a reduced ability to maintain an optimal level of readiness over time for rapid processing of simple sensory stimuli and for rapid motor responding. In their review, Nuechterlein and Dawson claimed that the cross-over pattern is one of the few promising vulnerability indicators because of its presence in both high-risk and schizophrenia populations (Nuechterlein & Dawson, 1984).

In 1954, Zubin founded the Biometric Research Unit at the New York Psychiatric Institute. His scientific approach was to seek a theoretical understanding of the etiology of schizophrenia, with objective measurement and strong experimental methodology emphasized. As an example of this integrative approach, Zubin and colleagues examined event related potentials (ERPs) in combination with cognitive tasks. This led to a long-standing examination of ERP abnormalities in schizophrenia, including the P300, a waveform used to reflect allocation of attentional processes (Sutton, Braren, Zubin, & John, 1965).

Another pioneering figure in experimental psychopathology research was Norman Garmezy, whose focus turned to childhood origins of psychopathology in his search for an understanding of the origins of schizophrenia. During his years at Minnesota University from 1961, he led an international “risk consortium” of investigators, including Arnold Sameroff, Sarnoff Mednick, Michael Goldstein and Norman Watt, who studied development in children at risk for severe mental illnesses. He directed a series of studies of children born to mothers with schizophrenia to isolate the cognitive and social precursors of this complex disorder. Garmezy and his students investigated attentional processes in adult schizophrenia and in children at risk (Garmezy, 1978; Nuechterlein, 1983).

Philip Holzman is another outstanding researcher of neuro-psychopathology from the early era of experimental schizophrenia research. His career meshed clinical psychology with laboratory neuroscience. In 1977, Holzman founded the McLean Hospital Psychology Research Laboratory, affiliated with Harvard. Building on earlier observations of eye movements in
schizophrenia patients, Holzman noted that some patients and their healthy relatives exhibited trouble in following moving objects within their vision. He developed random-dot tests and other methods to measure dysfunction, called eye tracking, as an entry to examine the broader genetic causes underlying mental disease (Holzman, Proctor, & Hughes, 1973).

The goal of the experimental psychopathology research was to closely measure deficits in schizophrenia in precise experimental paradigms, in order to be able to infer what the results mean about underlying deficits in the disorder based on existing experimental models. By using normal cognition models as the framework, the results in patients may implicate one process or one type of abnormality more than another. One example of such experimental research followed up in recent times is examinations of the so-called backward masking (BM) paradigm. This procedure taps the initial sensory memory stage and, with this procedure, the researcher has very precise control over how long a stimulus acts on sensory apparatus (Saccuzzo & Braff, 1981).

BM examines the subject’s ability to recognize briefly presented, single visual stimuli (most often letters or digits) when they are followed by a visual pattern mask after various brief intervals. The findings in early studies were interpreted as showing that patients with schizophrenia process sensory information more slowly from sensory memory to short-term memory than healthy controls because they required longer intervals to recognize the target stimuli under backward-masking conditions. It was believed for a time that findings from the BM tasks differentiated schizophrenia patients from other groups with mental disorders. However, together with colleagues, I have documented that poorer performance is not specific to schizophrenia patients. We found similar abnormalities in patients with affective disorders (Rund, 1993; Rund & Landro, 1990; Rund, Landro, & Orbeck, 1997; Rund, Oie, & Sundet, 1996; Thormodsen, Juuhl-Langseth, Holmen, & Rund, 2012). Furthermore, we (Thormodsen et al., 2012) found that patients with early-onset schizophrenia revealed no impairment of BM performance at all, although the patients demonstrated a deficit of simple early visual processing. This finding corresponds to some early reaction-time results in schizophrenia high-risk people, where increased simple RT was demonstrated without the typical schizophrenia cross-over pattern being present (Nuechterlein & Dawson, 1984). Instead, these BM and RT results indicate that schizophrenia performance is deeply influenced by an overall ability to process visual stimuli in general, which could be linked to deficits of the visual pathways in the brain or to a deficit of visual tuning in the lateral occipital complex.
Another example of experimental psychopathology research is Hugdahl’s extensive examinations of lateralization of speech perception, which has been studied with the dichotic listening task with consonant-vowel syllables. Hugdahl’s hypothesis is that auditory hallucinations are internally generated speech misrepresentations lateralized to the left temporal lobe. If hallucinations are misrepresentations involving the speech perception area of the left temporal lobe, then hallucinating patients should have problems identifying a simultaneously presented external speech sound, particularly when the sound is lateralized to the left hemisphere. In an examination of 87 right-handed patients with schizophrenia it was found a gradual decrease in the ability to process and report right-ear stimulus with an increasing frequency of hallucinations in schizophrenia patients (Hugdahl et al., 2008). This finding is seen as a confirmation of Hugdahl’s hypothesis.

Neuropsychological research

As early as in the 40s, psychologists had begun to use neuropsychological tests in schizophrenia research (Mirsky, 1969; Seidman, 1983). At that time, cognitive dysfunctions found in schizophrenia patients were referred to as formal thought disorder. Thought disturbances, such as "impairment of the abstract attitude" (Goldstein, 1959; Goldstein & Scheerer, 1941) and “overinclusive thinking” (Cameron, 1938) became the central focus of cognitive theories of schizophrenia, and these aspects of thought disorder were considered to be some of the most reliably distinguishing features of the schizophrenias (Chapman, 1979; Zimet & Fishman, 1970). The most widely used neuropsychological tasks to assess these formal thought disorders were word association tests, proverb tests, and object sorting tests. Eventually, the Wisconsin Card Sorting Test became the most acknowledged method.

In an extensive Schizophrenia Bulletin review in 1984 (Nuechterlein & Dawson, 1984), attention and information processing came into focus in the developmental course of schizophrenia. Throughout the 90s more extensive test batteries were adopted, where both verbal and visual memory were included. Gradually, tests of working memory were developed. A challenge in the field became clearer, namely that different test batteries were used in different studies. For the purpose of developing a consensus battery suitable for the assessment of cognitive function in clinical trials of cognition-enhancing drugs, the National Institute of Mental
Health (NIMH) funded the project, Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) (Nuechterlein et al., 2008). The task to develop a suitable test battery that could be adopted by as many researchers in this field as possible was “tendered.”

A research group at the University of California, Los Angeles (UCLA) was selected to develop the test battery. The result of this effort is the MATRICS Consensus Cognitive Battery (MCCB), a consensus battery consisting of 10 neuropsychological tests assessing the seven neurocognitive domains of speed of processing, attention/vigilance, working memory, verbal learning, visual learning, reasoning and problem solving, and social cognition (Nuechterlein & Green, 2006). Twenty neuropsychological tests were used in a study of 176 individuals with schizophrenia spectrum disorders in five US study sites (Nuechterlein et al., 2008). The results of this study were used to select 10 tests based on the following criteria: (a) The test–retest reliability should be high, (b) the tests should be suitable for repeated measurements, (c) the tests should assess functions relevant for activities of daily life, (d) the tests should demonstrate changeability to pharmacological and other clinical interventions, (e) the test instructions should be easy to understand due to their intended use by cognitively impaired individuals, and the testing procedure should be easy to carry out in a clinical community without access to advanced laboratory equipment (Green & Nuechterlein, 2004; Nuechterlein et al., 2008). Additionally, the 10 tests selected were evaluated against four functional co-primary measures. Two assess functional capacity and two are interview-based assessments of cognitive abilities, where individuals estimate their own cognitive abilities and impairments. MCCB is now in use worldwide. Our research group at the University of Oslo was one of the first to translate the MCCB into a foreign language (Norwegian) (Mohn, Sundet, & Rund, 2012), and the first to report MCCB data for a group of early-onset schizophrenia (Holmen, Juuhl-Langseth, Thormodsen, Melle, & Rund, 2010).

THE RESEARCH FUNDAMENT OF THE NEURODEVELOPMENTAL HYPOTHESIS

What are the cognitive dysfunctions in schizophrenia?

Over the past 30-35 years, disorders of cognitive functioning in schizophrenia patients have been documented in more than a hundred studies (Elvevag & Goldberg, 2000; Heinrichs & Zakzanis,
There is a consistent finding that all cognitive functions are affected to a greater or lesser extent, even if some meta-analyses have pointed to certain domains representing a larger impairment than others. Thus, in a recent review (Schaefer, Giangrande, Weinberger, & Dickinson, 2013), it is claimed that patients show somewhat larger impairments in the domains of processing speed and episodic memory than in other domains. Reichenberg and colleagues concluded that working memory and executive function are particularly affected, in addition to episodic memory (Reichenberg et al., 2010); while in the study by Holmen and colleagues from our research group (Holmen et al., 2010) attention was the cognitive domain with greatest impairment. However, Schafer and associates concluded that a substantial, generalized impairment is consistently found in schizophrenia over time, and across cultural and geographic variations (Schaefer et al., 2013). Moreover, in a meta-analytic review (Mesholam-Gately et al., 2009), moderate to large effect sizes were revealed across all cognitive domains in first-episode schizophrenia, with a magnitude and pattern of these deficits approximately like those documented in older and more chronic patients. The largest amount of variance appears to be explained by a global cognitive measure, so individual cognitive measures are often embraced in a composite score. In general, similar global cognitive deficit profiles have been found in psychoses outside the schizophrenia spectrum, but to a lesser degree than within schizophrenia.

It should be mentioned in this connection that it is difficult to distinguish between the cognitive domains/processes characterizing dysfunction in schizophrenia patients. Most of the tests used and domains examined are complex (Seidman et al., 2016). Cognitive functions overlap to a great extent, for instance executive functions and working memory. Furthermore, different terms have been used for the same domains, for instance executive function, reasoning, problem solving, and abstract thinking. Although one cannot distinguish schizophrenia patients from other psychotic patients with a simple test, it is possible to distinguish schizophrenia from other psychotic disorders with respect to cognitive profile and degree of deficit (Kahn & Keefe, 2013). But we must also be aware that there are some patients with schizophrenia who have no cognitive impairment compared with the average for normal controls. Thirty-five to forty percent do not have a significant deficit if we define a deficit as more than 1.5 standard deviations below the mean (Rund et al., 2006). But even those patients who do not score significantly worse than the average for healthy controls are probably performing below their premorbid functioning
Neurocognition has proven to be a better predictor than anything else for the daily functioning in patients with schizophrenia, also functioning in the long term. In one of the most influential articles in the field, Michael Green (Green, 1996) identified that neurocognition is a better predictor than symptoms, both for the course of the illness and for functional outcome. This has later been confirmed through a number of empirical studies (Allott, Liu, Proffitt, & Killackey, 2011; Stouten, Veling, Laan, van der Helm, & van der Gaag, 2014; Torgalsboen, Mohn, & Rund, 2014).

Over the past 10-15 years, there has been a growing interest in social cognition in schizophrenia. Social cognition refers to the domains of cognitive functions employed in socially relevant situations, i.e., the discovery and use of social information. These include emotion processing, social perception, theory of mind/mental state attribution and attributional style/bias, plus more complex and developed concepts like social metacognition. People with schizophrenia seem to be impaired in their ability to perceive emotions, understand the thoughts and intentions of other people, and to interpret social "cues." It is clear that social cognition is of considerable importance for understanding social outcomes, even more so than neurocognitive deficits (Green & Harvey, 2014) Some believe social cognition is a mediating factor between neurocognition and functional capacity in daily life (Vaskinn et al., 2008).

What is the course of cognitive functioning in schizophrenia?

Nearly 50 studies have been investigating how cognitive functioning evolves over time in patients with schizophrenia (Rund, 1998; Szoke et al., 2008). Still, only a few of them have studied the course over a period longer than two years, and only four studies have a follow-up period of 10 years or more, including two from Norway (Barder et al., 2013; Hoff, Svetina, Shields, Stewart, & DeLisi, 2005; Oie, Sundet, & Rund, 2010; Stirling et al., 2003). A majority of the studies reported a relatively high degree of stability in cognitive functioning, with the exception of the study by Oie et al. (Oie et al., 2010), and to some degree Barder and associates (Barder et al., 2013), where a certain decline was found for verbal learning and memory.
How is the neurocognitive functioning before onset of illness?

It has now been well documented that cognitive disturbances occur from four-five years of age in those later developing schizophrenia, but in a milder form than after illness onset. This has been shown both in high-risk studies and large birth cohort studies (Cornblatt, Obuchowski, Roberts, Pollack, & Erlenmeyer-Kimling, 1999; Crow et al., 1994; Fuller et al., 2002; Meier et al., 2014; Seidman, Buka, Goldstein, & Tsuang, 2006; Seidman et al., 2010; Seidman, Giuliani, et al., 2006; Seidman et al., 2016). There is ample evidence of significant impairment during the premorbid phase (Cannon et al., 2002; MacCabe et al., 2013; Niemi, Suvisaari, Tuuio-Henriksson, & Lonnqvist, 2003; Reichenberg et al., 2010; Seidman, Buka, et al., 2006; Seidman et al., 2016), and greater deficits in the prodromal phase (Brewer et al., 2005; Seidman et al., 2010). Neurocognitive impairment has also been documented as a robust characteristic of clinical high-risk participants subsequently developing psychosis (Fusar-Poli et al., 2012), especially in attention, working memory and declarative memory abilities (Seidman et al., 2016).

Moreover, it has been found that early motor disorders (Walker, 1994) and delayed developmental milestones - like walking, crabbing, sitting, lifting the head and smiling - are present to a significant extent in children developing schizophrenia as adults. This is seen as early signs of neuropathology (Sorensen et al., 2010), and can be an indication of non-specific neurocognitive abnormalities specific for schizophrenia at a more basic neuropathological level. Walker analyzed home videos taken in the early age of people who had developed schizophrenia as adults and their healthy siblings. Experts who rated the videos identified with great accuracy those later developing schizophrenia. They found neuro-motor abnormalities, particularly on the left side of the body, and poor motor skills. Abnormal movements, or the way they held hands, characterized those children who later developed schizophrenia. These "deviations" were most prominent in the period where motor skills are developing at the fastest rate, namely in the first two years of life (Walker & Lewine, 1990).

To conclude, neurocognitive impairment and the course of neurocognitive functioning may be important in understanding the pathogenesis of schizophrenia. Neurodevelopmental models posit that schizophrenia is the behavioral outcome of an aberration in neurodevelopmental processes that begins long before the onset of clinical symptoms (Rapoport, Giedd, & Gogtay, 2012), and that core cognitive deficits are the outcome of an abnormal development of the brain, leading to problems in acquiring cognitive abilities (Bora & Murray,
A neurodevelopmental disturbance, or a neurocognitive lag (Bora, 2014; R. C. Gur et al., 2014), probably begins very early (perinatally) (Brown & Derkits, 2010; Khandaker & Jones, 2011; Reichenberg et al., 2010; Walker, 1994), continues premorbidly, prodromally, and post-onset of psychotic symptoms (Landro, Orbeck, & Rund, 1993; Meier et al., 2014). The fact that the cognitive impairment starts early: Does it imply that it can also be read in structural changes in the brain?

IS SCHIZOPHRENIA A DEGENERATIVE DISORDER?

The question of whether schizophrenia is a neurodevelopmental disorder or a neurodegenerative disease has been a topic of discussion ever since Weinberger wrote one of the most cited articles in schizophrenia literature 30 years ago (Weinberger, 1987). The neurodevelopmental model (Rapoport et al., 2012) assumes that the abnormal development of the brain, which may involve both genetic and environmental factors, starts long before clinical symptoms arise and before the brain has fully developed into the anatomical structure in early adulthood. The cognitive disturbances in schizophrenia are seen as an expression of deviations from the normal neurocognitive development. The fact that onset of schizophrenia usually takes place in early adulthood is often assessed as support for the neurodevelopmental model because the disease then comes in the wake of the extensive re-modeling of brain circuits taking place through late adolescence.

The neurodegenerative model differs from the neurodevelopmental model in that the former also assumes that the dysfunctional neurocognitive development is progressive and continues after illness onset (dementia praecox), and that this is also manifested in structural changes in the brain. It typically includes cytopathology and loss of neurons and synapses followed by gliosis, i.e. scar tissue formation in the brain. Kraepelin was clear in maintaining that schizophrenia is a degenerative disorder (dementia praecox). This view prevailed until the mid-20th century. At that time, more optimism came into the treatment of the disease, both because of the antipsychotic drugs and because some psychiatrists reported that patients with schizophrenia could be cured by psychotherapy. Some began to ask the question: How can a disease be degenerative if it can be cured? Let me summarize the research that speaks for and against a degenerative process in the brains of patients with schizophrenia.
Findings that indicate a degenerative process

There is substantial empirical evidence that changes in the brain of patients with schizophrenia take place. More than 100 studies of structural changes have been carried out, including MRI techniques after 1984. These studies have been summarized and evaluated in several review papers (Harrison & Lewis, 2003; Nesvåg & Agartz, 2016; Niznikiewicz, Kubicki, & Shenton, 2003; Shenton, Dickey, Frumin, & McCarley, 2001; Weinberger & Marenco, 2003; Weinberger & McClure, 2002). The most robust findings seem to be that patients with schizophrenia have larger ventricles than healthy controls (Nesvåg & Agartz, 2016; Shenton et al., 2001) they have reduced volume in the frontal lobes compared to healthy controls (Niznikiewicz et al., 2003), and there is a reduction in the temporal lobes in the medial temporal lobe, including the amygdala-hippocampal complex and neocortical temporal lobe (Rund, 2009; Shenton et al., 2001).

Similar to the effects of early structural imaging, the functional neuroimaging studies forced a reconsideration of brains in schizophrenia. Not only did the brains look different from healthy brains, they also functioned differently, which can be read through functional MRI. A common finding has been that schizophrenia patients do not activate their frontal lobes as much and effectively as control samples. For instance, Hugdahl and associates found that patients with schizophrenia had less activation in prefrontal brain regions relative to the comparison participants (patients with unipolar depression and healthy controls). However, subtracting brain activation during a vigilance task from activation during a mental arithmetic task showed that the schizophrenia patients had activation in parietal areas. Hugdahl and collaborators concluded that the greater parietal lobe activation in the patients with schizophrenia may reflect a compensatory strategy for the failure to activate cognitive processes that involve frontal lobe areas when solving a mental arithmetic task (Hugdahl et al., 2004).

Studies that support degeneration are primarily more recent morphological long-term studies after onset of the illness. In general, these studies show that structural changes in the brain of schizophrenia patients continue after the onset of psychosis (Rund, 2009, 2016; Weinberger & McClure, 2002). I will summarize these findings.

Jacobsen and collaborators (Jacobsen et al., 1998) documented a reduction in the hippocampus of 7% per year. Rapoport and colleagues (Rapoport et al., 1997) reported a 7% reduction in the thalamus per year in adolescents with schizophrenia. Furthermore, they found an increase in ventricular volume of 10% per year. In a later publication, they (Rapoport et al.,
reported a significant reduction in gray matter in the frontal and parietal areas in these adolescent patients. Cahn and associates (Cahn et al., 2002) found that the gray matter throughout the brain decreased during a one year follow-up in first-episode schizophrenia patients. Van Haren (van Haren et al., 2007) found that loss of cortical gray matter was associated with relapse and re-treatment in a five-year follow-up study. Likewise, Whitford and colleagues found a reduction in gray matter in first-episode schizophrenia patients during a period of two-three years (Whitford et al., 2006). Sporn and associates (Sporn et al., 2003) found a significant loss of gray matter throughout adolescence in patients with early-onset schizophrenia. Kasai and collaborators reported a progressive reduction in gray matter in the left upper temporal gyrus over a period of 18 months after the initial hospitalization in patients with schizophrenia. This decrease was nearly 10% (Kasai et al., 2003). Mathalon and colleagues showed that the left lateral ventricle increased by 13% per year, or a doubling of the size over an eight-year period (Mathalon, Sullivan, Lim, & Pfefferbaum, 2001). DeLisi and collaborators (DeLisi, Sakuma, Ge, & Kushner, 1998) identified a clear reduction in hemispheric volume in 50 patients with first-episode schizophrenia over a four-year time period. Lawrie and associates (Lawrie et al., 2002) showed a reduction in temporal lobe volume over a two-year period in people in a high-risk group who developed psychotic symptoms during this period. Ho and colleagues (Ho et al., 2003) followed up patients with first-episode schizophrenia over a five-year period and found that white matter decreased significantly in the frontal parts of the brain. Job and collaborators (Job, Whalley, Johnstone, & Lawrie, 2005) followed the same prodromal cases as Lawrie (Lawrie et al., 2002) for another three-year period and confirmed the results of Lawrie and associates. And finally, in the most comprehensive follow-up study of brain structure, including more than 200 schizophrenia patients and 125 healthy controls, and with a follow-up period of 15 years after the start of treatment, Andreasen and collaborators found progressive changes in both gray and white matter in the early stages of the disease in a subset of patients (Andreasen et al., 2011).

The studies referred to provide an overall picture of quite extensive, multifocal structural changes in the brain over time in patients with first-episode psychosis. Nonetheless, such dramatic changes have not been found in all long-term studies. James and colleagues examined early-onset patients with schizophrenia and found enlarged lateral and third ventricle, plus a reduction in the left amygdala. However, they did not find any further deterioration over a period
of almost three years (James, Javaloyes, James, & Smith, 2002). And in a five-year follow-up of patients with schizophrenia who had been in treatment for a long time, no significant thinning of the cortex compared with healthy controls was found, suggesting that changes in the cortex stabilizes with a longer duration of the disease (Nesvag et al., 2012). Furthermore, the same research team found great stability in both cortical and subcortical brain changes in a group of patients in the early phase of psychosis disorder during a one-year follow-up (Haukvik et al., 2016).

Pol and Kahn (Pol & Kahn, 2008) summarized the results from follow-up studies by claiming that the progressive loss of brain tissue, which appears to be greatest in the frontal and temporal parts of the brain, is about twice as large as that found in healthy controls over a period of 20 years. In most of these studies, structural brain changes had taken place at the time of illness onset. Worth noting is that Pantelis and associates were able to register structural brain changes before disease onset in individuals at high-risk of developing psychosis. They found decreased gray matter in those who later developed a psychotic disorder compared to those who did not (Pantelis et al., 2003). Gur and associates (R. E. Gur et al., 1998) also found clear indications that changes in the brain occur before clinical symptoms. However, the more recent study referred to above (Haukvik et al., 2016; Nesvag et al., 2012) shows that the image is by no means clear for follow-up studies after illness onset.

It should be mentioned here that in addressing neurodegeneration, there are other features to consider than biological change. Also important is the profile of deficits. Neurodegenerative conditions can present with either a cortical or fronto-striatal profile depending on the localization of the neuropathology.

A neuropsychological study, which might also be seen as supporting the neurodegenerative hypothesis, is an examination of elderly patients by Harvey and collaborators (Harvey et al., 1996). They found a further decline in cognitive functions beyond what would be expected from aging. These findings were based on a large patient cohort, but only "rating scales" were used in the assessment, no neuropsychological tests. Harrison and Lewis have speculated that schizophrenia in one way or another makes a person highly vulnerable to dementia in old age, as eventually the brains of these patients are more vulnerable to cognitive disorders as a response to the normal age-related neurodegeneration (Harrison & Lewis, 2003). Recently, Harvey and collaborators (Harvey, Reichenberg, Bowie, Patterson, & Heaton, 2010)
have confirmed a certain cognitive decline over a four-year period in elderly schizophrenia patients.

**Findings that speaks against a degenerative process**

What primarily speaks against schizophrenia as a degenerative process are the many longitudinal studies of neurocognitive functions that show there is no deterioration after illness onset (see above). Rather, it looks like there is often some improvement in cognitive functioning, at least in the initial period after the patient has remitted from an acute phase (Rund et al., 2016; Rund et al., 2007). It seems unlikely that a person can perform as well or better on various neuropsychological tests if there is a structural degeneration of the brain (Rund, 2009).

Apart from longitudinal studies of neurocognition, are there other studies that argue against a degenerative process? Studies including several biological “markers” seem to do so. First and foremost, there is no evidence of gliosis in schizophrenia (Woods, 1998). Gliosis is a hallmark of degeneration. Moreover, there is no consistent evidence of degenerated neurons in postmortem studies. Neither cellular changes, loss of cell nuclei or molecular changes has been found in these studies.

As a third argument against schizophrenia as a degenerative disorder, it should be mentioned that many patients over the years improve clinically. As has been noted, clinical improvement is not what one would expect as a result of a progressive loss of brain tissue (Weinberger & Marenco, 2003).

**Degeneration or neurodevelopmental disorder?**

There is no final clarification of the question of whether or not schizophrenia is a degenerative disorder, although most empirical evidence indicates that it is not. The strongest indication of degeneration are the longitudinal studies after illness onset, which mostly shows that structural changes continue after the disease has begun. The great stability of cognitive functioning after onset speaks against degeneration. How is it possible that a person performs equally well on cognitive tests as before if parts of the brain have disappeared (Weinberger & McClure, 2002)?
It should be added in this connection that processes other than neurodevelopmental and neurodegeneration can affect a patient's cognitive functioning. Both compensation and regression are phenomena that characterize the normal brain. There is reason to assume that these are also effective in patients with schizophrenia, namely the brain's ability to compensate for the loss of neurons by significant synaptic plasticity. There are also many examples of regressive changes in the human brain. There is a loss of synapses without a loss of brain cells. These can usually not be "read" in the form of macroscopic structural changes.

It has also been pointed out that various external factors can lead to morphological changes, such as the stress caused by the psychotic experience. The neurotoxic hypothesis postulates that the psychosis itself is toxic, and that this is revealed in structural changes (Rund, 2014). Stress leads to increased cortisol levels, which can cause changes in the brain, e.g. by affecting the volume of ventricles or hippocampus. Cannabis, alcohol, tobacco, and physical inactivity are also mentioned as factors that may contribute to changes in cortical and ventricular volumes (Zipursky, Reilly, & Murray, 2013). Moreover, several studies have shown that antipsychotic treatment over long periods is associated with loss of brain tissue (Andreassen, Thompson, & Dale, 2014; Ho, Wassink, Ziebell, & Andreasen, 2011; Lieberman et al., 2005; Moncrieff & Leo, 2010; Navari & Dazzan, 2009).

Another factor that can affect structural changes is that there is considerable plasticity in the human brain. For instance, DeLisi and colleagues have shown that the size of the ventricles can increase, decrease and then increase again over short time periods (DeLisi et al., 1998).

In order to explain the apparently contradictory findings between morphological and neuropsychological research, it is important to be aware that the brain is likely to compensate for part of the shrinkage that may occur in neurons or neuropil. Animal studies suggest that damage in the brain promotes compensatory responses. A compensatory reaction may involve an increase of synapses, or that there is a reorganisation of synaptic connections without any degeneration. It is also possible that there may be the formation of new cells in the human brain. Or it may be that the brain uses existing brain networks more efficiently, or operates alternative networks as asserted by the Cognitive Reserve Theory (Stern, 2002).

Another idea is that there are two pathogenic processes in schizophrenia, as Lieberman (Lieberman, 1999) and other researchers have pointed out. One is a neurodevelopmental disorder and another is a limited neurodegenerative or neuroregressive process. For instance, Gur and
collaborators (R. E. Gur et al., 1998) found that only a subset of patients showed progressive structural changes after disease onset. The two pathogenic processes might represent two types of schizophrenia, one with a good prognosis and one with a poor prognosis where the biological causes are more significant. This is a hypothesis that has been topical throughout the history of schizophrenia research, with Gabriel Langfeldt and Robin Murray (Murray, Castle, Ocallaghan, & Lewis, 1992) among the foremost advocates for this idea.

WHAT INITIATES A DEVIANT NEUROCOGNITIVE DEVELOPMENT?

Most evidence suggests that there is no neurodegeneration in schizophrenia, and that this disease fits better into what is called a neurodevelopmental disorder. But we still have a limited understanding of what triggers the deviant development in cognitive functioning, and why symptoms do not appear before early adulthood. The pathogenesis of schizophrenia seems to be complex, with many and interwoven "mediating variables" and no single factor that triggers the deviant neurocognitive development.

One of the most studied pathogenic factors is a dysfunctional dopamine regulation. The original dopamine hypothesis built on the fact that neuroleptics block dopamine D2/3 receptors, as well as amphetamine and other substances that activate the dopamine system, can induce psychotic symptoms. It has later been discovered by molecular imaging techniques that the dopaminergic dysregulation occurs on a presynaptic level (Howes & Murray, 2014). It could be this dopaminergic dysregulation is an intermediate link between neural damage and the positive symptoms in schizophrenia.

A factor with a certain evidence of initiating an abnormal neurocognitive development is prenatal exposure to viral infections (Brown & Derkits, 2010). For example, Mednick et al. (Mednick, Machon, Huttunen, & Bonett, 1988) found a correlation between exposure to influenza during the second trimester and development of schizophrenia in adulthood in the fetus that was affected by the infection. But there are also meta-analyses pointing out that the evidence for gestational influenza as a psychosis risk factor is insufficient (Selten & Termorshuizen, 2016). In contrast, several recent studies support the hypothesis that other types of virus or bacteria may play a role in this connection, or that activation of cytokine responsive processes in the placenta or fetus may lead to developmental disorders of the brain (Ormstad & Rund, 2016).
Another indication that something goes wrong early in development is the fact that there is a significant predominance of obstetrics complications (OC) in those who later develop schizophrenia, such as low birth weight, hypoxia and cesarean (Teigset, Mohn, & Rund, 2016). A meta-analysis showed that OC increased the risk of developing schizophrenia by 1.3 to 2 times (Geddes et al., 1999). Such birth complications may be due to abnormalities before birth (which also affects birth), or that the birth injury causes or initiates a disturbance in the neurocognitive development postnatally. As mentioned before, some studies (Rosso et al., 2000; Schiffman et al., 2004; Walker, 1994) have documented neuromotor abnormalities in infants that develop schizophrenia in adulthood, indicating that damage in the neuromotor development occurs at an early stage. It is also possible that genetic factors may affect such disturbances in the neurodevelopment, probably interacting with some of the above-mentioned factors.

Recently, it is also well documented that being exposed to trauma in childhood increases the risk of developing schizophrenia. Some believe the increased vulnerability of those who have been exposed to trauma is because such dramatic events lead to changes in the brain, particularly those involving the hippocampus and the HPA axis (Morgan & Fisher, 2007; Read, Fosse, Moskowitz, & Perry, 2014).

CONCLUSION

Early studies in experimental psychopathology and neuropsychological research that took place in American laboratories laid the groundwork for later neurocognitive studies. Long-term studies have provided solid evidence that cognitive deficits are relatively stable for a long time after onset. There is also a large body of evidence showing that cognitive impairment is present in a milder form in the premorbid and prodromal phase. Furthermore, we know that there are some delays in cognitive and neuro-motor skills in childhood among those who later develop schizophrenia. These findings are the basis for asserting that schizophrenia is a neurodevelopmental disorder. However, we have a limited understanding of what initiates an abnormal development. There is an additional need for more methodologically refined studies to determine whether the accentuated fall in neurocognitive function found in elderly patients is caused by a degenerative process that inserts itself at a late stage of the disease (Harvey et al., 1996). There is also need for studies with longer follow-ups after illness onset. Ideally, such
neurocognitive follow-up investigations should run in parallel with structural and functional MRI.
References


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