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Hospitalization and Psychosis: Influences on the Course of Cognition and Everyday Functioning in People with Schizophrenia

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Abstract

Long term institutional stay has decreased markedly in people with schizophrenia, although there are still many individuals with a history of long-term institutional stay residing in the community. In addition, although the average duration of acute admissions for schizophrenia is also decreasing, there are indications that psychotic episodes leading to acute admissions are associated with risk for cognitive and functional declines and changes in brain structure. In this paper we review the literature on cognitive changes with aging and institutionalization in schizophrenia, reaching the conclusion that the reasons for chronic institutionalization in the current include largely severe psychosis and aggressive behavior. Thus, these factors may be the operative factor in the age-related declines in cognition and functioning reported in this population. We also present evidence to suggest that these changes may be similar to those seen in younger patients who experience repeated psychotic episodes leading to hospitalization. Our conclusion is that there is minimal evidence that hospitalization, long or short, leads to cognitive and functional changes, but rather that the reason for these hospitalizations may underlie cognitive and functional declines. Prevention of relapse and discovering treatments to assist patients with resistant symptoms may reduce the risk of cognitive and functional decline across the lifespan in people with schizophrenia.

Keywords

Schizophrenia; Aging; Neuropsychology; disability; psychosis; institutionalization; hospital

The Background Context

Long stay institutional treatment was the norm for people with schizophrenia for the first part of the 20th century. Large hospitals were established in rural areas and patients remained there for extended periods of time. Dramatic and pathetic pictures were disseminated, showing disheveled and strange looking people, often assuming unusual poses or grimacing and gesturing in incomprehensible ways. The fact that there were no treatments that were effective for any of the symptoms of schizophrenia or other conditions led to

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extended stays and a bleak future. Further, the concept was advanced that institutionalization itself was partially or largely responsible for the behaviors seen on the part of these patients.

In the mid 1950s chlorpromazine was introduced for the treatment of people with schizophrenia. As the first medication that reduced psychotic and disorganized symptoms, it had an enormous and significant impact on lengthy hospital stays for schizophrenic patients. There were wholesale discharges of patients from long-stay care and by the late 1970s the remaining patients in long-stay care were those who were largely non-responsive to the effects of antipsychotic treatments. Further, the entire inpatient treatment model for schizophrenia has changed drastically, from stays that averaged 6–12 weeks for “acute admissions” 25 years ago, to 5–7 day stays or even admissions that are not designated as admissions because the patient stays in the emergency room for up to 72 hours.

As recently as the mid 1990s, however, there were still substantial numbers of long stay psychiatric patients in several locations in the country. Both state and VA facilities had large numbers of these patients, with many of these patients being over the age of 65 and often never having recovered from their first psychotic episode, even they had been hospitalized for 40 years or more (Davidson et al., 1995). These patients, by virtue of having remained behind during several waves of deinstitutionalization efforts, manifested multiple significant symptom features. In contrast to non-institutionalized patients, they had substantial positive and negative symptoms (Davidson et al., 1995), had profound cognitive impairments (Harvey et al., 1998), significant functional impairments (Harvey et al., 1997), and substantial levels of aggressive and unpredictable behaviors (Bowie et al., 2001). Despite their severe levels of impairment, many of these patients were ultimately discharged from long stay care and moved to nursing home facilities (White et al., 1997), even at fairly young ages (Adelsky et al., 2011). Some were, however, sent to community facilities that had higher levels of opportunities for independence (Bowie et al., 2006). Several studies have been conducted on the characteristics of these patients.

The Goal of This Review

The goal of this review is to present information about hospitalization in schizophrenia and how it relates to the course of illness, assessment of patients, and general understanding of schizophrenia. Changes in health care delivery have been substantial for people with schizophrenia and it is not clear whether the illness has changed as much as the way we treat it. Chronic hospital stays certainly appear to have the potential to lead to adverse impacts on functioning, but in the current model of care, there is an increased risk for medication nonadherence and psychotic relapses. It is not clear which has a worse long term impact. Measurement of functioning was easier if patients were observed every day by patient care staff; nowadays it is often a challenge to find someone who knows the patient. Overall, there are several issues that have evolved in terms of the impact of hospitalization on the symptoms and cognitive and functional capacity of patients with schizophrenia. It is important to know whether being treated in a hospital, for either the short or long term, is an antecedent or consequence of clinical symptoms, cognitive deficits, and disability. It is also important to understand whether psychotic symptoms have a deleterious effect on other aspects of functioning and whether the presence of continuous psychosis, in the presence or absence of antipsychotic treatment leads to functional and cognitive deterioration. There are several lines of research that address these questions, including longitudinal and cross-sectional studies of individuals with schizophrenia who were previously or current chronically institutionalized. Additional studies have examined the consequences of both repeated psychotic episodes and continuous psychotic symptoms on cognition, functioning, and brain structure.

In this paper, we review the relationship between hospitalization, both acute and chronic several other features of the illness, including aggression and hostility, cognitive impairments and functional capacity, and overall functional outcomes. We also elucidate exciting new developments in the direct assessment of functional abilities and present data of our own that addresses the validity of these assessment strategies in healthy older people. Finally, we address whether institutionalization itself has a toxic effect on outcomes or whether the contemporaneous causes of long-term hospitalization are the potential causal factor for age-related changes in cognition, functional capacity, and everyday functioning.

Contemporary Reasons for Long Term Hospital Care

Studies of the characteristics of patients discharged from long-stay psychiatric facilities provide some information about the transition from these long stay facilities. In a series of studies of the characteristics of patients discharged from long-stay psychiatric care, White and colleagues discovered several informative facts (White et al., 1997, White et al., 2006). This study followed 551 older (mean age=76) long-stay (mean length of stay 34 years) for a three year period and examined three different possible outcomes: staying in the hospital (n=289, 53%), being sent to a nursing home (200, 36%), and being sent to a community placement (62, 11%). Interestingly, greater disability or more severe cognitive impairments did not differentiate patients who went to nursing home care from those who remained in the hospital. In fact, the patients who remained behind were more symptomatic and more aggressive than those who were discharged. In a later comparative study of patients previously discharged to nursing home care compared to those who were still hospitalized, similar findings were revealed in that patients who remained in long-stay psychiatric care had more severe positive psychotic symptoms and less severe negative symptoms than those who had been discharged to a nursing home. Also, in that study, nursing home patients had more severe cognitive deficits and impairments in everyday living skills than patients still in a hospital. As discussed below, the possibility exists that cognitive functioning declines in older people with schizophrenia who have a history of extended institutional stay. As a result, a cross-sectional study cannot really address the cognitive performance of these nursing home residents at the time of discharge, which was up to 10 years previously.

Aggressive and disruptive behavior is a common antecedent to acute admission in the current care environment. It is also a primary correlate of being difficult to discharge even during times of high pressure to reduce inpatient census. For example, the White et al. (1997) data just described cognitive impairments and hostility posed the greatest barriers to discharge and in a systematic study of aggression at that research site Bowie et al. (2001) found that the prevalence of aggression in long stay patients was equivalent to that seen in acutely admitted patients admitted within the last 3 days in earlier studies. There is a large literature on aggression as a precipitant of acute admissions and in long stay patients (See Serper et al., 2008). Most studies find that deficits in frontal lobe function, measured either with neurological or neuropsychological assessments predict aggression (Krakowski and Czobor, 1997). Interestingly, several studies also show that negative symptoms are associated with aggressive behavior as well (Krakowski, 2005). These negative symptom correlate results have been interpreted in terms of frontal lobe dysfunction as alterations in emotional functioning are common in individuals with frontal lobe damage.

The challenge of reducing aggression associated with cognitive deficits is challenging, because of the lack of interventions that target cognition and the possibility that cognitive functioning declines over time. Clearly, the prevalence of aggression in older institutionalized patients is greater than in younger patients because not all younger patients are hospitalized for aggressive behavior. In the sections below we will examine data on the course of cognitive functioning in aging and evaluate whether there are changes over time.

Cognitive Changes as of Function of Aging in Schizophrenia

In the following sections, we review the literature on cognition and functioning in schizophrenia, as is relevant to hospitalization and the reasons for hospitalization. We focus first on research on cognitive and functional decline with aging in schizophrenia. These studies have focused on the characteristics and course of cognitive impairments and have compared individuals with an extended history of institutional stay to patients who lived their whole lives in the community with only sporadic exacerbations. Then we discuss the characteristics of cognition, functioning, and brain structure as a consequence of psychosis. In this section we focus first on the impact on continuous psychosis in ambulatory and hospitalized patients and then upon the consequences of repeated psychotic relapses on these same variables.

There has been considerable debate as to whether patients with schizophrenia are more generally susceptible to the effects of aging than the healthy individuals (Kirkpatrick et al., 2008). Cross-sectional studies have been mixed. Some studies have indicated that the aging effects associated with schizophrenia are no different than that observed aged healthy individuals (Mockler et al., 1997, Eyer Zorilla et al., 2000, Hijman et al., 2003). Conversely, other investigations have shown considerably more impairment than what would be expected as a function of normal aging (Fucetola et al., 2000, Arnold et al., 1995). Mixed results have also occurred in longitudinal studies with some investigations suggesting no significant aging effects relative to healthy individuals (Heaton et al., 2001), while others have either suggested worsening (Harvey et al., 2003, Friedman et al., 2001, Loewenstein et al., 2010) or at least that certain subgroups of schizophrenia patients may be particularly vulnerable to cognitive deterioration in certain domains as they age (Bowie et al., 2008; Granholm et al., 2010).

In one large-scale (n=424) longitudinal (6-year) follow-up study, albeit without a comparison sample of healthy controls, Harvey et al. (2003) examined changes in cognition and observer-rated everyday functioning. The findings indicated that patients with higher and lower baseline performance manifested equivalent and statistically significant cognitive declines, but differences in decline on basic activities of daily living. Random effects regression analysis indicated that functional changes were significantly correlated with cognitive changes for the sample as whole and that cognitive changes were the best predictor of changes in functional status over time. Baseline cognitive status was not a statistically significant covariate for functional change, nor was the course of negative symptoms over the follow-up period. Cognitive change appeared very similar in magnitude across older poor outcome patients with different baselines of cognitive impairment. In contrast, functional decline was limited to patients with lower levels of functioning at baseline. These findings suggest that cognitive thresholds for impairments in different aspects of functional status may exist in patients with schizophrenia. Finally, the results indicated a small, but nonsignificant, relationship with the course of psychosis over the follow-up period. Thus, suggesting evidence of a “toxic psychosis” effect, an issue to be returned to later in this paper.

One reason for these apparent discrepancies across studies is that aging effects may be quite modest until persons have reached their 70s and beyond (Friedman et al., 2001). In the Harvey et al. (2003) study, risk for functional decline was predicted by older age at the time of assessment, which had a greater influence than age at onset. Further, the control samples in many of these studies have both been younger than 65 years with very modest sample sizes. Finally, comparing chronically institutionalized patients with schizophrenia over the age of 65 with healthy control subjects (e.g., Friedman et al., 2001) may not control for much, as the two subjects samples have lead entirely different lives.

We attempted to address these issues in a recent study with 226 community dwelling schizophrenic subjects ranging in age from 40 years to 80+ years of age and over 800 normal elderly controls for comparison purposes (Loewenstein et al., 2010). We found that the performance of healthy subjects age 70 years and older was far superior to the performance of younger schizophrenic subjects aged 40–49 years on tests tapping memory, executive function and psychomotor speed. In particular, age effects were most pronounced for schizophrenia subjects who are 70 years or greater and age effects for schizophrenia patients were much more pronounced relative to healthy normals on tests of verbal learning and speed of processing measures. The finding that age influences cognitive decline for schizophrenia patients was particularly profound on tests of speed of processing and verbal memory are consistent with the literature showing that these tend to be the most persistent deficits in schizophrenia (Aleman et al., 1999, Knowles et al., 2010), and the most robust predictors of everyday functional disability in schizophrenia (Ojeda et al., 2008), particularly for residential status (Shamsi et al., 2011, Leung et al., 2008).

Although cross-sectional, our recent findings (Loewenstein et al., 2010) have significant implications for longitudinal research with institutionalized patients. First, although the life expectancy is lower for schizophrenia patients than normal elderly, it is critical to study patients aged 65 and older if one is going to discern the true effects of aging in schizophrenia. Due to advances in medical treatment the number of older schizophrenic patients will increase in the near future. However to truly discern the trajectory of cognitive changes over time, there needs to be adequate samples of healthy normal subjects. It is also important to have reliable and valid measures of cognitive and functional capacity in patients with schizophrenia. This can be particularly challenging with older patients. These issues are discussed in the following sections.

Assessment of Everyday Functional Outcomes and Functional Capacity in Schizophrenia: Informant-Based Reports—It is quite common to base assessment of functional ability of schizophrenic patients on reports from informants such as a relative or friend or the patient themselves. While this is a well-accepted practice, it is increasingly recognized that patients with severe mental illness or age-related cognitive disorders and their informants may be inaccurate in their judgments regarding their own cognitive performance, functional capacity, and everyday functioning (Loewenstein et al., 2001, Keefe et al., 2006, Bowie et al., 2007, Goldberg et al., Sabbag et al., 2011). This may be due to such factors as informant biases which may include denial, minimization or oversensitivity to perceived impairments. Informants who are very depressed or anxious may over report functional deficits. Other informants such as friends or more distant relatives may not have ample opportunity to observe and interact with the patient to make valid functional judgments. For example, we are finding that friends tend to overestimate the functional abilities of patients (Sabbag et al., 2011). This overestimation may be a function of the fact that friends may have limited opportunity to observe certain functional behaviors or in the cases of homeless schizophrenic patients, may themselves be prone to psychiatric illness. Patients also tend to overestimate their functional abilities.

Ratings of everyday functioning on the part of high contact clinicians seem much more related to other aspects of functioning than reports from other sources. Regardless of whether the clinician informants see the patients every day as inpatients (Harvey et al., 1998), provide outpatient case management services (Bowie et al., 2008), or are their counselors in intensive rehabilitation services (Sabbag et al., 2011), these ratings have shown convergent validity with performance-based measures.

Other Indices of Everyday Functioning—Other indices of everyday functioning can include milestone achievements. This can include employment, the ability to function

residentially, and social outcomes. Measurement of milestone achievements may be more complex than it appears, because of the intrinsic relationships between opportunities, finances, and other constraints. It is actually easier to measure functional abilities in an inpatient setting and our studies of the everyday adaptive functioning of people who are sent to nursing homes (Harvey et al., 1998) suggests that everyday functioning of nursing home referrals and state hospital patients are quite similar. Real-world milestone achievement can be rare in people with schizophrenia and in a recent paper we (Harvey et al., in press) found that 1). achievements of real-world milestones were very minimally related to each other and 2). that achievement of multiple current functional milestones across employment, residential independence, and social outcomes was very low at 6%. This low base-rate of milestone achievement is one of the reasons that assessment of everyday functioning has often relied on ratings of sub-threshold milestones: looking for a job; performing ADLs in a supported environment, or socializing in groups.

There is a paucity of research on the longitudinal course of everyday functioning following long hospitalizations. Such studies are challenging, because people discharged after a particularly long stay may be elderly and likely lack resources, which leads to placements in restrictive environments. There are longitudinal data available on the course of functional capacity as described below, which is easier to measure because of reduced reliance on the immediate residential environment.

Measures of Functional Capacity—As a result of the issues associated with informant reports, there has been a greater reliance on performance-based measures than can provide an objective assessment of functional capacities, i.e., the skills that are critical to the performance of everyday living tasks. For example, one can objectively obtain data as to whether the individual can pay a bill, manage and balance a checkbook, write a check, count currency and make change for a purchase. This type of objective measurement of functional capacity is now widely employed in the study of severe mental illness. Based on the findings that these measures are highly and consistently related to cognitive functioning on the one hand and everyday real-world functioning on the other, these measures and the skills they assess have been proposed to be an important mediator of the influence of cognitive functioning on real-world everyday outcomes (Bowie et al., 2006, Bowie et al., 2008, McClure et al., 2007). In both schizophrenia and bipolar illness, performance on a measure of everyday functional skills, the UCSD Performance based Skills Assessment (UPSA) (Patterson et al., 2001) was the best predictor of real world outcomes in vocational and residential domains, even when the influences of cognition and symptoms were considered (Bowie et al., 2010, Mausbach et al., 2010). Measurement of possible changes in functional capacity has also been suggested as a co-primary assessment in treatment studies aimed at cognitive enhancement in schizophrenia (Green et al., 2011, Leifker et al., 2011).

The UPSA includes paper and pencil simulations of activities performed in everyday life and includes: **Communication** (i.e., dialing the telephone to schedule a physician appointment, obtaining and dialing a number from an information operator); **Finance** (counting currency, making change, and paying a bill); **Transportation** (using a bus schedule in planning a trip and understanding charges and obtaining information) and **Comprehension/Planning** (reading and planning a recreational outing based on scenarios about a trip to the beach on a hot sunny day and the zoo on a cold rainy day); and **Household Management** skills (e.g., shopping for grocery items). Some versions of the UPSA also include a medication management subtest and are referred to as the UPSA-II (Green et al., 2011).

Overall, the convergence between measures of functional capacity such as the UPSA and cognitive performance in people with schizophrenia has been quite strong. To date, at least

10 studies using 6 different cognitive assessment strategies have yielded correlation coefficients ranging from $r=0.6$ to $r=0.7$ between total scores on three versions of the UPSA and composite neuropsychological (NP) test scores. Further, studies examining the correlations between individual neuropsychological test scores and scores on the UPSA have correlations in the range of $r=0.2$ to $r=0.4$ (McClure et al., 2007). Thus, performance on tests of cognitive ability is related to the ability to perform everyday living skills, with both global impairments (i.e., composite scores) and specific ability domains are related to performance.

Deterioration in Functional Capacity over time—As cognitive performance is highly associated with measures such as the UPSA in people with schizophrenia, the question arises as to whether changes in functional capacity would be similar to previously reported declines in cognitive performance over time. In a study aimed at examining the direct effects of a history of long-term institutional stay, Harvey et al (2010) followed 111 community dwelling people with schizophrenia and 76 healthy controls for up to 45 months. The people with schizophrenia ranged in their longest hospitalization from less than one month to over 36 years. Functional capacity was assessed with the UPSA and with the Social Skills Performance assessment (SSPA) (Patterson et al., 2001). There were significant declines in both functional capacity measures, but no time effects for neuropsychological performance in the patient sample. The interaction of longest institutional stay and time was significant for UPSA scores, meaning that patients with longer durations of institutional stay manifested greater worsening over time. When current residential status (independent vs. supported) was examined, the effect of institutionalization remained significant and current residential status was not, arguing that current opportunities contributed to performance.

The fact that that HC participants manifested practice effects on both the SSPA and NP assessment suggests that the modest worsening seen in NP performance on the part of the older people with schizophrenia was even more significant. When compared to healthy controls, patients with schizophrenia worsened by .15 SD on their NP performance across 1 or two reassessments, while the HC improved by .35 SD, suggesting an aggregate worsening (decline plus lack of practice effects) of 0.5 SD in 45 months ($p<.05$). While not associated with a history of institutionalization, this is still a substantial effect.

The Utility of the UPSA as a Measure of Functional Capacity in Non-Impaired Adults—The UPSA has been used as a functional capacity measure in over 50 studies of people with schizophrenia. Further, it has been endorsed as the best performance-based outcomes measure for use in clinical treatment studies (Green et al., 2011). It has also been used with minor modifications in studies of mild cognitive impairment and methamphetamine abuse (Gomar et al., 2011, Henry et al., 2010). The psychometric properties of the UPSA are good, and it appears sensitive to disability in a wide array of pathological conditions

However, one of the criticisms of the UPSA is the concern about ceiling effects, both for patients and for healthy, normal community-dwelling elders. In impaired populations with considerable disability and cognitive impairments, global factors such as poor motivation could produce the apparent association between cognitive abilities, both global and specific, and UPSA scores. A similar relationship between performance based assessments of cognitive functioning and functional capacity in community dwelling healthy people who lack disability and severe performance deficits on cognitive measures would suggest a more direct relationship between UPSA scores and cognitive abilities. Previous studies of healthy people with the UPSA have not focused on specific abilities or have performed combined analyses with healthy and impaired populations. In fact, in the multiple studies of functional capacity with other assessment methods reviewed by Moore et al (2007), the majority of the

studies that examined the correlations between functional capacity measures and cognitive performance used global cognitive assessments including the Mini-Mental State Examination (MMSE) (Folstein et al., 1975) or the Mattis Dementia rating scale.

To address this issue, we examined a sample of healthy individuals on whom we previously reported on the psychometric properties of the UPSA and composite NP performance (Leifker et al., 2011). Specifically, we examined data regarding the extent to which performance on the UPSA was related to neuropsychological measures of varying component cognitive abilities. The sample included 89 cognitively normal individuals living in the community (40 males and 49 females) 49–89 years of age who were recruited as healthy controls for a longitudinal study of cognitive and functional decline in older people with schizophrenia (see Leifker et al., 2010) for a more detailed description). All participants had to demonstrate intact mental status as assessed by the Folstein Min-Mental State Examination score of 26 or greater. Further, no subject met current or lifetime criteria for either mood disorders or psychotic disorder by DSM-IV criteria (American Psychiatric Association, 1994) and no subjects were receiving psychotropic medications for psychiatric conditions.

All subjects were administered a cognitive assessment battery that measured episodic memory measured by the five learning trials of the Auditory Verbal Learning Test (RAVLT) (Spreen and Strauss, 1998), processing speed measured by the Trail Making Test (TMT) (Reitan and Wolfson, 1993) Parts A and B, and Wechsler Adult Intelligence Scale 3rd Edition (WAIS-III) (Wechsler et al., 1997) Digit Symbol tests, working memory measured with the WAIS-III Digit Span Forward and Backward tests, and executive functioning measured by the Color, Word, and Color-Word Interference Conditions of the Stroop Color Word Test (Golden, 1976). Also, to avoid restriction of range, raw rather than corrected scores on the neuropsychological measures were employed in data analyses.

The mean age of the sample was 66.9 years (SD=10.9 years) with an average educational attainment of 14.61 years (SD=2.4 years; 9–20 years). The average MMSE score was 28.58 (SD=1.3). The mean UPSA total score for the sample was 85.80 (SD= 7.8; range =60–100). The mean for the Comprehension/Planning domain was 22.19 (SD= 1.8; range= 16.7–25.0); the mean for the Finance domain was 22.04 (SD= 2.8; range= 11.4–25.0); the mean for the Communication domain was 19.04 (SD= 4.0; range= 8.3–25.0) and the mean for the Transportation domain was 22.38 (SD= 3.5; range= 12.5–25.0).

As depicted in Table 1, there were a number of statistically significant relationships between neuropsychological test performance and total UPSA scores. Correlations between total UPSA scores and neuropsychological tests such as Digit Symbol, Letter-Number Sequencing and Stroop Color-Word Interference scores were found to account for 23.0 % to 28.1% of the total variance in UPSA total scores. Financial Skills were best predicted by Trails B and Letter-Number Sequencing while Communication was best predicted by Trails A, and RAVLT total learning. Transportation was best predicted by Stroop Color-Word Interference and Digit Symbol. The UPSA Comprehension and Planning subscale was not predicted at the corrected level of significance by any of the neuropsychological measures.

We regressed the UPSA total score on all of the neuropsychological test predictor variables in the study and found that the neuropsychological variables accounted for 40.6% of the total variability in functional capacity. Neither age or educational attainment or their interactions with neuropsychological variables added significant explained variability to the model.

Overall, we found considerable variability in performance on the UPSA as evidenced by the wide range of scores for the UPSA and its subscales among cognitively normal adults living

independently within the community. For example, only 1 member of this sample of healthy controls received a perfect total score on the UPSA. We also found strong associations between scores on the neuropsychological tests and performance on the UPSA. The multiple R^2 of .40 is particularly impressive when one considers that imperfect reliability of any psychometric instrument. We have previously shown that cognitive and functional capacity performance accounts for a similar amount of explained variance in directly observed real-world functional outcomes in Alzheimer's disease (Loewenstein et al., 1995), schizophrenia (Harvey et al., 2009), and bipolar disorder (Bowie et al., 2010).

Our data suggest that measures such as the UPSA are resistant to ceiling effects in healthy adults and like psychiatric populations, specific types of neuropsychological test performance are related to measures of functional capacity. Overall these findings suggest that the UPSA can be used as a measure to reliably assess differences in functional capacity between schizophrenia patients and non-impaired samples of older adults.

Data Regarding the NeuroToxicity of Psychosis

In addition to understanding the association of long-stay hospitalization and aging on the cognitive, emotional and functional capacity of schizophrenic patients it is also important to understand the impact of prolonged psychosis on functional outcomes. The notion that antipsychotic treatment can alter the natural course of schizophrenia was introduced by Wyatt (Wyatt, 1991), who reviewed data from studies of patients who experienced extended periods of psychosis prior to their initial treatment with antipsychotic medications and compared them to patients whose first psychotic episode received medication treatment. His data suggested a disease modifying effect of antipsychotic treatment early in the course of illness. While this concept has been the subject of much research and controversy, it seems plausible that reduction of psychosis may have a beneficial effect. There are inconsistent results regarding duration of untreated psychosis and lifelong functional outcomes. Many of the inconsistent results may be due to research designs that are simply not adequate to address the question of whether lengthy periods of untreated psychosis lead to poorer outcomes, specifically in terms of very short durations of untreated psychosis examined in the study. In the studies reviewed by Wyatt, many of the patients experienced decades of untreated psychosis, while in many studies of first episode patients the duration of untreated psychosis is measured in weeks or months.

There are two lines of research suggesting that psychosis, even in ambulatory patients, is associated with deterioration in functioning and alterations in brain structure. One is the longitudinal study of treatment refractory patients, who experience continued psychosis despite adequate antipsychotic treatment. The second is the longitudinal study of early-course patients across the course of multiple psychotic episodes. Both have suggested that continuous psychosis or multiple psychotic episodes have adverse consequences.

In a four-year longitudinal study of brain structure using CT scan technology, Davis et al. (1998) compared deteriorated, disabled patients who had experienced continuous psychosis despite adequate treatment for at least 5 years to similar-aged patients who were treatment responsive. Those patients who experienced continuous psychosis demonstrated longitudinal ventricular enlargement that was greater in the left hemisphere than the right. Neither the treatment responsive patients nor a sample of healthy controls demonstrated any ventricular enlargement during this time frame. In addition, a single study of the correlation between cortical changes and cognitive performance in chronic patients (Gur et al., 1998) found that reductions in temporal and frontal lobe volumes were associated with greater cognitive decline. These findings combine with studies of older patients with schizophrenia (Friedman et al., 2001, Harvey et al., 1999; 2003) that have suggested that more severe psychotic symptoms predict greater cognitive and functional decline over various follow-up periods.

Thus, persistent psychosis seems associated with progressive brain volume loss as well as with cognitive and functional declines and losses in critical brain regions may be the substrate for these changes.

The aforementioned studies are typically confounded by a series of issues, including institutionalization, medication status, and critical differences in age and other characteristics of the patient samples. The concept of schizophrenia as a chronically active brain process starting at or before the time of the first episode was introduced by DeLisi et al (1999). Reviews of the state of this research (DeLisi et al., 1999) reached the conclusion that brain volumes do decrease progressively starting at the time of the first episode or before. However, the data collected in a series of important studies in the Netherlands, comprehensively assessing early and mid-course patients, addresses this issue quite convincingly and thoroughly. Specifically, Kahn and colleagues in the Netherlands have performed a series of important studies on patients with schizophrenia with 5-year follow up methods, including a substantial number of patients identified and followed from the time of their first episode. A sample of 96 patients with schizophrenia and 113 healthy controls were followed for a 5-year period (Van Haren et al., 2007). During this time, patients were followed clinically and their number of relapses was measured, with this number ranging from 0 to 8. It was found that there was a statistically significant reduction in brain volume, specifically in left frontal and temporal regions. Loss of frontal gray matter was also significantly associated with the number of number of relapses experienced. Interestingly, treatment with either clozapine or olanzapine attenuated those changes. This is a finding that has been replicated elsewhere, suggesting that treatments that are effective for treatment refractory patients, clozapine in specific, also appear to have neuroprotective effects.

In the subsample of 34 first episode patients in the study, several other additional findings emerged (Cahn et al., 2006). Volume loss in the first year of illness was associated with 5-year clinical and functional outcomes. Enlargement of the lateral ventricle predicted reduced likelihood of independence in residence at the follow-up. This is an interesting parallel to the findings of Davis et al.(1998) who found that patients with persistent psychosis and disability also demonstrated longitudinal enlargements of the left lateral ventricle.

Duration of untreated psychosis at the time of the first entry into treatment was found to be unassociated with 5-year volume changes (Boonstra et al., 2011) While DUP was related to the severity of psychosis at baseline, intervening treatment events (including relapses) accounted for more variance in cortical atrophy over five years than did DUP. In terms of the clinical significance of these brain changes, van Haren et al. (2011) demonstrated that the patients with the greatest cortical thinning over the 5-year follow-up period also had the worst five year functional outcomes.

Conclusions

Hospitalization for people with schizophrenia is a consequence of several different behavioral and social psychosocial factors. The characteristics and reasons for hospitalization seem markedly different now than in 1900 or even in 1990. While it is difficult to disentangle the consequence of the reasons for hospitalization from the effects of hospitalization, most contemporary hospitalizations are extremely brief and the cause is typically psychotic exacerbation or aggressive and hostile behavior. While some patients historically experienced extraordinarily long stays, research on patients who were discharged document continued worsening of impairments after discharge. This finding can be interpreted as suggesting persistence of the poor outcome processes that led to extended institutional stay.

A common factor possibly linking cognitive changes with aging and early in the course of illness is psychosis. Either recurrent or persistent, there are indications that higher psychosis doses, particularly if treated with conventional antipsychotic medications, are associated with cortical deterioration with correlated functional impairments. Similar processes may be responsible for the cognitive and functional decline seen in older institutionalized patients who has an extended period of illness prior to the availability of any treatments. Finally, by the time that people with schizophrenia have reached old age they have been exposed for the most part to a lifetime of continuous or sporadic psychotic symptoms which may contribute to the persistence of cognitive decline even in cases where the experience of psychosis is still episodic.

Thus, these data suggest that continued efforts to engage people with schizophrenia in treatment can serve to prevent cognitive and functional decline associated with psychosis. Second, clozapine treatment has been shown in several studies to be associated with a reduced risk of cortical degeneration and is well known to reduce psychosis in a proportion of treatment-resistant patients. Finally, these data suggest that cognitive enhancing treatments may require continued control of psychosis in order to be effective and to lead to improved outcomes. Data to date suggests that these cognitive enhancement treatments are not effective on psychosis, so further developments in the treatment of non-adherent and treatment resistant patients seem required.

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TABLE 1

CORRELATIONS BETWEEN UPSA AND SELECTED NEUROPSYCHOLOGICAL VARIABLES AMONG HEALTHY NORMAL INDIVIDUALS (MMSE > 26)

	AGE	UPSA TOTAL SCORE	UPSA COMP/PLANNING	UPSA FINANCIAL	UPSA COMMUNICATION	UPSA TRANSPORTATION
Age	NA	-.25	-.12	-.07	-.23	-.23
Education	.20	.21	.10	.20	.15	.08
RAVLT Total Recall	-.11	.33 **	.27	.21	.37 ***	.01
Trials A	-.23	-.45***	-.25	-.19	-.35***	-.30**
Trials B	.18	-.42***	-.21	-.34***	-.26	-.26
Stroop Color Word Interference	.38 ***	.53 ***	.26	.31 **	.30 **	.44 ***
Digit Span Forwards	.08	.26	.16	.19	.19	.06
Digit Span Backwards	.05	.21	.17	.18	.08	.12
Letter Number Sequencing	-.28**	.48 ***	.25	.34 ***	.28 **	.30 **
Digit Symbol	-.32**	.49 ***	.23	.31 **	.20	.46 ***

Due to multiple comparisons, only p values of p < .01 are reported as statistically significant

** P .01;

*** P .001