



# Is there a degenerative process going on in the brain of people with schizophrenia?<sup>†</sup>

Bjørn Rishovd Rund<sup>1,2\*</sup>

<sup>1</sup> Vestre Viken Hospital Trust, Rud, Norway

<sup>2</sup> Department of Psychology, University of Oslo, Oslo, Norway

## Edited by:

Kenneth Hugdahl,  
University of Bergen, Norway

## Reviewed by:

Ole A. Andreassen, Ullevål University  
Hospital, Norway; University of Oslo,  
Norway

Thomas Dierks, University Hospital of  
Psychiatry, Switzerland

## \*Correspondence:

Bjørn Rishovd Rund, Vestre Viken  
Hospital Trust, Asker og Bærum  
Hospital, P.O. Box 83, Rud, Norway.  
e-mail: bjorn.rishovd.rund@sabhf.no

<sup>†</sup>This paper is based on an article  
published in *Nordic Journal of  
Psychiatry*, 2009, Volume 63(3), pp.  
196–201, by the same author and with  
the title “Is schizophrenia a  
neurodegenerative disorder?”

Schizophrenia is a biological and behavioural disorder which manifests itself in neurocognitive dysfunctions. The question of whether these key characteristics of the disorder are due to schizophrenia being a degenerative disorder has been discussed for more than 100 years. Neuropsychological data indicate that neurocognitive functions are relatively stable over time after illness onset. Several studies show that there is a decline in neurocognitive functioning prior to and in connection with onset of illness. There is no convincing evidence, however, that there is a progressive neurodegenerative process after onset of illness. Morphological data, on the other hand, indicate a degenerative process. Several novel longitudinal studies indicate a rapid reduction of vital brain tissues after onset of illness. In this paper some ideas about compensatory reactions and Cognitive Reserve Theory is outlined as possible explanations of the recent magnetic resonance imaging studies that show structural changes in the brain after the onset of schizophrenia, at the same time as cognitive functioning does not become more impaired. Determining whether schizophrenia is a neurodegenerative illness with progressive structural changes in the brain after debut of the illness, or a neurodevelopmental disorder starting in early life, is of significant importance for understanding the pathophysiology of the illness and its treatments.

**Keywords:** schizophrenia, neurocognition, degeneration, neurodevelopmental process, compensatory reactions

## INTRODUCTION

Schizophrenia is a complex biological and behavioural disorder which manifests itself in neurocognitive dysfunctions. The question of whether these key characteristics of the disorder are due to schizophrenia being a degenerative disorder has been discussed for more than 100 years.

Before we go into the main theme of this paper, a clarification of a central concept might be necessary, namely degeneration. What characterizes a neurodegenerative process? The main issue is that brain tissue is destroyed. This usually includes cytopathology as well as neuronal and synaptic loss followed by gliosis, i.e. scar tissue development of the brain. It can also include programmed cell death, such as apoptosis, which does not lead to any scar tissue. Further, probably loss of isolated nerve cells may occur without gliosis. A degenerative process is the basis for most states of dementia. However, we must also be aware of the fact that a decrease in the brain volume (grey matter) occurs in healthy people, starting at the age of 15–20 years (Rapoport et al., 1999; Hulshoff Pol and Kahn, 2008). An important emerging research area is the role of glia cells in the regulation of neurodegeneration. A comprehensive treatment of this topic is beyond the scope of this paper. A review of this topic is to be found in Müller and Schwarz (2007).

Kraepelin (1919) was clearly of the opinion that schizophrenia is a degenerative disorder (dementia praecox). This view held stance until the middle of the last century. At that time some reports began to emerge that patients with schizophrenia could be cured

through long term psychotherapeutic treatment or in some other way recover completely from the disorder. How could an illness be degenerative if it was possible to recover from it?

During the 1980 and 1990s several longitudinal studies of neurocognitive functioning in patients with schizophrenia began to emerge. These studies showed no evidence of decline in function over time. This was taken to indicate that there is no ongoing degenerative process in the brain, at least not after the onset of illness (Rund, 1998). Instead, a neurodevelopmental model emerged as the dominant explanatory framework for schizophrenia. According to this model normal brain development is disturbed by genetic or environmental factors in patients with schizophrenia. The model is supported by findings like higher prevalence of obstetric complications, minor physical anomalies, and neurological soft signs among people who later develop schizophrenia; as well as brain morphology findings that show smaller brain volumes even before the emergence of psychotic symptoms. The neurodevelopmental hypothesis was put forward as an alternative to the neurodegenerative hypothesis, although the two models do not stand in opposition to each other.

However, a few years ago the hypothesis of schizophrenia as a degenerative disorder re-emerged. This was primarily based on several new longitudinal magnetic resonance imaging (MRI) studies that showed substantial increases in the brains cavities (see next section), and corresponding excessive shrinkage of vital brain tissue, during the first years after the onset of illness. These studies

have led some to opine that the neurodegenerative hypothesis may have been overshadowed by the ascendancy of the neurodevelopmental hypothesis (Weinberger and McClure, 2005).

### WHAT DO WE KNOW ABOUT STRUCTURAL CHANGES IN THE BRAIN OF PATIENTS WITH SCHIZOPHRENIA?

First of all, we have clear empirical support to state that there are changes occurring in the brains of patients with schizophrenia (Shenton et al., 2001; Harrison and Lewis, 2003; Weinberger and Marenco, 2003; Weinberger and McClure, 2005). The most robust findings seem to be that patients with schizophrenia have:

- a. Larger ventricles than healthy controls. An increase in the lateral ventricle was found in 80% of the studies, while an enlarged third ventricle was found in 73% of the studies (Weinberger and Marenco, 2003). Seen together, 30 studies have found that patients with schizophrenia had 26% larger ventricles than healthy controls.
- b. The volume of the frontal lobes is reduced compared to healthy controls. This was found in 59% of the studies. Parietal- and occipital lobe-abnormalities have also been found in several studies (Niznikiewicz et al., 2003).
- c. There is a reduction in the volume of the temporal lobes, amongst other areas in the medial temporal lobe, which includes the amygdala–hippocampal complex and the neocortical temporal lobe. Temporal lobe reduction was found in 74% of the studies (Shenton et al., 2001).

However, it is primarily the fact that these changes in the brain seem to progress at rapid speed after the patient has become ill, at least the first years after the onset of illness, which has strengthened the hypothesis of an ongoing degenerative process. This has been shown in recent longitudinal studies including several first episode studies. In most of these studies structural brain changes have been found already at the time of onset of the psychosis. Pantelis and colleagues (Pantelis et al., 2003) found structural brain changes already prior to illness onset in high risk individuals. They found reduced grey matter in individuals who later developed a psychotic illness compared to those who did not. Gur et al. (1998) have also found clear indications that changes in the brain take place before the clinical symptoms emerge. While the early longitudinal studies did not indicate any progressive deterioration of the brain early in the illness (Weinberger and Marenco, 2003), the pattern is different in many of the more recent studies. Several of these studies showed dramatic structural changes over a relatively short time period:

- Chakos et al. (2005) showed that patients with schizophrenia had less hippocampal volume than age matched healthy controls and that the volume reduction was larger in older, than in younger patients.
- Jacobsen et al. (1998) documented a 7% reduction of the hippocampus per year.
- Rapoport et al. (1997) reported a 7% reduction of the thalamus per year in adolescents with schizophrenia. Further they found a 10% increase in ventricular volume per year. In a later publication the same research group (Rapoport et al., 1999) reported a significant reduction in grey matter in frontal and parietal areas in these adolescent patients over a 3- to 5-year period.

- Mathalon et al. (2001) showed that the left lateral ventricle increased by 13% a year, or a doubling of the size within an 8-year period.
- DeLisi et al. (1998) identified a clear reduction in hemispheric volume in 50 patients with first episode schizophrenia followed over a 4-year period.
- Sporn et al. (2003) found a substantial loss of grey matter through the teenage years in patients with early onset schizophrenia.
- Kasai et al. (2003) found a 9.6% progressive reduction in grey matter in the upper left temporal gyrus over a period of 1.5-year after the first hospitalization in patients with schizophrenia.
- Lawrie et al. (2002) showed a reduction in temporal lobe volume over a 2-year period in individuals at high risk who developed psychotic symptoms during this period.
- James et al. (2002) investigated early onset patients with schizophrenia and found enlarged lateral and third ventricle, in addition to a reduction in the left part of the amygdala. However, these researchers did not find further deterioration over a 3-year period.
- Cahn et al. (2002) found that the whole brain grey matter decreased during a 1-year follow-up of first-episode patients with schizophrenia.
- Ho et al. (2003) carried out a 5-year follow-up study of first-episode schizophrenia patients and found that the frontal white matter decreased.
- Jacob et al. (2005) followed the same prodromal cases as Lawrie et al. (2002) over another 3 years and confirmed their findings.
- Whitford et al. (2006) found grey matter reductions in first-episode patients with schizophrenia that were followed-up 2–3 years.

Taken together these studies indicate fairly comprehensive, multi focal structural changes in the brain over time in patients with first episode psychosis. Progressive volume loss seems most pronounced in the frontal and temporal areas. Progressive brain tissue loss in schizophrenia is, during a 20-year time period, found to be approximately twice that found in healthy people due to normal ageing (Hulshoff Pol and Kahn, 2008).

Another issue supporting a neurodegenerative hypothesis can be found in a study by Harvey et al. (1996). They found that in elderly patients with schizophrenia (above 65 years) there is a further reduction of neurocognitive functions beyond what would be expected from ageing. These results are based on a large patient sample. The findings of Harvey et al. (1996) may lead to speculation as to whether schizophrenia in some way makes the person particularly sensitive to the development of dementia in old age, or whether the brain in this group of patients is more sensitive to neurocognitive impairments as a response to normal age-related neurodegeneration (2003).

### WHAT DO THE NEUROPSYCHOLOGICAL LONGITUDINAL STUDIES OF PATIENTS WITH SCHIZOPHRENIA SHOW?

The strongest argument against schizophrenia being a neurodegenerative disorder is the many longitudinal studies of neurocognitive functions that show that there is no worsening after the onset of

illness. Rather in general there seems to be some improvement in neurocognitive functioning, at least during the first period after the patients have gone into remission (Rund et al., 2006). It seems unlikely that a person can perform as well or better on various neuropsychological tests over time, if there is a simultaneously ongoing structural degeneration of the brain.

In 1998 Rund summarized the results of the 14 existing longitudinal studies of neurocognitive functioning in patients with schizophrenia (Rund, 1998). Only studies that had a follow-up time of at least 1 year were included in the analysis. It was concluded that after the onset of illness neurocognitive functioning is relatively stable over time. Kurtz (2004) have updated Rund's analysis with eight new longitudinal studies that have been published since 1997. Kurtz et al's results confirm the conclusion of Rund (Rund, 1998).

After this review article was published, Andreasen et al. (2005) have published results from a 9-year follow-up study. They show the same improvement in neurocognitive functioning that has been found in a number of studies the first years after the onset of illness. However, after 5 years the upward curve flattens out, and after 9 years the patients perform at the same level as they did at the first assessment.

Two studies with a 10-year follow-up time (Stirling et al., 2003; Hoff et al., 2005) show the same trend. Hoff et al. (2005) found no further reduction in neurocognitive functions over the first 10 years in patients that were assessed the first time at the onset of illness. However, they showed less improvement after 10 years than healthy controls on specific functions when controlling for differences between the groups at the first assessment. Hoff and colleagues concluded that patients remain relatively stable with regard to their level of neurocognitive functioning, at least through the first 10 years after the onset of illness.

Finally, these findings are confirmed and strengthened by a recent report from Øie et al. (2008). She has followed a group of early-onset schizophrenia over a 13-year period; a longer follow-up than in any other study. The main finding in this study is a significant decline in verbal memory and learning, and an arrest; i.e. lack of improvement, in attention and processing speed.

Beyond this general pattern of stability over the first years after illness onset, there is probably a certain fluctuation in level of functioning, particularly in functions that are state related (i.e. influenced by clinical state). In one study Rund et al. (1997) investigated 15 patients with schizophrenia with a battery consisting of 10 neuropsychological tests in two distinct different phases; an acute phase and a remission phase. We found a clear tendency that patients performed better when they were in remission. This may indicate that the psychotic experiences/symptoms themselves make it more difficult to concentrate on the test, something which is necessary to perform well. It is difficult to know whether it is the fact that the psychotic symptoms disappear that makes the patient also perform better on neuropsychological tests, or whether the improvement is caused by other factors, such as for instance the direct chemical effect of medication.

What else, in addition to the longitudinal studies of neurocognitive functioning, goes against schizophrenia being a degenerative disorder? Several biological "markers" appear to do so. First of all, there is no evidence of gliosis in schizophrenia (Woods, 1998),

which is a sign of degeneration (see Section "Introduction"). Also, in post mortem studies there is no consistent evidence of degenerated neurons, cellular changes, loss of cell embryos, or molecular changes (Weinberger and Marenco, 2003).

A third argument against schizophrenia being a degenerative disorder is the fact that many patients show clinical improvement over time. In several of the longitudinal MR-studies (Rapoport et al., 1997; DeLisi et al., 1998; Gur et al., 1998; Jacobsen et al., 1998) the patients showed clinical improvement during the same time period that large structural changes took place in the brain. As Weinberger and Marenco (2003) pointed out, clinical improvement is hardly what one would expect as a result of progressive loss of brain tissue. This is, however, a more likely combination than performing as well on neuropsychological tests over time, while at the same time losing brain tissue. Actually, Sporn et al. (2003) found that a greater degree of clinical improvement was significantly related to a reduction in grey matter.

### WHEN DO THE COGNITIVE IMPAIRMENTS EMERGE?

There is no doubt that neurocognitive impairments are evident at the onset of illness in most patients who develop schizophrenia. However, we must also be aware that 35–40% of the patients do not have a significant impairment in neurocognitive functioning (Rund et al., 2006); i.e. they function within what must be characterized as the normal range (some healthy controls also function below average). Nevertheless, patients functioning within the normal range may have had a reduction in neurocognitive functioning after they became ill. Also several studies of high risk groups have found that these individuals show signs of neurocognitive deficits many years prior to the onset of illness (Jones et al., 1994; Cornblatt et al., 1999; Cannon et al., 2000; Fuller et al., 2002; Niendam et al., 2003; Ang and Tan, 2004). Moreover, several prodromal studies indicate that the neurocognitive impairments evident after the psychotic breakthrough are also evident prior to the onset of illness (Caspi et al., 2003; Gschwandtner et al., 2003; Wood et al., 2003; Hawkins et al., 2004; Brewer et al., 2005). Probably there is a further reduction in neurocognitive functioning just prior to the first psychotic episode (Caspi et al., 2003). A preliminary conclusion is that precursors to the cognitive deficits are evident relatively early, that these develop gradually and that they are found in corresponding form and approximately the same degree in the prodromal phase, as in remission. The psychotic experiences or symptoms exacerbate the neurocognitive deficits somewhat during the acute phase. Such a development with an early insult in the neural development that remains for the duration of life, but that does not get worse over time, may best be characterized as a static encephalopathy (Rund, 1998).

### HOW CAN THE CONTRADICTORY FINDINGS FROM MORPHOLOGICAL AND NEUROPSYCHOLOGICAL STUDIES BE EXPLAINED?

There is no doubt that there is a "deterioration" of most neurocognitive functions in patients who develop schizophrenia. But much of this seems to occur prior to the onset of illness. We also have reason to believe that this neurocognitive deterioration to some degree runs parallel with structural changes in the brain. If one chooses to use the term neurodegeneration about what happens prior to the onset of illness, there is evidence suggesting that

schizophrenia is a degenerative disorder. But this is not the regular use of the term degeneration, nor was this how Kraepelin used the term. With his “dementia praecox” term he was referring to the assumption that there is a progressive worsening of the condition after the onset of illness.

We cannot provide a definite answer as to whether schizophrenia is a degenerative disorder (in the sense of a progressive degenerative state after the onset of illness). Longitudinal studies of neurocognitive functioning provide a relatively consistent indication that the impairment does not progressively worsen the first years after the onset of illness. However, some longitudinal studies with a very long follow-up period indicate that there is a certain decline after many years of illness. This may be due to medication or other biological effects. The decline may also be caused by under-stimulation from the environment. (Such under-stimulation may also to a certain degree explain the structural changes evident in the brains of patients with schizophrenia.) In essence, we need to realize that the morphological data to a great extent are inconsistent. There are no two studies that have found the exact same structural changes in this patient group (Weinberger and McClure, 2005).

How can we then explain more recent MRI studies that show clear cut structural changes in the brain after the onset of illness, at the same time as neurocognitive functioning does not become more impaired? Two issues can be pointed out:

The first issue may be what Lieberman (1999) amongst others has suggested, i.e. that there may be two ongoing pathogenic processes in schizophrenia; one neurodevelopmental process and a limited neurodegenerative or neuroprogressive process. McGlashan and Hoffman (2000) suggest that such neuroprogressive processes are a developmentally determined reduction in the connections between cortical synapses. (If we emphasize the fact that post mortem studies first and foremost show loss in neuropil and not in nerve cells in the cortex in patients with schizophrenia, the term neuroprogressive is more adequate than neurodegenerative). In Gur et al.’s (1998) study for instance, they only identified a sub-group of patients that showed progressive structural change after the onset of illness. Thus, it is possible that there are at least two types of schizophrenia; one with a good prognosis and one with a poorer prognosis and a clearer biological basis. This would mean a return to a hypothesis which has been of great interest throughout the history of schizophrenia research (see, for instance, Murray et al., 1992).

A second issue concerns the plasticity in the human brain. DeLisi et al. (1998) have for instance showed that the size of the ventricles may alternatively increase, decrease, then increase again over such short time periods as months. In the previously referred study by Lawrie et al. (2002), they found the same reduction in ventricular volume in healthy controls

as in the high risk group that developed psychotic symptoms. It is also likely that the brain compensates for some of the loss that occurs in nerve cells or neuropil.

Animal studies indicate that damage to the brain may illicit compensatory reactions such as synaptic growth. It is also possible that new cells may develop in the human brain. Stern (2002) suggests that the brain actively attempts to cope with, or compensate for, pathology. The idea of reserve against brain damage stems from the repeated observation that there does not appear to be a direct relationship between degree of brain damage and the clinical manifestation of that damage. Cognitive Reserve Theory explains why individuals evidence different neuropsychological deficits following the same neurological damage. Cognitive reserve may be based on more efficient utilization of brain networks or of enhanced ability to recruit alternate brain networks as needed.

There are several possible alternative models that may explain the brain changes occurring after the onset of illness: It could be degeneration occurs with varying degrees of compensation or it could be that there are regressive processes that are undetectable in macroscopic investigations of the brain. It is also possible that there is a reorganization of synaptic connections without any form of degeneration or regression. Further, it could be that the brain more efficiently utilizes brain networks or enhances the ability to recruit alternative brain networks as needed, as Cognitive Reserve Theory suggests.

Still another possibility is that brain structural or volumetric changes affect certain sub-groups of patients more than others. A complicating matter could, however, be the heterogeneity of schizophrenia and individual variation regarding both functional and structural brain measures. In a recent meta-analysis of MR volumetric changes in schizophrenia and bipolar disorders, compared to healthy controls (Arnone et al., 2009), it was found that schizophrenia patients differed from bipolar patients with more regional structural changes compared to global changes in bipolar disorder patients. Implicated regions were enlargement of the lateral ventricles, pointing to frontal and temporal volumetric reductions in schizophrenia, and reduction of amygdale volume (Arnone et al., 2009). In addition, Kalus et al. (2004) reported reduction of hippocampal volume in patients with schizophrenia, which was related to alterations in white matter coherence between hippocampal sub-structures. In particular the hippocampal alterations could be related to the psychopathology of schizophrenia that could be more critical for sub-groups of patients with clearly defined cognitive impairments. It is therefore possible that previous studies of neurodegeneration have not paid enough attention to the symptomatic heterogeneity of the disorder, and that this could be related to brain structural changes over time, pointing to a possible degenerative process.

## REFERENCES

- Andreasen, N. C., Moser, D. J., O’Leary, D. S., and Ho, B.-C. (2005). Longitudinal changes in neurocognition during first decade of schizophrenia illness. *Schizophr. Bull.* 31, 348.
- Ang, Y. G., and Tan, H. Y. (2004). Academic deterioration prior to first episode schizophrenia in young Singaporean males. *Psychiatry Res.* 121, 303–307.
- Arnone, D., Cavanagh, J., Gerber, D., Lawrie, S. M., Ebmaier, K. P., and Mackintosh, A. M. (2009). Magnetic resonance imaging studies of bipolar disorder and schizophrenia: a meta-analysis. *Br. J. Psychiatry* 195, 194–201.
- Brewer, W. J., Francey, S. M., Wood, S. J., Jackson, H. J., Pantelis, C., Phillips, L. J., Yung, A. R., Anderson, V. A., and McGorry, P. D. (2005). Memory impairments identified in people at ultra-high risk for psychosis who later develop first-episode psychosis. *Am. J. Psychiatry* 162, 71–78.
- Cahn, W., Hulshoff Pol, H. E., Lems, E. B., van Haren, N. E., Schnack, H. G., van

- der Linden, J. A., Schothorst, P. F., van Engeland, H., and Kahn, R. S. (2002). Brain volume changes in first-episode schizophrenia: a 1-year follow-up study. *Arch. Gen. Psychiatry* 59, 1002–1010.
- Cannon, T. D., Bearden, C. E., Hollister, J. M., Rosso, I. M., Sanchez, L. E., and Hadley, T. (2000). Childhood cognitive functioning in schizophrenia patients and their unaffected siblings: a prospective cohort study. *Schizophr. Bull.* 26, 379–393.
- Caspi, A., Reichenberg, A., Weiser, M., Rabinowitz, J., Kaplan, Z., Knobler, H., Davidson-Sagi, N., and Davidson, M. (2003). Cognitive performance in schizophrenia patients assessed before and following the first psychotic episode. *Schizophr. Res.* 65, 87–94.
- Chakos, M. H., Schobel, S. A., Gu, H., Gerig, G., Bradford, D., Charles, C., and Lieberman, J. A. (2005). Duration of illness and treatment effects on hippocampal volume in male patients with schizophrenia. *Br. J. Psychiatry* 186, 26–31.
- Cornblatt, B., Obuchowski, M., Roberts, S., Pollack, S., and Erlenmeyer-Kimling, L. (1999). Cognitive and behavioral precursors of schizophrenia. *Dev. Psychopathol.* 11, 487–508.
- DeLisi, L. E., Sakuma, M., Ge, S., and Kushner, M. (1998). Association of brain structural change with the heterogeneous course of schizophrenia from early childhood through five years subsequent to a first hospitalization. *Psychiatry. Res.* 84, 75–88.
- Fuller, R., Nopoulos, P., Arndt, S., O'Leary, D., Ho, B. C., and Andreasen, N. C. (2002). Longitudinal assessment of premorbid cognitive functioning in patients with schizophrenia through examination of standardized scholastic test performance. *Am. J. Psychiatry* 159, 1183–1189.
- Gschwandtner, U., Aston, J., Borgwardt, S., Drewe, M., Feinendegen, C., Lacher, D., Lanzarone, A., Stieglitz, R. D., Riecher-Rössler, A., and Basel Early Detection of Psychosis Study – Früherkennung von Psychosen (FEPSY). (2003). Neuropsychological and neurophysiological findings in individuals suspected to be at risk for schizophrenia: preliminary results from the Basel early detection of psychosis study – Früherkennung von Psychosen (FEPSY). *Acta Psychiatr. Scand.* 108, 152–155.
- Gur, R. E., Cowell, P., Turetsky, B. I., Gallacher, F., Cannon, T., Bilker, W., and Gur, R. C. (1998). A follow-up magnetic resonance imaging study of schizophrenia. Relationship of neuroanatomical changes to clinical and neurobehavioral measures. *Arch. Gen. Psychiatry* 55, 145–152.
- Harrison, P. J., and Lewis, D. A. (2003). Neuropathology of schizophrenia. In *Schizophrenia*, 2nd Edn, S. R. Hirsch, and D. R. Weinberger, eds (London, Blackwell Publishing), pp. 310–325.
- Harvey, P. D., Lombardi, J., Leibman, M., White, L., Parrella, M., Powchik, P., and Davidson, M. (1996). Cognitive impairment and negative symptoms in geriatric chronic schizophrenic patients: a follow-up study. *Schizophr. Res.* 22, 223–231.
- Hawkins, K. A., Addington, J., Keefe, R. S., Christensen, B., Perkins, D. O., Zipurksy, R., Woods, S. W., Miller, T. J., Narqueez, E., Breier, A., and McGlashan, T. H. (2004). Neuropsychological status of subjects at high risk for a first episode of psychosis. *Schizophr. Res.* 67, 115–122.
- Ho, B. C., Andreasen, N. C., Nopoulos, P., Arndt, S., Magnotta, V., and Flaum, M. (2003). Progressive structural brain abnormalities and their relationship to clinical outcome; a longitudinal magnetic resonance imaging study early in schizophrenia. *Arch. Gen. Psychiatry* 60, 585–594.
- Hoff, A. L., Svetina, C., Shields, G., Stewart, J., and DeLisi, L. E. (2005). Ten year longitudinal study of neuropsychological functioning subsequent to a first episode of schizophrenia. *Schizophr. Res.* 78, 27–34.
- Hulshoff Pol, H. E., and Kahn, R. S. (2008). What happens after the first episode? A review of progressive brain changes in chronically ill patients with schizophrenia. *Schizophr. Bull.* 34, 354–366.
- Jacob, D. E., Whalley, H. C., Johnstone, E. C., and Lawrie, S. M. (2005). Grey matter changes over time in high risk subjects developing schizophrenia. *Neuroimage* 25, 1023–1030.
- Jacobsen, L. K., Giedd, J. N., Castellanos, F. X., Vaituzis, A. C., Hamburger, S. D., Kumra, S., Lenane, M. C., and Rapoport, J. L. (1998). Progressive reduction of temporal lobe structures in childhood-onset schizophrenia. *Am. J. Psychiatry* 155, 678–685.
- James, A. C., Javaloyes, A., James, S., and Smith, D. M. (2002). Evidence for non-progressive changes in adolescent-onset schizophrenia: follow-up magnetic resonance imaging study. *Br. J. Psychiatry* 180, 339–344.
- Jones, P., Rodgers, B., Murray, R., and Marmot, M. (1994). Child development risk factors for adult schizophrenia in the British 1946 birth cohort. *Lancet* 344, 1398–1402.
- Kalus, P., Buri, C., Slotboom, J., Gralla, J., Remonda, L., Dierks, T., Strik, W. K., Shroth, G., and Kiefer, C. (2004). Volumetry and diffusion tensor imaging of hippocampal suregions in schizophrenia. *Neurereport* 15, 867–871.
- Kasai, K., Shenton, M. E., Salisbury, D. E., Hirayasu, Y., Lee, C. U., Ciszewski, A. A., Yurgelun-Todd, D., Kikinis, R., Jolesz, F. A., and McCarley, R. W. (2003). Progressive decrease of left superior temporal gyrus gray matter volume in patients with first-episode schizophrenia. *Am. J. Psychiatry* 160, 156–164.
- Kraepelin, E. (1919). *Dementia Praecox and Paraphrenia*. Edinburgh, E and S Livingstone.
- Kurtz, M. M. (2004). Neurocognitive impairment across lifespan in schizophrenia: an update. *Schizophr. Res.* 74, 15–26.
- Lawrie, S. M., Whalley, H. C., Abukmeil, S. S., Kestelman, J. N., Miller, P., Best, J. J., Owens, D. G., and Johnstone, E. C. (2002). Temporal lobe volume changes in people at high risk of schizophrenia with psychotic symptoms. *Br. J. Psychiatry* 181, 138–143.
- Lieberman, J. A. (1999). Pathophysiologic mechanisms in the pathogenesis and clinical course of schizophrenia. *J. Clin. Psychiatry* 60(Suppl. 12), 9–12.
- Mathalon, D. H., Sullivan, E. V., Lim, K. O., and Pfefferbaum, A. (2001). Progressive brain volume changes and the clinical course of schizophrenia in men: a longitudinal magnetic resonance imaging study. *Arch. Gen. Psychiatry* 58, 148–157.
- McGlashan, T. H., and Hoffman, R. E. (2000). Schizophrenia as a disorder of developmentally reduced synaptic connectivity. *Arch. Gen. Psychiatry* 57, 637–648.
- Müller, N., and Schwarz, M. J. (2007). The immunological basis of glutamatergic disturbance in schizophrenia: towards an integrated view. *J. Neural Transm. Suppl.* 72, 269–280.
- Murray, R. M., O'Callaghan, E., Castle, D. J., and Lewis, S. W. (1992). A neurodevelopmental approach to the classification of schizophrenia. *Schizophr. Bull.* 18, 319–332.
- Niendam, T. A., Bearden, C. E., Rosso, I. M., Sanchez, L. E., Hadley, T., Nuechterlein, K. H., and Cannon, T. D. (2003). A prospective study of childhood neurocognitive functioning in schizophrenic patients and their siblings. *Am. J. Psychiatry* 160, 2060–2062.
- Niznikiewicz, M. A., Kubicki, M., and Shenton, M. E. (2003). Recent structural and functional imaging findings in schizophrenia. *Curr. Opin. Psychiatry* 16, 123–148.
- Øie, M., Sundet, K., and Rund, B. R. (2008). Neurocognitive decline in early-onset schizophrenia compared with ADHD and normal controls: evidence from a 13-year follow-up study. *Schizophr. Bull.* doi: 10.1093/scbul/sbn 127.
- Pantelis, C., Velakoulis, D., McGorry, P. D., Wood, S. J., Suckling, J., Phillips, L. J., Yung, A. R., Bullmore, E. T., Brewer, W., Soulsby, B., Desmond, P., and McGuire, P. K. (2003). Neuroanatomical abnormalities before and after onset of psychosis: a cross-sectional and longitudinal MRI comparison. *Lancet* 361, 281–288.
- Rapoport, J. L., Giedd, J., Kumra, S., Jacobsen, L., Smith, A., Lee, P., Nelson, J., and Hamburger, S. (1997). Childhood-onset schizophrenia. Progressive ventricular change during adolescence. *Arch. Gen. Psychiatry* 54, 897–903.
- Rapoport, J. L., Giedd, J. N., Blumenthal, J., Hamburger, S., Jeffries, N., Fernandez, T., Nicolson, R., Bedwell, J., Lenane, M., Zijdenbos, A., Paus, T., and Evans, A. (1999). Progressive cortical change during adolescence in childhood-onset schizophrenia. A longitudinal magnetic resonance imaging study. *Arch. Gen. Psychiatry* 56, 649–654.
- Rund, B. R. (1998). A review of longitudinal studies of cognitive functions in schizophrenia patients. *Schizophr. Bull.* 24, 425–435.
- Rund, B. R., Landro, N. I., and Orbeck, A. L. (1997). Stability in cognitive dysfunctions in schizophrenic patients. *Psychiatry Res.* 69, 131–141.
- Rund, B. R., Sundet, K., Asbjørnsen, A., Egeland, J., Landro, N. I., Lund, A., Roness, A., Stordal, K. I., and Hugdahl, K. (2006). Contrasts in neuropsychological test profiles between patients with schizophrenia and recurrent non-psychotic major depression. *Acta Psychiatr. Scand.* 113, 350–359.
- Shenton, M. E., Dickey, C. C., Frumin, M., and McCarley, R. W. (2001). A review of MRI findings in schizophrenia. *Schizophr. Res.* 49, 1–52.
- Sporn, A. L., Greenstein, D. K., Gogtay, N., Jeffries, N. O., Lenane, M., Gochman, P., Clasen, L. S., Blumenthal, J., Giedd, J. N., and Rapoport, J. L. (2003). Progressive brain volume loss during adolescence in childhood-onset schizophrenia. *Am. J. Psychiatry* 160, 2181–2189.
- Stern, Y. (2002). What is cognitive reserve? Theory and research application of the reserve concept. *J. Int. Neuropsychol. Soc.* 8, 448–460.
- Stirling, J., White, C., Lewis, S., Hopkins, R., Tantam, D., Huddy, A., and Montague, L. (2003). Neurocognitive function and outcome in first-episode schizophrenia: a 10-year follow-up of an epidemiological cohort. *Schizophr. Res.* 65, 75–86.
- Weinberger, D. R., and McClure, R. K. (2005). Neurotoxicity, neuroplasticity, and magnetic imaging morphometry. *Arch. Gen. Psychiatry* 59, 553–558.

- Weinberger, R. D., and Marenco, S. (2003). Schizophrenia as a neurodevelopmental disorder. In *Schizophrenia*, 2nd Edn., S. R. Hirsch and D. R. Weinberger, eds (London, Blackwell Publishing), pp. 326–348.
- Whitford, T. J., Grieve, S. M., Farrow, T. F., Gomes, L., Brennan, J., Harris, A. W., Gordon, E., and Williams, L. M. (2006). Progressive grey matter atrophy over the first 2–3 years of illness in first-episode schizophrenia: a tensor-based morphometry study. *Neuroimage* 32, 511–519.
- Wood, S. J., Pantelis, C., Proffitt, T., Phillips, L. J., Stuart, G. W., Buchanan, J. A., Mahony, K., Brewer, W., Smith, D. J., and McGorry, P. D. (2003). Spatial working memory ability is a marker of risk-for-psychosis. *Psychol. Med.* 33, 1239–1247.
- Woods, B. T. (1998). Is schizophrenia a progressive neurodevelopmental disorder? Toward a unitary pathogenetic mechanism. *Am. J. Psychiatry* 155, 1661–1670.
- Conflict of Interest Statement:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.
- Received: 14 June 2009; paper pending published: 05 August 2009; accepted: 05 October 2009; published online: 26 October 2009.
- Citation: Rund BR (2009) Is there a degenerative process going on in the brain of people with schizophrenia? *Front. Hum. Neurosci.* 3:36. doi: 10.3389/neuro.09.036.2009  
Copyright © 2009 Rund. This is an open-access article subject to an exclusive license agreement between the authors and the Frontiers Research Foundation, which permits unrestricted use, distribution, and reproduction in any medium, provided the original authors and source are credited.