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TIME ESTIMATION IN SCHIZOPHRENIA:

RELATIONSHIP TO CLINICAL AND

NEUROPSYCHOLOGICAL FUNCTIONING

by

Marcela A. Bonafina-Caraccioli

A dissertation submitted to the Graduate Faculty in Psychology, in partial fulfillment of the requirements for the degree of Doctor of Philosophy, The City University of New York

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Date

Executive Officer

Doreen Berman, Ph.D.

Jill M. Harkavy-Friedman, Ph.D.

John Keilp, Ph.D.

Kenneth Perrine, Ph.D.

Supervisory Committee

THE CITY UNIVERSITY OF NEW YORK

Abstract

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Marcela A. Bonafina-Caraccioli

Adviser: Jeffrey M. Halperin, Ph.D.

A considerable amount of literature indicates that dopamine has a central role in the etiology of schizophrenia, as well as in underlying mechanisms of time estimation. Despite these apparent common neurobiological bases, the investigation of time estimation in schizophrenia has been fairly neglected. The main purpose of this study was to extend our understanding of the perception of time among patients with this disorder. This may very well facilitate the reconceptualization of its core cognitive and clinical characteristics and promote effective interventions. Our approach included the use of two computerized tasks that required the verbal estimation and production of brief durations (i.e., 5 s to 90 s).Time estimation performance was compared between 38 adult inpatients with schizophrenia and 47 participants in a non-patient comparison group. In the patient group, time estimation was assessed after four weeks on the same dose of neuroleptic

medication. To study the impact of antipsychotic medication on time perception, a subgroup of 10 inpatients kept medication-free during three weeks was repeatedly evaluated off and on medication. Overall, patients with schizophrenia, particularly females, exhibited a faster internal time sense compared to the non-patient comparison group. After neuroleptic medication, the perception of time became significantly accelerated. Indeed, this finding led us to speculate that the faster time sense observed in patients with schizophrenia was a medication effect. Moreover, the synergistic effect of adjunctive medication indicated that anticonvulsants appear to further accelerate the patients' internal time sense. The relationship between time estimation and clinical variables such as psychotic symptomatology, impulsiveness, and suicidal behavior was also investigated. A moderate relationship was found between time estimation and positive symptoms, but this function was uncorrelated with impulsiveness. No significant differences were found between suicide attempters and non-attempters. However, several indicators of suicidal behavior were differentially associated to time estimation. While a high number of prior suicide attempts was associated with a fast internal time sense, high scores on scales assessing suicidal intent and suicidal ideation were correlated with a slow internal time sense. Future research on time estimation would benefit from further investigating the role of medication and gender on time estimation.

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I. INTRODUCTION

"Time has no divisions to mark its passage; there is never a thunderstorm or blaze of trumpets to announce the beginning of a new month or year. Even when a new century begins, it is only we mortals who ring the bells and fire off pistols." (Thomas Mann, "The Magic Mountain," 1924, Chap. 5).

The overall goal of the current project was to extend the neuropsychological understanding of the perception of time in patients with schizophrenia.

A considerable amount of research has been generated that strengthens (Snyder, 1976), challenges (e.g., Knable et al., 1994), and expands (e.g., Creese, Burt & Snyder, 1976; Seeman & Lee, 1975) the dopamine (DA) hypothesis of schizophrenia (Carlsson & Lindqvist, 1963). Throughout the years, a dopaminergic dysregulation underlying this psychiatric disorder remains as the most influential theoretical framework in the field. On the other hand, it has been repeatedly reported that DA plays a crucial role in the regulation of internal time sense in animals (Meck, 1986; 1996) and humans (Gibbon, Malapani, Dale & Gallistel, 1997; Malapani, et al., 1998; Malapani et al., 2002; Rakitin, Stern & Malapani, 2002).

Given that both schizophrenia and the regulation of the internal sense of time share DA function as a core underlying neurobiological mechanism, it seemed highly compelling to study the perception of time in patients with schizophrenia.

Moreover, in view of the heterogeneous presentation of this disorder, a more profound knowledge of this cognitive function could broaden our comprehension of the

etiology and brain functioning in schizophrenia. Neuropsychological research in this area may well have important clinical and treatment implications and could contribute to the reconceptualization of some its core cognitive and clinical characteristics. As such, timing deficits could potentially be reflected in attention and working memory difficulties, disorganized speech and behavior, motor retardation, perseveration, and impulsiveness.

Historically, the concept of time has been considered one of the most complex in psychology. The passage of time is not immediately perceptible with our senses, making its experience inherently subjective. Thus, the estimation of duration becomes central in our relationship with the surrounding world and in the regulation of our behaviors. While behaviorist researchers initially excluded the perception of time as a measurable variable, the advent of experimental psychology introduced a shift in this field. This occurred because experimental psychologists were able to incorporate in their theoretical framework the concept of a subject perceiving relative experiences, and not only absolute ones (Fraisse, 1984). In the 1980s, the development of information-processing models of time perception was enriched by the introduction of biological clock models and the hypothesis of an "internal clock" (Treisman, 1963) underwent rich modifications with the advance of research in animal and human timing mechanisms (Church, 1981; Roberts, 1981). Further, the introduction of the Scalar Timing Theory (Gibbon, 1977) and the Scalar Timing Model (Gibbon, Church and Meck, 1984), applied mathematical properties to formalize the cognitive operations hypothesized to underlie the processing of temporal discriminations. At this time, internal clock models (Church 1984; Gibbon, 1977; Meck, 1983; Gibbon et al., 1984) became the mainstream foundation for a considerable amount

of research intended to establish the anatomical and physiological correlates of time perception, including cognitive functions such as attention for time and temporal memory. Though there was frequent lack of agreement among researchers in terms of methods and terminology used to approach this issue, numerous studies were generated, using both animals and humans.

Of particular interest has been the use of pharmacologic agents to manipulate the rate of the hypothesized internal clock and to establish the neurochemical profile involved in temporal integration in animals (Maricq & Church, 1983; Meck, 1986). As mentioned above, such studies revealed that DA plays a central role in the accurate estimation of durations in animals (Meck, 1986; 1996). This led to research examining neurobiological correlates of the perception of time among patient populations, particularly those with disorders related to DA dysfunction, such as Parkinson's disease (PD) and schizophrenia. During the last decade, investigators have consistently reported deficits in timing behaviors in patients with PD. The data indicate that PD patients' subjective perception of time is slower than the elapsed measured duration of time (Artieda, Pastor, Lacruz & Obeso, 1992; Gibbon, Malapani, Dale & Gallistel, 1997; Malapani et al., 1998; Pastor, Artieda, Jahanshahi & Obeso, 1992). Not surprisingly, these deficits in the estimation of time appear to be linked to the unbalanced dopaminergic system characteristic of the core impairments of PD. The investigation of timing behavior in schizophrenia has been staggeringly neglected. Since the 1950s, only five published studies (Clausen, 1950; Densen, 1977; Lhamon & Goldstone, 1956; Rammsayer, 1990; Tysk, 1983) addressed the estimation of time in schizophrenia.

This study analyzed the time estimation performance of adult inpatients with a

DSM-IV diagnosis of schizophrenia or schizoaffective disorder. The use of inpatients who were maintained on the same stable-dose of neuroleptic medication, and the inclusion of a subgroup of inpatients kept neuroleptic-free, provided a unique opportunity to examine the distortions in the perception of time in schizophrenia, as well as any changes in this function before and after antipsychotic medication. In view of the fact that animal research and clinical studies with PD patients have shown that pharmacologic manipulations to the dopaminergic system effectively produce a shift in timing, it was appealing to implement a similar approach in patients with schizophrenia. In addition, this study provided an excellent opportunity to investigate the relationship between accuracy in the perception of time and other variables profiling schizophrenia, such as clinical symptoms, intellectual functioning, and suicidality.

Suicide is the leading cause of early death among individuals with schizophrenia (Sartorious et al., 1987) and early reports (Neuringer, & Levenson, 1972; Neuringer, & Harris, 1974) indicated that suicide attempters tend to experience a distorted sense of the passage of time. A better understanding of the neuropsychological characteristics of time perception among subjects with schizophrenia at risk for suicidal behavior could contribute to the comprehension of the complex cognitive factors that interact with genetic, social, and clinical indicators of such destructive behavior.

The behavior most likely to be impacted by poor time estimation abilities is impulsiveness. Most definitions of impulsive behavior include a timing component associated with rapid responses and lack of planning (Barratt & Pattton, 1983; Buss & Plomin, 1975). However, research (Bachorowski & Newman; 1985; Barratt, 1967, Barratt, Patton, Olsson, & Zucker, 1981; Lennings & Burns, 1998; Standford and Barratt,

1996) is frequently complicated by obscure definitions of impulsiveness, heterogeneous samples, and some approaches to the study of time estimation that are unsound. No research has been published which examined the relationship between time estimation and impulsiveness in patients with schizophrenia. The present study investigated this relationship to determine whether internal time sense contributes to impulsive behaviors in schizophrenia.

In summary, the primary goals of this study were to study in patients with schizophrenia: (1) the ability to estimate time, both off and on neuroleptic medication; (2) the relationship between time estimation and symptomatology; (3) the relationship between time estimation and impulsive behavior; and also (4) to compare time estimation abilities in patients with schizophrenia with and without a history of suicide attempt.

It was hypothesized that: (I) patients with schizophrenia would exhibit deficits in their ability to accurately estimate time, as compared to non-patients; (II) among patients with schizophrenia, estimation of time intervals (i.e., the subjective perception of chronological time as passing too slowly) would be positively correlated with positive symptoms, while there would be a negative or no direct relationship between estimation of time intervals and negative symptoms; (III) patients on a fixed-dose of medication would have lower estimates on time perception and higher estimates on time production tasks as compared to their performance when unmedicated; (IV) neuroleptics would affect both positive symptoms and time estimation abilities, such that after medication there would be a reduction in symptomatology and in estimation of time intervals, while no specific relationship was posited between negative symptoms and time estimation abilities after neuroleptic medication; (V) time estimation would be positively related to

impulsiveness, such that highly impulsive individuals would exhibit longer estimates compared to less impulsive individuals; and (VI) time estimation would be related to suicidal behavior, particularly current suicidal ideation, such that attempters would estimate longer intervals than non-attempters.

II. LITERATURE REVIEW

A. DEFINITIONS AND HISTORICAL BACKGROUND

The Concept of Time in Psychology

The notion of time has long intrigued psychologists. Numerous studies, particularly in the areas of experimental psychology and psychophysics, have provided findings that contributed to the richness and intricacy of our understanding of the perception of time. It is generally accepted that the experience of time involves two concepts: 1) succession, as the order of two-or-more discrete events that are perceived at different times and organized in a sequence; 2) duration, which entails temporal continuity marked by two discrete events ((Fraisse, 1984). In this same line of thought, authors make a distinction between the perception of "instantaneity," which applies to stimulus durations of less than 100 milliseconds; perception of duration of the "present," which includes stimuli ranging from 100 milliseconds to 5 seconds; and estimation of "duration," for stimuli lasting longer than 5 seconds, a function that is considered to involve memory processes associating a past and a current event, or two events in the past.

A longstanding difficulty in doing research in the field is that time does not correspond to any physical change that can be perceived with our senses. Its perception relies largely on the subjective experience of the individual. For this reason, time perception poses a true measurement problem.

In general, the field devoted to the study of the perception of time has been aware of the distinction between absolute, objective time and perceived, subjective time. Isaac

Newton (1726) approached the problem by stating that, "Absolute time and mathematical time, in and of itself, and from its own nature, flows equitably without relation to anything external, and by another name is called duration: relative, apparent, and common time, is some sensible and external (whether accurate or unequal) measure of duration by the means of motion, which is commonly used instead of true time, such as an hour, a day, a month, a year."

Accordingly, it is assumed by theorists in the field that external time, as measured by clocks, is metric time. Metric time is characterized by an independent existence that cannot be inferred or influenced by other dimensions (i.e., motion, space) and it has an exact and objective measurability only limited by the accuracy of our instruments and our perceptions (Szamosi, 1992). Its continuity assumes a flow through continuous point values that should be arbitrarily small to ensure accuracy, but which allow for their measurement by specifically designed devices such as clocks. However, the idea of a completely independent existence of continuous time with unlimited measurability and "without relationship to anything external" was questioned by Einstein's theory of relativity that showed that all properties of time and space depend on the distribution of matter and energy.

Researchers have approached time as a multifaceted and complex concept. It has been argued that organisms function, relying mainly on the dual nature of experiential time (Michon, 1990). One aspect of this experience evokes the concept of implicit timing, construed as a mechanism that helps the organism stay tuned to the constantly changing environment. This mechanism does not require any internal temporal

representation or encoding of time. Traditionally included within this type of experience are periodic phenomena like the circadian rhythm, as well as single and sudden mechanisms triggered only under specific conditions, like the reflex action. Most of these events are neither directly observable (i.e., heartbeat) nor fixed (i.e., length of day and night). Therefore, keeping track of these phenomena involves a process of behavioral adaptation to periodic internal and external changes (Szamosi, 1992). The second aspect of the dual nature of experiential time involves the processing of information referring to the present, the past, and the future, as well as information involving sequences and durations. Unlike the first mechanism, this one requires an explicit and conscious activity of reflection and processing. In this sense, time appears to evoke a subjective representation that bears some correspondence between external and internal information. This representation of time measurement is characterized by its essential dynamism, in the sense that it mimics external time in its directionality. As such, external time moves forward and continuously so that between any two points in time, an infinite number of points in time exist (Freyd, 1992).

Internal Clock Models

Internal clock models rely on a clock metaphor and assume that the experience of time involves an explicit mechanism that is essentially different from the implicit mechanism involved in the timing of periodic phenomena. While periodic clocks, like those underlying circadian rhythms, are likely to run continuously and relatively independently of external clues, internal clocks require a signal to be initiated. During the

past four decades, the hypothesis of an internal clock (Treisman, 1963) has undergone significant development, (Church, 1984; Gibbon, 1991; Roberts, 1981) particularly with the introduction of Scalar Timing Model proposed by Gibbon, Church, and Meck in 1984. This mathematical model formally describes the cognitive operations occurring when a subject is required to perform temporal discriminations. Three stages were hypothesized for the information-processing system: 1) the clock stage, which includes a pacemaker, a switch, and an accumulator; 2) the memory stage, with two systems of storage of information, one of working memory, and the second of reference memory; and 3) the decision stage, which is achieved by a comparator. These stages are distinct to the extent that each can presumably be altered without affecting the functioning of the others. As explained by Meck (1983), the first stage (clock stage) transforms objective time into subjective time, a function frequently designated as "clock reading." The second stage (memory stage) involves the storage of the value read by the clock. And finally, during the third stage (decision stage), the clock reading is compared to the memory of previously reinforced times when a decision was successfully applied in the timing task. Within the model, a scalar property is assumed such that the standard deviation of the estimated time increases with the mean (Gibbon, 1977).

Most clock models assume the existence of a certain periodicity in physical time that is likely to be perceived by organisms. In order to keep the correspondence between subjective, internal periodicity and external, objective periodicity, models of internal clocks are comprised of several components, as mentioned above. In the clock stage (Gibbon et al., 1984) a "pacemaker" is assumed to generate pulses and maintain a

regularity that tends to be stable within a certain range but may be distorted by various factors. For instance, the pacemaker's rate appears to be affected by pharmacological manipulations with drugs, as well as changes in the organisms' diet and environment. Evidence in support of these effects was provided mainly by Meck (1983, 1996), who demonstrated a faster or a slower response by animals after injections of amphetamine or haloperidol, suggesting an increase or a decrease, respectively, in the pacemaker speed. Hence, deviations in estimation occur when the organism fails to match its own behavior, regulated by the rhythm and the pulses of the pacemaker, with some external periodicity.

Analogizing with a clock that utilizes on small units of time to ensure precision, it is generally assumed that the rate of the internal pacemaker must be rapid to ensure accurate discrimination of small differences in durations. At the same time, the rate of the pacemaker needs to be stable to account for the reliability of temporal discriminations. To date, there is no direct measure of the internal pacemaker rate. However, the relationship between the pacemaker and the temporal judgment provided by the subject under experimental conditions should be such that both mechanisms are affected by the same manipulations to an equivalent degree. Also, moment-to-moment variations in the measure of the pacemaker should be correlated with equal variations in the temporal judgments obtained in the experiments.

There has been a considerable amount of research done to establish the anatomical and physiological correlates of the presumed pacemaker. Treisman (1963) postulated that the rate of the pacemaker should be linked to the level of arousal in the organism. In 1984, he attempted to link the rate of an internal pacemaker in humans, as evidenced by

estimations in time judgment of auditory stimuli, with the alpha rhythm of the electroencephalogram. This study yielded inconclusive results, with the stability of the alpha rhythm much greater than that of temporal estimations obtained over a single session. More recently, proposals for mechanisms to encode the rate of the pacemaker have ranged from neural networks with explicit temporal characteristics (i.e., pacemaking properties) to neural networks characterized by continuous and recurrent feedback loops, with intrinsic delays that could have a predictive quality for the desired interval (See Miall, 1992, 1996, for reviews based on different models of oscillatory mechanisms and time perception).

Miall (1996) proposed a model of a pacemaker-accumulator in which a population of neural oscillators emits discrete pulses that are integrated over time. Thus, the pulses represent time in a continuous fashion and translate real time into subjective time with each occurrence of the pacemaker pulse. These neural oscillators are conceived as "neural nodes" that are either in an active ("on") state or inactive ("off") state. The emission of each pulse occurs with a probability of turning an "off" node into an "on" state, a process Miall describes as a "gain" because it determines the basic rate of the accumulator, or vice versa, turning an "on" node into an "off" state, a transition referred to as "decay." The total number of nodes in the "on" state are accumulated and summed, a process that determines the estimation of real time at a certain moment. Experimental simulations of different conditions with varied values of "gain" and "decay" processes (i.e., combinations of low/high gain and low/high decay) were used to model the psychophysical profile of the pacemaker pulses. The relationship between the passage of

real time, as measured by the occurrence of pacemaker pulses, and subjective time, as represented by the total number of activated nodes after each pacemaker pulse, was shown to be curvilinear. These results were replicated by Malapani, Deweer and Gibbon (2002), who used this model to explain temporal memory deficits in patients with Parkinson's disease, and will be discussed in further detail later in this review.

As a second component, clock models also assume the existence of a "switch" that gates pulses from the pacemaker into an "accumulator" that acts as a counter of units (Gibbon, Church & Meck, 1984; Meck, 1983). These pulses increment in a linear fashion over time and their number is recorded and stored by the accumulator. The activation of such a switch appears to vary depending on the nature of the stimulus (i.e., light versus sound) and the degree of preparation for the signal (i.e., expected versus unexpected). In tasks involving time estimation, it is suggested that subjects compare subjective elapsed time, based on the number of pulses recorded by the accumulator, with representations of durations already stored in memory. Thus, the absolute value stored in the accumulator is compared to the absolute value of a relevant event acquired from training in repeated trials. If both values are "close enough" (Meck, 1996), the response provided by the subject is correct and the value in the accumulator is reinforced.

In the second phase, the "memory stage" of the model introduced by Gibbon and colleagues (1984), psychological processes involved in timing appear to rely on two memory registers: 1) a "working memory" system, which stores temporal information for the current trial in the absence of the signal, and 2) a "reference memory" system that stores information of past durations. After reinforcement, working memory contents are

stored in the reference memory for further comparison on subsequent trials. Therefore, the various value outputs of the clock are likely to be stored either temporarily or relatively permanently.

Finally, the third phase, or "decision stage," (Gibbon et al., 1984) assumes the existence of a fifth component in the clock model, labeled as "comparator." This component measures the ratio of the two time values by comparing the value registered in the accumulator or working memory with the value stored in reference memory. After this process of comparison, the organism makes a response decision.

The clock model functions on a Scalar Timing rule (Gibbon, 1977), which assumes that, for different physical durations, equal proportions of elapsed time are judged as subjectively equivalent. Thus, the standard deviation of time estimates increases with the mean. Accordingly, the scalar property is strongly based on Weber's Law, such that the standard deviation divided by the mean, the coefficient of variation or Weber's fraction, remains constant for different target times (Gibbon, Church & Meck, 1984).

The proposal of three identifiable stages in clock models in combination with Scalar Timing theory warrants the formulation of specific assumptions with regard to the precise source of variance in estimations of durations. For this reason, it is assumed that variance is likely to arise from the clock, the memory, or the comparison processes. Experimental manipulations, particularly with pharmacological agents, have been successfully used to isolate the relative contribution of each stage of the clock processing model, as well as the participation of different underlying neurotransmitter systems in the

overall timing performance of the organism (see Meck, 1996 for an extensive review on this topic).

As shown in Figure 1, the internal clock model constitutes a useful tool to isolate sources of variance that operate simultaneously during time estimation performance.

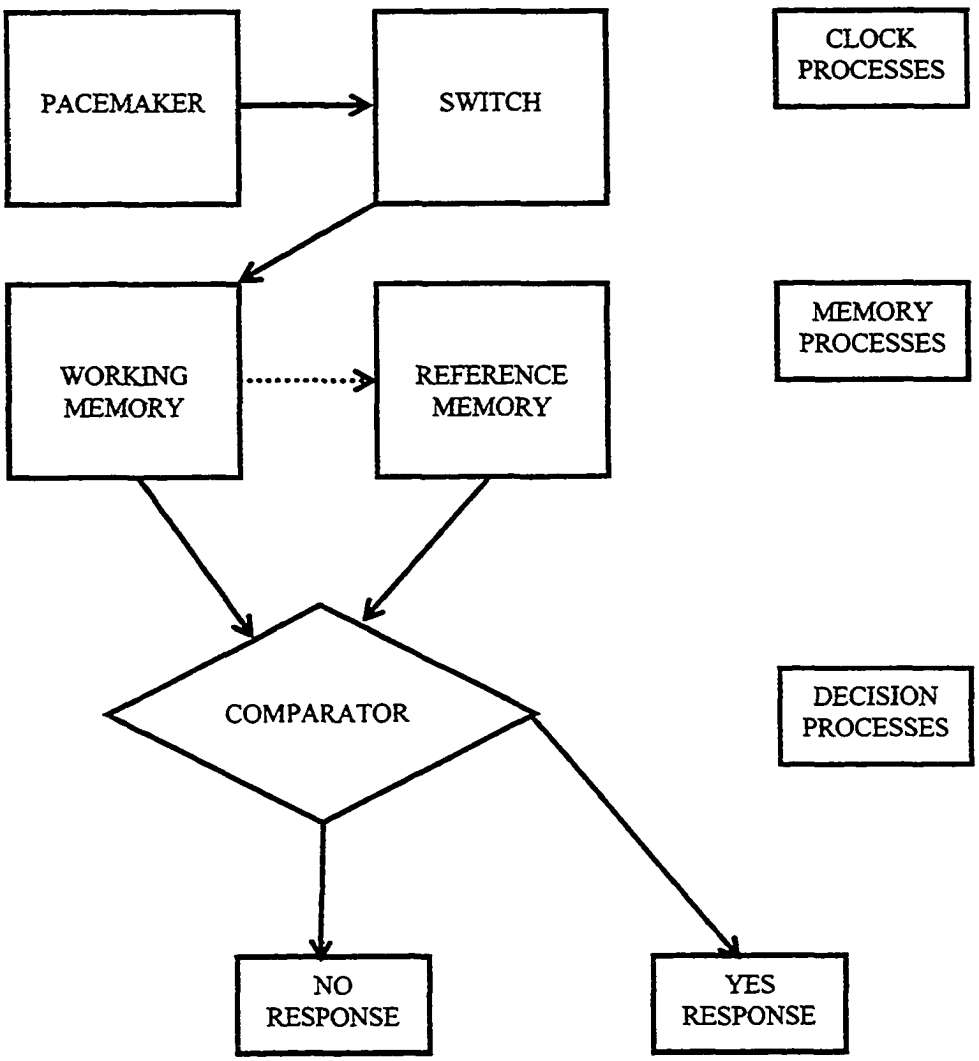


Figure 1. Internal clock model. From "Scalar Timing in Memory," by J. Gibbon, R.M. Church, and W.M. Meck, 1994, Annals of the New York Academy of Sciences: Timing and time perception, 423, p. 54. Copyright by the New York: New York Academy of Sciences.

The previously discussed three-stage clock model proposed by Gibbon and collaborators (1984), predicts that the first source of variability will be the switch. It is hypothesized that this clock component may fluctuate in latency to open and close the gating of pulses into the accumulator and working memory. Decreased variability and increased accuracy is achieved by training. A second source of variation has been repeatedly suggested in the literature for various perceptual models and has been named "Poisson," a process in which successive pulses emitted per time unit by the pacemaker into the accumulator have a central tendency and variability that are independent with respect to objective time, thus following the Poisson law (Creelman, 1962; Treisman, 1963). Gibbon and colleagues (1984), however, introduced a scalar source of variance, which is postulated to increase with the square of the mean. These authors also contemplated the possibility of additional variance generated by the memory components of the model -the working memory component and the reference memory component- and theorized that both storage mechanisms are likely to introduce variability in the scalar form. When the accuracy of these two memory systems is compared, the reference memory appears to have a greater impact on the variability of performance, perhaps because the storage in this system could be additionally distorted when used by the comparator to estimate the ratio between the value stored in reference memory to the value stored in working memory.

Overall, internal clock models lead to helpful theoretical and methodological strategies to approach the complex process of time perception and its multiple implications.

B. THE DOPAMINE SYSTEM

The central dopaminergic system is complex and quite heterogeneous with regard to its biochemistry, physiology, pharmacology, and regulatory properties. Over the past 50 years, systematic research into the specific characteristics of this central neurotransmitter has contributed to a better understanding of the pathophysiology of psychiatric and neurological disorders, as well as to their effective treatment with drugs.

It is well acknowledged in the literature that the prefrontal cortex (PFC) is profusely innervated by a relatively dense projection from the ventral tegmental area (VTA) and the medial aspect of the dorsal section of the substantia nigra pars compacta (SNc). This pathway has been investigated as a crucial site of modulation for various cognitive functions and a possible source of abnormal behavior, particularly given its large number of interconnections with other neural structures and neurotransmitter systems (see review in Oades & Halliday, 1987).

The Dopamine Hypothesis of Schizophrenia

After a century of extensive research, the pathophysiology of schizophrenia remains controversial. Animal studies have provided valuable information with regard to the anatomy and physiology of the brain systems hypothesized to be involved in this disorder. However, the absence of an animal model that includes all aspects of schizophrenia, including both behavioral and cognitive features, has limited the research over the years.

The dopamine (DA) hypothesis of schizophrenia proposes that the disorder results from excessive DA activity in the brain. It originated in the discovery that chlorpromazine

and other neuroleptic drugs were effective in the treatment of schizophrenia (Carlsson & Lindqvist, 1963). Neuroleptics have a specific affinity for dopamine receptors that is associated with their clinical potency, as evidenced by the pioneering in vitro study of Snyder (1976) and replicated by several researchers (e.g., Creese, Burt & Snyder, 1976; Seeman & Lee, 1975). Other researchers, however, often failed to replicate alterations in DA receptor binding (e.g., Knable et al., 1994). This issue will be discussed in more detail later in this section.

Another source of evidence for the DA hypothesis of schizophrenia derives from the fact that sustained exposure to DA agonists such as amphetamine and L-Dopa (e.g., Angrist, Peselow, Rubinstein, Wolkin & Rotrosen, 1985; Davidson et al., 1987; Janowsky, Huey, Storms & Judd, 1977; Jenkins and Groh, 1970; Lieberman et al., 1984) may exacerbate symptoms in patients with psychosis, and induce a psychotic state with symptoms such as paranoid delusions and hallucinations in non-psychotic individuals (e.g., Janowsky & Rich, 1979; Snyder, 1972).

For the last four decades, the dopamine hypothesis of schizophrenia has been expanded and challenged, but has provided the most influential theoretical framework for understanding this disorder and has generated an abundant, and informative, body of research.

Research done on plasma (e.g., Bowers, Heninger & Sternberg, 1980) and cerebrospinal fluid (e.g., Sedval, Fyro, Nyback, Wiesel & Wode-Helgodt, 1974) of patients with schizophrenia showed evidence of abnormal levels of DA metabolites. Despite findings suggesting the presence of DA dysregulation in schizophrenia, the

absolute confirmation of this possibility appears still remote. Some authors (e.g., Carlsson, 1988; Meltzer, 1989) have speculated that dopaminergic activity is likely to be increased in schizophrenia to counteract the deficiency of other neurotransmitter systems, such as glutamate (GLU) or 5-HT. According to this perspective, the pathophysiology of schizophrenia is not restricted to a DA dysfunction exclusively, but is the result of a process of imbalance-counterbalance among several neurotransmitter systems. For example, the blockade effect of neuroleptics on D_A receptors would reestablish a missing balance between dopaminergic and glutaminergic systems and/or dopaminergic and serotonergic systems.

Another critical contribution to knowledge in the field arises from postmortem studies measuring DA receptors and their metabolites in the brains of individuals who had schizophrenia. Several early studies indicated that this patient population, compared to a control sample, showed an increase in dopamine receptors (e.g., Cross, Crow & Owen, 1981; Tyrone & Seeman, 1980), an elevation that was frequently associated with delusions and hallucinations. However, subsequent findings have been inconsistent (see Davis, Kahn, Ko & Davidson, 1991, for a more comprehensive discussion of this literature). In addition, most of these findings are controversial because postmortem studies in patients with schizophrenia have important limitations. First, the samples used in most investigations include patients with ages over 50-years. At such an age, it is less likely that patients included in studies were neuroleptic-naïve. Antipsychotics per se are likely to generate neurochemical changes in the dopaminergic system and this interaction tends to confound research findings, including reports of D_1 and D_2 receptors

upregulation in the striatum (e.g., Farde, et al., 1992). Second, the most prominent psychotic symptomatology (i.e., positive symptoms) is reported to be more prevalent during earlier years and to diminish with age. Therefore, the anatomo-pathological study of older brains decreases the chance to carefully evaluate the neurobiological changes underlying such symptomatology.

To further complicate the elusive findings of DA abnormalities in schizophrenia, some researchers have argued that dopamine activity is reduced in this disorder (e.g., Early, Posner, Reiman & Raichle, 1989; Heritch, 1990; Rao and Möller, 1994), while others suggest that it is increased (e.g., Snyder, 1972; 1976).

Given the heterogeneous symptom profile of this disorder, from chronic and severe psychosis to schizophrenia-like personality disorders (i.e., paranoid, schizoid, and schizotypal personality disorder), grouped with its fluctuations at different stages of the illness, and its varied responsivity to treatment, it has been repeatedly argued that this disorder encompasses a wide continuum of pathophysiology (see Siever, Kalus & Keefe, 1993, for a detailed review). In accordance with this perspective, authors such as Crow (1980) and Mackay (1980) proposed that both a deficit and an elevation of the dopaminergic tone may occur and would account for the heterogeneity between individuals or even within the same patient. These authors proposed that increased dopaminergic activity is behaviorally reflected in the positive/psychotic-like symptoms (i.e., hallucinations and delusions), while dopamine deficits, affecting mainly the PFC, are likely to underlie the negative/deficit symptoms (i.e., flat affect, anhedonia, asociality, poverty of speech) that are characteristic of this disorder.

In summary, the specific role of DA in schizophrenia remains a source of disagreement among investigators in the field.

Anatomy of Dopaminergic Neurons in Schizophrenia: Clinical Implications

Early studies of the neurobiological systems underlying schizophrenia have suggested that DA appears to mediate positive, but not negative, symptoms. Although a detailed description of projections and interactions among neurotransmitter systems is beyond the scope of this review (see Knable and Weingberg, 1997, for a more comprehensive discussion), it is relevant to note the importance of GLU regulation of VTA dopaminergic neurons to ensure a normal physiological activity. The nucleus accumbens (NA) of the striatum provides one of densest dopaminergic interaction to cortical areas, which seems to be involved in the expression of positive symptoms. In this line of thought, Grace (1991) proposed a model in which reduced activity in the frontal cortex is associated with increased activity in the NA. According to this model, the complex DA regulation in the striatum relies on two mechanisms: 1) a phasic inhibitory DA release into the NA; and 2) a basal, tonic DA release regulated by GLU inputs. The NA receives excitatory GLU input from the PFC as well as inhibitory DA projections from the VTA. A reduced activity in PFC results in low GLU secretion into the NA, which eventually reduces the tonic release of DA. This causes a compensatory increase in the sensitivity of postsynaptic DA receptors, and a reduced activation of the DA autoreceptors that regulate the secretion of phasic DA. Due to lower basal levels of extracellular DA and the absence of autoregulatory suppressive systems, the amount of

phasically released DA increases. A reduced DA tonic release diminishes the spread of excitation in the NA, while an increased phasic DA secretion decreases the NA cell excitability. According to this model, most of the PFC inputs are insufficient to excite NA neurons. Only adequately strong PFC inputs are likely to overcome these barriers, potentiate any excitatory drive that arises and, indeed, stimulate inappropriate cell groups in the NA. Grace proposes that, eventually, this excitatory loop in the NA also activates inappropriate cell groups in the cortex. Such activation, coupled with the absence of adequate DA regulation in the PFC to inhibit this out-of-place information, could underlie hallucinatory phenomena.

In recent years, there has been considerable research on the impact on this disease of dopaminergic pathways that project from the mesencephalon (either from the VTA or the SNc) to telencephalic areas (including the PFC, the anterior cingulate, and the perirhinal cortices). The idea that frontal-cortical DA depletion, particularly in the DLPF cortex, is responsible for negative symptoms (Andreasen, et al., 1986; Andreasen, Flaum, Swayze, Tyrrell & Arndt, 1990; Goldman-Rakic, 1991; Levin, 1984) has been the center of systematic investigations. In a milestone research work, Goldman-Rakic (1991) provided the "working memory hypothesis of schizophrenia" which states that working memory impairments constitute the core cognitive deficits in this disorder and depend on the dysfunction of the DLPF cortex and subcortical areas (i.e., the NA and the neostriatum). This author suggests that such deficits in this population are not limited to poor performance in working memory tests. In everyday life, the inability to hold "on-line" symbolic representations to organize internal schemas to guide behaviors could

derive in loose associations, scrambled language, disorganized thinking, as well as apathetic and erratic behavior. Although the specific neural circuitry involved in the pathophysiology of these deficits in humans is presently insufficiently described, Goldman-Rakic emphasizes that it is most likely an integrated view of several neurotransmitter systems, namely DA, 5-HT, GLU, and gamma-amynobutyric acid (GABA), which is likely to account for these working memory impairments. However, the role of DA remains crucial. Animal studies show that local infusion of DA antagonists into the PFC caused working memory deficits that were as severe as full surgical ablation of this area (Sawaguchi & Goldman-Rakic, 1994). The recovery of performance was almost complete after the injection of DA agonists such as L-Dopa and apomorphine. These findings suggest that DA deficiency in the PFC could play a role in the emergence of behaviors and cognitive deficits (i.e., negative symptoms) related to the functioning of this type of memory.

In a compromise approach that attempted to account for both positive and negative symptoms, Weinberger, Berman & Zec (1986) suggested that schizophrenia results from an imbalance between cortical and subcortical DA transmission. This imbalance occurs due to two concurrent DA abnormalities: 1) a decreased in the PFC dopaminergic activity, particularly in the DLPF cortex, which leads to well documented changes in cognition and behavior (i.e., flat affect, social withdrawal, avolition, inattentiveness, anhedonia, poor concentration, and an overall diminution in behavioral spontaneity); and 2) an increased limbic dopaminergic activity, which is linked to positive symptomatology. With regard to this last case, Weinberger et al. indicate that lesion

studies with 6-hyroxydopamine in the PFC of the rat produce hyperactivity in subcortical DA systems, particularly in the NA and the striatum. These findings are consistent with the antipsychotic effects of neuroleptics, particularly on positive symptoms, which mainly act by blocking DA receptors in the nigrostriatal and mesolimbic systems. Although the twofold effect of dopaminergic activity in the PFC and limbic system is strongly suggested in animal data, comparable research findings in humans remain to be convincingly demonstrated.

To summarize, schizophrenia is not the result of focal disruptions in singular DA systems but, most likely, involves the dysfunction of multiple interactions between cortical and subcortical structures. A careful consideration of specific cognitive and behavioral impairments among the heterogeneity of information-processing deficits, will contribute to gain insight into the pathophysiology of this disorder.

The Effects of Medications on Psychotic Symptomatology: Typical versus Atypical Drugs

In the early 1950s, the first trial of chlorpromazine, initially designed for anesthetic purposes, led to the serendipitous observation of its tranquilizing effects and antipsychotic properties. At the time of its discovery, the mechanism of action of this neuroleptic was entirely unknown. Dopamine was only identified as a neurotransmitter near the end of that decade, and it was not until 1963 that inhibition of the DA system was recognized as the main target of action of antipsychotic drugs. As mentioned in the previous section, this finding guided some researchers to postulate that schizophrenia is

caused by hyperactivity of the dopaminergic system. According to widely supported theory, neuroleptic activity depends on the blockage of postsynaptic receptors in DA-pathways from the midbrain to the limbic system as well as to the temporal and frontal cortices. Antipsychotics also block DA receptors in a pathway from the substantia nigra to the caudate nucleus and in the tubero-infundibular system.

After investigators acknowledged the role of the DA systems in the mediation of psychotic symptoms and the essential need to antagonize them, the specific blockade of D_2 receptors became the focus of psychopharmacological research. Chlorpromazine is included among the "first generation" of antipsychotics, also referred to as "conventional," and "typical" drugs, which are mostly effective in the treatment of positive symptoms, presumably associated with hyperdopaminergic function. As an important limitation, typical antipsychotics frequently induce extrapyramidal signs (EPS) and their level of efficacy in controlling the entire spectrum of psychotic symptoms is far from optimal.

In humans, there are five classes of DA receptors. Types 1 and 5 have similar structure and drug sensitivity and are usually designated as "D_1-like." Receptor types 2, 3, and 4 have similar characteristics but they display heterogeneous sensitivity to neuroleptics. Nevertheless, this group is designated as "D_2-like" receptors. While D_1 is considered the primary target for antipsychotics (Duncan, Zorn & Lieberman, 1999; Lidow, Williams & Goldman-Rakic, 1998), this receptor does not appear to be clinically relevant in improving psychotic symptoms (Karlson, Smith, Farde, Härnryd & Sedvall, 1995). Moreover, it has been reported that only five percent of D_1 receptors in the

putamen of patients with schizophrenia is occupied with therapeutic doses of haloperidol (Farde & Nördstrom, 1992). Among the three D2-like receptors, it is the blockage of the D2 receptor itself, most probably in the limbic area, which appears to bear a direct relationship to the clinical improvement of psychotic symptoms (Creese, Burt & Snyder, 1976).

Since the discovery of the mechanism of action of chlorpromazine and, later, of haloperidol, most research efforts centered on developing highly selective antagonists of the D2 receptor (see Duncan, Zorn & Lieberman, 1999; Seeman, 2002, for further discussion of the literature). Despite the high affinity for the D2 receptor, this group of neuroleptics has demonstrated a varying range of serotonergic interactions. For example, while chlorpromazine has a moderate relationship with 5-HT, the interaction of haloperidol with the serotonergic system is only minor.

The introduction of clozapine, the prototype of the second group of neuroleptics designated as "second generation" of drugs, also named "atypical" or "novel" antipsychotics, represented an important development in the pharmacotherapy of schizophrenia. From a clinical perspective, clozapine does not induce acute EPS and proved to be superior to typical drugs in the treatment of neuroleptic resistant cases. In addition, it is more successful than typical antipsychotics in the amelioration of negative symptoms and cognitive deficits, usually related to a hypodopaminergic state in the frontal lobes, although this improvement remains a broad and contentious issue. In this regard, it is difficult to determine whether the diminishment of negative symptomatology is a direct treatment effect of atypical agents. This improvement could also be interpreted

as a secondary effect to a reduction of EPS, which could result in enhanced facial expressiveness and amelioration of psychomotor slowing.

Atypical neuroleptics act through mechanisms that are still unclear. Presumably, given the contrasting distribution of 5-HT2 and D2 receptors in the frontal cortex (i.e., rich in 5-HT2 receptors but meager distribution of D2), atypical agents act by decreasing DA release through serotoninergic inhibition. For example, it has been established that clozapine has a relatively low affinity for the D2 receptor, while being a potent antagonist of 5-HT2A mediated responses in vivo (Fink, Morgenstern & Oelssner, 1984). Meltzer (1989) postulated that a ratio indicating a relatively high affinity for the 5-HT2A receptor with a relatively low antagonism for the D2 receptor could be a predictor of atypicality of antipsychotics. This 5-HT2A/D2-ratio hypothesis led to the development of other atypical drugs that fit this profile, including risperidone, olanzapine, quetiapine, and sertindole. Meanwhile, other investigators (Kapur, Zipursky & Remington, 1999; Seeman & Tallerico, 1998) have suggested that it is the looseness of attachment of antipsychotic drugs to the D2 receptor that seems to differentiate typical and atypical drugs. While typical antipsychotics are firmly attached to the D2 receptor, atypical agents are loosely bound and released from it. This observation was confirmed by imaging studies, which showed that a high occupancy of D2 receptors coupled with a fast release from them, is likely to be the main mechanism of action of atypical drugs (see Duncan, et al., 1999, for further discussion). Indeed, some authors (Seeman & Tallerico, 1999) observed that, in contrast to in vivo studies of radioligand receptor occupancy, clinical brain imaging studies demonstrate that therapeutic doses of clozapine exhibit a higher than expected

occupancy for the D2 receptor when competing with endogenous DA. In addition, it is believed that the rapid dissociation of clozapine from D2 receptors by endogenous dopamine may contribute to early clinical relapse upon withdrawal of these medications. Whereas clinical imaging studies of therapeutic doses of haloperidol revealed an occupancy rate between 70% and 90% of D2 striatal receptors, the occupancy rate of D2 receptors at therapeutic levels of clozapine and quetiapine range between 20% to 63%, 75% and 80% for risperidone, 68% and 84% for olanzapine. And finally, an occupancy rate between 52% and 68% for sertindole, also at therapeutic doses (see Kasper, Tauscher, Küfferle, Barnas, Pezawas & Quinner, 1999; Remington & Chong, 1999, for further discussion).

To allow adequate comparisons among subjects receiving different dosages and neuroleptic medications, a widespread practice (Davis, 1976) is to convert daily antipsychotic medication doses into chlorpromazine equivalents (CPZE). These equivalents are a measure in milligrams that is indexed to the potency of a standard dose of chlorpromazine.

Evidently, the specific antagonistic actions of atypical drugs upon D2/5-HT2 receptors are insufficiently explained with the current available clinical and pharmacological data. In this regard, it has been suggested that hypofunction of other neurotransmitters, such as NMDA, could be involved in the pathophysiology of schizophrenia (see Duncan et al., for a review on this issue).

Despite the ongoing debate regarding the D2/5-HT2 ratio hypothesis, recent literature provided strong support for the rebirth of the dopamine hypothesis (Kapur &

Seeman, 2001).

Time Estimation and Dopamine

The biological basis of time perception has been extensively researched in animal studies and, more recently, in humans. Findings provide significant support for the relationship between processing of temporal information, in the range of seconds to minutes, and dopamine (DA) function. Moreover, pharmacological manipulations have provided detailed data with regard to central nervous system structures and DA receptors that appear to mediate timing functions and regulate the speed of a hypothesized internal clock.

Animal Studies: Procedures and Challenges

In classical conditioning experiments, animals are able to learn and discriminate temporal durations. It has been a consistent observation that the time of highest conditioned response rate generally coincides with the time of presentation of the unconditioned stimulus. This indicates that basic timing mechanisms underlie animals' performance in these prototypical experiments.

However, the investigation of the neurobiology of time estimation in animals has been complicated by methodological differences, including heterogeneous intervals -ranging from seconds to several minutes-, as well as dissimilar procedures, obscuring meaningful comparisons across studies. This issue was clearly identified by Gibbon, Malapani, Dale, and Gallistel (1997), who reviewed 15 prominent animal studies in the

field and pointed out the that duration of intervals used in experiments spanned at least six orders of magnitude (i.e., 1s to 120s). They warned that such wide ranges are likely to involve different neurobiological mechanisms for timing; thus researchers must be cautious when interpreting results.

It is also the case that the performance of animals in timing experiments is likely to vary depending on the characteristics of the procedures used, such as the number of reinforced signal durations, the number of response alternatives, and the response measure (i.e., probability or rate).

In general, most studies in the field have used one of three procedures to investigate timing mechanisms in animals: 1) the temporal generalization (e.g., Church & Gibbon, 1982), 2) the peak interval (PI) (e.g., Catania, 1970), and 3) the temporal bisection procedure (e.g., Church & Deluty, 1977).

For the temporal generalization procedure, a standard signal duration (e.g., 5s) is presented. The animal is rewarded with food only if it presses a lever immediately after the standard duration, which has a probability of occurrence of 0.5 in each trial. The experimenter measures the probability of a single response (i.e., "yes" versus "no") as a function of the standard duration. In general, this function rises to a maximum near the time of the reinforced duration and falls with a fairly symmetrical shape.

In the peak-interval procedure, a trial starts with the onset of a signal. On some trials, the experimenter delivers food only after the standard duration (e.g., 20s) has elapsed. On the rest of the trials, the signal duration is relatively long (e.g., 130s) and there is no reinforcement. In this method, the animal must respond during the

presentation of the signal and the experimenter measures the maximum response rate as a function of time since the beginning of the trial. When data are plotted on a linear time scale, the function displays a fairly symmetrical fashion with the highest point near the time when the reward is likely to be delivered.

For the temporal bisection procedure, two standard stimuli are initially presented (e.g., a 2s versus an 8s signal) in a two-lever box. Food reinforcements are provided by the experimenter only if the animal accurately discriminates the two standard durations (e.g., a "left" lever response to a short signal versus a "right" lever response to a long signal) from random intermediate durations. For this procedure, the response measure is the probability of a long response (e.g., "right" lever response) as a function of the signal duration. When data are plotted against a logarithmic time axis, the shape of the function is ogival and moderately symmetrical. For this method, the animal must produce a single response between two alternatives (i.e., "left" versus "right" lever) after the duration has elapsed.

The main characteristics of these three procedures are summarized in Table 1.

Table 1

Time Estimation Procedures in Animal Studies

Procedure	Reinforced signals	Time for response	Response alternatives	Response Measure
Generalization	1	After	1	Probability
Peak	2	During	1	Rate
Bisection	2	After	2	Probability

Note. From "Properties of the Internal Clock," by R.M. Church, 1994, Annals of the New York Academy of Sciences: Timing and time perception, 423, p. 569. Copyright by the New York: New York Academy of Sciences.

Some variations of these three basic procedures, maintaining their basic principles, have been used in research on timing behaviors in animals. When interpreting data to construct neurobiological models of time perception, it is important that between-procedure comparisons be considered.

Recent Animal Neurobiological Models

In 1983, Maricq and Church published a pioneering paper regarding the central role of the DA system in time perception. Their study provided a careful description of the differential effect of pharmacological manipulations in animals required to discriminate temporal durations. In this study, they focused on the effects of metamphetamine and haloperidol on the speed of a hypothetically DA-mediated internal clock. These authors assumed that metamphetamine increases the level of DA in the brain by stimulating its release and inhibiting its reuptake. In constrast, haloperidol reduces the central dopaminergic transmission by blocking its specific receptors. Rats were trained using the temporal bisection procedure, with extreme signal durations of 2.5s for the "short" left lever response and of 6.3s for the "long" right lever response. The median proportion of "long" responses for each signal duration was obtained by first averaging them over days and, second, over rats. The performance of rats on probe days, when they were administered either of these two drugs, was compared to their performance on saline-control days. Maricq and Church found that methamphetamine shifted the obtained psychophysical function leftward, while haloperidol shifted it rightward. A combination of metamphetamine and haloperidol led to results similar to the saline-control function.

These authors concluded that a leftward shift presumably indicates an increase in the perceived duration associated with each physical signal and, most probably, reflects an increase in the speed of the internal clock. Conversely, a rightward shift is likely to indicate a decrease in the perceived duration associated with the stimulus and, therefore, a decrease in the speed of the internal clock. Accordingly, Maricq and Church concluded that, given the mechanisms of action of metamphetamine and haloperidol, it is plausible that these horizontal shifts in the psychophysical functions reflect fluctuations in the speed of the internal clock as a result of changes in dopaminergic transmission.

In an effort to establish a detailed pharmacological profile of the neuroleptic action on DA-releasing neurons involved in temporal integration, Meck (1986) examined the effect of five neuroleptics (chlorpromazine, haloperidol, pimozide, promazine, and spiroperidol) on time estimation in the rat. This investigator selected the temporal discrimination procedure for short noise durations (i.e., 2s and 4s) rewarded with food after a left lever response and long noise durations (i.e., 8s and 16s) reinforced after a right lever response. Rats were trained during 45 sessions with an increased probability (i.e., 0.5 to 0.25) of intermediate random durations. No food reinforcement was delivered after incorrect responses. After 25 training sessions, animals received one each of five drugs (chlorpromazine, haloperidol, pimozide, promazine, and spiroperidol) on a random half of the days and saline solution on the remaining days. The initial dosage of each drug was either increased or decreased depending on the drug's ability to produce a 15-20% reduction in time judgments as evidenced by an equivalent rightward horizontal shift in the psychophysical function that plotted the probability of "long" responses to signal

durations. Their results indicate that the dose of the neuroleptic required to produce a rightward shift was strongly correlated with the drug's affinity for the dopamine D_2 receptor site, as measured in vitro using ^{3}H-haloperidol as radioactive ligand. There was no significant correlation between the percentage of "long" responses and in vitro ligand affinity for most aminergic receptors, including the D_1 and D_3 dopamine receptors, the alpha noradrenergic receptor, and the serotonin (5-HT) receptors (5-HT_1 and 5-HT_2). Although Meck pointed out that the lack of findings could be attributed to the controversial nomenclature used for DA receptors, particularly for the D_1 and D_3 receptors, he concluded that the absence of significant results was not applicable for the D_2 receptor. This receptor reliably predicted that the drug potency required to produce a 15-20% rightward shift was the same despite the duration of the signal, indicating a general "slowing" of the timing function. This slowing held a constant relationship with the duration to be timed and appeared to be independent of the number of seconds. Nonetheless, this author cautioned that neuroleptics and amphetamines interact with other neural receptors sites such as the alpha noradrenergic, and the 5-HT_1 and 5-HT_2 serotonergic receptors. While time perception is not generally affected by serotonergic manipulations, lesion studies (Morrisey, Ho, Wogar Bradshaw & Szabadi, 1994) indicate that this neurotransmitter could be crucial for the regulation of the timing involved in the response threshold. Low levels of 5-HT appear to underlie low response thresholds allowing responses to occur earlier. To conclude, Meck reviewed the internal clock model (Gibbon et al., 1984) and proposed that neuroleptic drugs affect time estimation by decreasing the rate at which the pacemaker emits pulses, slowing its rate and providing

longer subjective durations.

Together with the study of the role of DA in time perception, other studies (Meck, 1996) researched the anatomical distributions of the dopaminergic systems underlying timing mechanisms. Meck performed selective neurochemical lesions with 6-hydroxydopamine in the mesolimbic, mesocortical, and nigrostriatal dopaminergic systems in rats. Animals were trained and tested post-operatively using the PI procedure for discrimination of two target durations (i.e., 10s and 60s). Results indicated that lesions either in the SNc or in the caudate/putamen are critical for the impairment of timing behavior. Thus, the SNc and the striatum are believed to be crucial anatomical elements underlying the monitoring of the current passage of time, a function that is performed by the pacemaker-accumulator in the modeled internal clock (Gibbon, Malapani, Dale & Gallistel, 1997).

While dopaminergic input is believed to regulate the speed of the pacemaker accumulator, acetylcholine likely modulates the memory for duration in higher cortical areas (see Meck, 1996, for a review).

Clinical Studies: Neuropharmacology and Neuroanatomy of Time Estimation

The study of the neurobiological correlates of time perception was, until recently, a largely neglected area in neuropsychological research. This late introduction accompanies the relatively novel conception that duration is a stimulus that, despite differences with stimuli perceivable by our senses, also requires investigation. Like any other stimulus, it is assumed that the processing of duration should involve specific

neural circuitries, including memory and attentional resources. Contemporary work in this area suggests that time perception mainly involves three cerebral areas: the striatum, the cerebellum, and the frontal cortex.

During the last decade, most of the contributions to the field of time perception in humans derived from studies of patients with basal ganglia disorders. Since the early 1990s, investigators have reported that this patient population demonstrates deficits in timing behaviors that include tapping (Freeman et al., 1996; O'Boyle, Freeman & Cody, 1996; Pastor, Jahanshahi, Artieda & Obeso, 1992); verbal estimation (Pastor, Artieda, Jahanshahi & Obeso, 1992), and reproduction tasks (Malapani et. al, 1998; Pastor, Artieda, Jahanshahi & Obeso, 1992). Most researchers document subjective overestimation of elapsed durations (i.e., internal clock units are smaller than objective clock units) for brief intervals ranging from 350ms to 1000ms (Freeman et al., 1996; O'Boyle, Freeman & Cody, 1996; Pastor, Artieda, Jahanshahi & Obeso, 1992), and underestimation of longer durations ranging from 3s to 29s, when assessed both with the methods of verbal estimation and reproduction (Pastor, Artieda, Jahanshahi & Obeso, 1992). Particularly these latter findings suggest that for extended intervals, patients with Parkinson's disease (PD) show a subjective underestimation of elapsed time, a timing distortion which implies that the hypothesized rate of the internal clock is slower than that of the objective clock. In contrast, cerebellar lesions have demonstrated to impair timing abilities in the ms range. In a study designed by Ivry and Keele (1989), cerebellar patients were assessed on two separate timing measures that included a motor production task (i.e., tapping to maintain a simple rhythm at regular intervals of 550ms) and perception

task (i.e., discrimination between small differences in the duration of two intervals, with a standard duration of 400ms and comparison intervals ranging from 160ms to 640ms). Results from this study indicate that cerebellar patients exhibit significant timing deficits for both motor and perceptual tasks. Later, these findings led Ivry (1996) to hypothesize that a single timing mechanism, with pathways passing through the cerebellum, is likely to underlie both motor and perceptual tasks for duration in the ms range. Furthermore, since cerebellar dysfunction appears to impair timing of short durations (i.e., ms) and the basal ganglia presumably affect longer intervals (i.e., seconds), Ivry proposed a dichotomous function for timing between these two anatomical structures. This idea was contradicted by findings reported in a study by Nichelli, Alway, and Grafman (1996) who used an interval discrimination task, similar to the one used by Ivry (1996), and a temporal bisection procedure both for short durations, in the range of 100ms to 600ms, as well as long durations in the range of 8s to 32s. Nichelli and colleagues showed profound deficits in perceptual timing in patients with cerebellar degeneration both for short and long durations. However, these authors characterized the errors observed during long intervals as deficits in precision. Thus, these deficits were more likely to be related to attentional components rather than timing components. Similarly, studies in PD patients have shown that this population exhibits timing deficits in motor and perceptual tasks for short, as well as long durations (O'Boyle, Freeman & Cody, 1996; Pastor, Jahaahi, Artieda & Obeso, 1992).

Hypotheses regarding the functional role of other cortical and subcortical structures involved in timing have also been tested in patients with focal lesions,

particularly to the frontal lobes. In the study mentioned previously, Ivry and Keele (1989) also included a group of patients with lesions in the posterior region of the frontal lobes. Subjects were asked to perform the same tapping and perception tasks that were assessed in cerebellar patients. Subjects with frontal lobe lesions demonstrated a significant variability in the performance of periodic responses, as measured by the tapping task, when compared to age-matched normal controls and elderly controls. However, these authors were unable to report the directionality of the errors (i.e., under- versus overestimation). No deficits were found for this group in the perception task.

Furthermore, Harrington, Haaland, and Knight (1998) investigated the role of the cerebral hemispheres in time perception in individuals with focal left (LH) or right hemisphere (RH) lesions. These authors employed two time perception tasks to test the hypothesis that frontal cortical systems that have reciprocal pathways to the striatum, such as the supplementary motor area (SMA), the frontal eye fields (FEF), the and DLPF cortex, as well as from the cerebellum, including the DLPF and premotor cortices, are likely to have a predominant role in time perception. Patients with focal LH and RH lesions were compared to matched normal controls on a perception task in which subjects were required to judge the relative duration of an interval between two tone pairs (i.e., standard intervals of 300ms and 600 ms with 60 possible longer and shorter intervals). These investigators found that judgments of duration were significantly impaired in the RH group relative to the control group, particularly for the longer interval (i.e., 600ms), while there was only a trend reported for the LH group. No significant differences were obtained for between-subject analyses of lesion location (i.e., anterior versus posterior).

Lesion reconstruction data obtained by averaging superimposed scan images indicate that the exclusive shared area of infarction, with 100% lesion overlap in the anterior region, was the lateral premotor area, including the FEF, as well as the middle and superior gyri of the DLPF cortex. Harrington et al. suggested that their results provided support to the assumption that these areas of the PF cortex of the RH are likely to be involved in working memory functions related to timing (i.e., holding representation of a standard duration on-line for comparison during temporal judgment). This idea is further supported by anatomical findings that document reciprocal connections between these regions and the basal ganglia, a structure that is hypothesized to play a key role in the regulation of internal timing.

In 1996, Maquet et al. published a study using positron emission tomography (PET) during a time estimation task. Participants were required to discriminate a visual standard duration of 700ms from shorter and longer comparison durations by pressing one of two keys (i.e., equal versus different to the standard duration). Each duration was separated by interstimulus intervals (ISI) ranging from 1500ms to 2300ms. When these authors compared the results obtained during this timing task to those corresponding to two non-temporal processing tasks, they found a significant increase in regional cerebral blood flow (rCBF) in the right prefrontal cortex, right inferior parietal lobule, anterior cingulate cortex, cerebellar vermis, and a region corresponding to the left fusiform gyrus. Maquet and collaborators concluded that these regions appear to underlie attentional and memory processes associated with prospective time judgments. Later, this research group (Lejeune et al., 1997) designed a new task with the goal of increasing the period of actual

time perception, which was approximately one quarter of the scanning time in their previous work. This prior experimental artifact was due to relatively long ISIs that required no temporal processing. For this latest study, Lejeune et al. used PET in a group of right-handed normal controls that were asked to complete a time synchronization task, which included longer durations and avoided ISIs. These researchers designed this new duration task to be performed during the scans. Subjects were required to judge the duration of an interval (i.e., the target interval length was 2.7s) separating successive colored illuminations. The estimation of the duration of the interval was measured by asking participants to press a button in a synchronic fashion with each illumination. Lejeune and colleagues were able to replicate their earlier findings while analyzing specific rCBFs for the duration task compared to a control task that did not require temporal processing. Six areas were consistently activated in both studies despite large differences in target durations (700ms versus 2700ms) and the nature of the temporal stimulus per se (ISI versus visual signal itself). These six areas were: 1) the right ventrolateral prefrontal cortex; 2) the right DLPF cortex; 3) the right inferior parietal lobule; 4) the anterior cingulate cortex; 5) the left putamen; and 6) the left cerebellar hemisphere. These authors speculated that the activated areas execute a crucial role for processing information related to temporal working memory and attention. Also, replicating other studies, Lejeune et al. observed that the activation of the cerebellum indicates that this structure is involved in the temporal processing of both short and relatively longer durations (i.e., ranging between 2s and 3.4s), as is the case of the current task. Furthermore, they hypothesized that the finding that the left cerebellum is activated,

despite the use of the subjects' right hand, confirms that this region is likely to underlie higher cognitive processes rather than simple motor functions. Recently, this same research group (Macar et al., 2002) published an article that partially replicated their earlier findings. For this most recent study, the investigators obtained PET data from a group of normal participants. Subjects were asked to perform a time reproduction task involving tactile stimuli with durations within a designated "short" range (i.e., 2.2s to 3.2s) versus a "long" range (9s to 13s). The standard tactile stimuli were applied as vibrations to the participants' middle finger and, once elapsed, participants were asked to reproduce the perceived length of the intervals by pressing a response button. Analysis of the rCBF data indicate that, when compared to the performance of a non-temporal control task, four main areas were activated with no significant difference based on duration range (i.e., short versus long). These areas were the right DLPF cortex, the right inferior parietal, the right anterior cingulate, and the supplementary motor area (SMA). The activation of the first three regions is a replication of prior findings and strengthens their role as attentional resources for the cognitive processing of time. However, the role of the SMA in temporal processing is questionable in light of the demand to process motor information for the performance of the experimental task.

Consequently, the specific neural systems that underlie the perception of time appear to interact actively with other cognitive functions involved in the processing of temporal information, such as attention and memory (Harrington, Haaland & Knight, 1998; Lejeune et al., 1997; Maquet et al, 1996). Mainly DA guarantees the functioning of these neural systems. In general, adequate DA regulation ensures accurate timing abilities

with variability that fits the scalar property. An interesting experimental variable considered by some of the studies reported above on patients with PD (Artieda, Pastor, Lacruz & Obeso, 1992; Malapani et al., 1998; Pastor, Artieda, Jahanshahi & Obeso, 1992; Pastor, Jahanshahi, Artieda & Obeso, 1992) consists on the manipulation of the medication status of the sample. For these studies, timing performance was tested when they were off and on levodopa medication. Consistently, repeated findings indicate a greater degree of variability on timing abilities when patients are assessed off medication. Pastor and collaborators authors demonstrated that following the administration of levodopa, patients show a significant improvement in time estimation tasks. This finding provided further support to the assumption that DA plays a central role in internally regulated timing abilities, a finding that is consistent with animal work.

In a compelling review article of time estimation studies, Gibbon, Malapani, Dale, and Gallistel (1997) acknowledged consistent reports of large differences in timing abilities between PD patients and normal controls. Gibbon and colleagues argued that, for both short and long intervals within the seconds range, studies fail to demonstrate range effects beyond those reported for normative data (i.e., an increased coefficient of variation for ranges below 1s to 2s and above 500s, suggesting two possibly different neurobiological mechanisms; see Gibbon et al., 1997, for further discussion on this subject). These authors concluded that more studies are required to determine which specific stage of the internal clock model (i.e., clock, memory, and/or comparison process) accounts for the increased variability observed without fail in patients populations.

In this line of thought, Gibbon and Malapani (Gibbon, Malapani, Dale & Gallistel, 1997; Malapani, et al., 1998) collaborated in a series of studies in patients with PD and focused on determining the precise role of DA underlying each stage of the internal clock. Based on the internal clock model, animal research suggests that the striato-nigral dopaminergic system is involved in the regulation of the speed of the pacemaker and in the emission of pulses into the accumulator (Meck, 1986). However, its role in the memory stages of this model is unclear. Adapting the use of the PI procedure from animal research to patients with PD, Gibbon and Malapani were able to determine specific temporal memory processes that are DA-dependent. For the human analog of the PI (Malapani, et al., 1998), a standard duration consisting of a visual signal on a computer screen is presented to subjects a certain number of times. Subsequently, these investigators ask subjects to reproduce the standard duration from memory by pressing a response key before the expected end of the interval and releasing it afterwards. In some of the trials, subjects receive feedback on their performance, either in terms of their accuracy (i.e., indicating if the response was too long or too short compared to the standard) or by the reinforcement of the standard duration in reminder trials. In one of their experiments, Malapani et al. requested PD patients to reproduce two target durations (i.e., 8s versus 21s) both on and off levodopa medication. While patients provided an accurate performance during the on-medication state for both durations (i.e., mean peak times of 7.8s and 21.1s), the same subjects demonstrated a significant timing impairment when they were tested off medication. Analyses of the results indicated that patients off medication overestimated the short duration and underestimated the long one. Malapani

and collaborators labeled this effect as "migration," such that both peaks approached each other and the two targets appeared more alike and "coupled" in memory. This effect was consistently observed in unmedicated PD patients over a large number of trials and was not rectified despite repeated corrective feedback. Moreover, when these patients were evaluated off medication and asked to reproduce only one interval (i.e., 21s), they demonstrated an overestimation of the standard duration and a "slowing" of temporal processing. These results led the authors to formulate a DA-related "memory failure" hypothesis that accounts for the reported inaccuracies and for the "migration" effect. In a meticulously constructed experimental methodology, referred to as "encode/decode" design, Malapani and colleagues (Malapani et al., 2002; Rakitin, Stern & Malapani, 2002) were able to delineate the distinct role of DA function during two different temporal memory stages: the encode/storage and the decode/retrieval of memories pertinent to durations. Basically, this design consisted of manipulating the PD patients' medication status (on versus off medication) during two successive days: one day for training and the other day for testing. Malapani et al., assigned patients to one of four experimental groups: 1) the ON-ON group (PD patients were administered L-Dopa on both the training and testing days); 2) the OFF-OFF group (PD patients did not receive L-Dopa either of the two days and were trained and tested off medication); 3) the OFF-ON group (PD patients were trained without L-Dopa but received this medication during the testing day); and 4) the ON-OFF group (PD patients were trained while receiving L-Dopa, and were tested without medication). Malapani and collaborators designed the experiment to examine whether DA deficiency during the PD patients off medication

state, likely to cause dysfunction in the basal ganglia, was involved in the regulation of memory encoding, assessed by the patients' response to corrective feedback, memory decoding, or both processes. Results of this study replicated earlier findings (Malapani et al., 1998), such that deficits in dopaminergic function produced the expected migration effect (i.e., longer responses compared to the 6s standard interval and shorter responses compared to the 17s standard). These authors observed this effect in all three groups when tested and/or trained off medication, despite the presence of corrective feedback during the encoding temporal information. With such findings, Malapani and colleagues were able to demonstrate the existence of two separate DA-dependent memory systems with well-differentiated psychophysical characteristics. While DA-dependent encoding deficits result in overestimation (i.e., a slowed "internal clock") of memorized intervals that conform to the scalar property, DA-related decoding deficits of stored durations caused both under- and overestimation (i.e., the migration effect with bi-directional errors) of intervals that fail to reflect the scalar property of timing variability. To account for these results, Malapani and colleagues adapted Miall's (1996) pacemaker-accumulator model to explain some of these findings. These authors assumed that DA deficiency increases both the "gain" and the "decay" processes proposed by Miall and, consequently, generates a "slowed encoding" (Gibbon & Malapani, 2002). In agreement with prior animal work (Meck, 1996) that reported that DA-depleted organisms demonstrate a slowed subjective estimation of elapsed time, Gibbon and Malapani hypothesize that PD patients translate veridical accumulations of objective time into exaggerated (slowed) memory values. Therefore, these authors emphasize that it is in a later stage of the

internal clock model, during the encoding process from working memory to reference memory, and not during the pacemaker stage that this timing distortion (i.e., overestimation) occurs. Furthermore, based on the idea that encoding and decoding of durations are two dissociated and independent cognitive functions, Malapani and Gibbon suggested that it is conceivable that independent brain circuits with differential dopamimergic action underlie each of these two temporal memory functions. These authors postulate that it is the depletion of DA in the cortical-striatal pathway, particularly the loss of D_2 receptors in the striatum, which accounts for distorted storage and retrieval of temporal memories in PD. By conveying that DA has such a central role in the processing of temporal information, Malapani and Gibbon disagree with Meck's (1986, 1996) assignment to Ach such function of regulating memory processes for time.

It remains a challenge to understand the complex neurobiological mechanisms underlying timing deficits associated with neurological and psychiatric disorders (i.e., PD, schizophrenia). Future models should include structures such as the striatum, the cerebellum, and the frontal cortex into integrated functional systems most likely regulated by DA. Furthermore, a comprehensive framework of time perception should include other time-related processes like temporal attention and memory.

An Integrative View of Neurobiological Models of Time Estimation and Dopamine: Impact for Future Research in Schizophrenia

At this point, it is evident that a substantial amount of animal and clinical work supports the belief that the dopaminergic system plays a major role in the regulation of

timing behaviors. Despite the challenges and limitations of the procedures used to investigate this subject, researchers report reliable findings that lend support to the idea that abnormal levels of DA cause a significant impairment in the normal perception of time.

During the last two decades, animal studies have convincingly demonstrated that pharmacological manipulations with DA agonists and antagonists, particularly of the D_2 receptor, are capable of producing a general slowing and/or acceleration of the internal sense of time as evidenced by animals' inaccurate performance in timing tasks.

Simultaneously, extensive research done on PD patients complemented the findings provided by animal work. Indeed, the vast consistency of data suggesting that depletion of dopaminergic systems, particularly in the striato-nigral pathway, produces a general slowness in the perception of time cannot be ignored. Clinical pharmacological manipulations with patients on and off levodopa medication show that accurate performance on time estimation tasks depends on adequate levels of DA. Researchers were able to demonstrate that DA not only appears to mediate perceptual aspects of timing functions (i.e., the clock functions of the hypothesized internal clock including the pacemaker/accumulator and the switch), but it also seems to regulate memory functions assigned to this model. Encoding and decoding of durations have been found to be two separate DA-dependent processes. These are presumably involved in the conversion of temporal memories maintained "on-line" to more permanent reference memories that are likely to be used in future temporal comparisons.

Despite the longstanding controversy regarding the DA hypothesis of

schizophrenia, whether it is dopaminergic upregulation in the limbic and striatal areas or the downregulation in the PFC, to date this conceptualization stands as the most satisfactory neurobiological explanation for this disorder. In addition, despite the disagreement regarding the mechanisms of action of typical and atypical drugs, the pharmacological and clinical efficacy of antipsychotics that antagonize the D_2 receptor, is well documented in the literature.

Certainly, such compelling evidence of overlapping neuroanatomical and neurochemical substrates for timing functions and psychiatric disorders like PD and schizophrenia obliges one to concede that research designed to study these possibly related topics is highly appealing. A better comprehension of time perception processes in schizophrenia, including underlying cognitive and neurobiological mechanisms, could eventually shed light on other fundamental cognitive functions. For example, working memory appears to be intimately related to time estimation and it seems to share with it some common anatomical and physiological substrates, such as the PFC.

C. TIME ESTIMATION IN SCHIZOPHRENIA

Background Information and Methodological Issues

Despite the seemingly logical call for research on timing deficits in schizophrenia, the literature on this subject has been restricted to the publication of five studies since the 1950s. Since the 1970s, interest in this topic has faded rapidly. The explanation for the absence of original research on time perception in schizophrenia is still unclear. Perhaps, samples of patients with schizophrenia are not always readily available; certainly they are

less capable than are normal subjects of undergoing testing sessions on time estimation tasks, which are likely to last between 15min to an hour and which, in most cases, demand full attention to a task which may consist of only empty intervals.

In addition, those studies which have been published have methodological limitations. First, samples tend to be relatively small, thus limiting statistical power and generalization of the findings. Second, patient groups are frequently not matched to normal controls in age, education, and IQ, with a general lack of control for these variables. Obviously, this inadequate sampling poses an important risk for the interpretation of results. Third, the methods used to assess time perception have been heterogeneous, hindering the possibility of comparing results across studies. Finally, studies tend to disregard the medication status of the patients included in their samples. As was extensively discussed in the previous section, this failure could prove to be a serious mistake, given the impact that neuroleptics appear to have on timing tasks. These limitations should be carefully considered when analyzing the studies described in the following section.

Early Studies: Relevant Findings

In a pioneering study designed to compare methods of time estimation using a sample of patients with schizophrenia, Clausen (1950) used intervals of 5s, 10s, and 15s to test the methods of reproduction, verbal estimation, and operative estimation. For all three methods, an equal number of trials was assigned to both unfilled durations (i.e., only a light signal) and filled durations (i.e., a light plus a buzzer) for each interval.

During the reproduction task, patients were presented one of the three standard intervals, in a random fashion, and were required to replicate each duration by pressing a key. The method of verbal estimation used a similar presentation. However, no reproduction was required but patients were asked to verbalize the elapsed duration. For the method of operative estimation, patients were required to press a key for a duration stated by the experimenter. As was described earlier in this review, this method is classically referred to as "time production." Clausen used a total of 43 patients with schizophrenia. Nineteen of these underwent surgical ablation of frontal lobe regions, while the remaining 24 were used as controls. The surgical patients were tested prior to the frontal ablation, and four months after the surgery. Analysis of the results showed that there were no significant differences between filled and unfilled intervals, indicating that this experimental manipulation did not have any impact on attentional resources allocated to the processing of temporal information. Surprisingly, there were no significant differences between pre- and post-operative time judgments. Among the three procedures, the verbal estimation method yielded the largest overestimation of standard durations for all three intervals (i.e., pre-and postoperative means of 14.5s and 10s for the 5s interval, 27.4s and 20.5s for the 10s interval, and 33.8s and 29.6s for the 15s interval). When assessed with the methods of reproduction and production, patients demonstrated contradictory results. There was a tendency to overestimate the 5s interval in both methods. However, the 10s and 15s durations were consistently underestimated, particularly for the longer interval (i.e., 13.7s and 13.5s pre- and post-surgery for reproduction, 11.6s and 13s, respectively, for production). Again, these results suggest that the patients' subjective temporal units

were smaller than the objective ones and the rate of the hypothesized internal clock appears faster than the external clock. In this study, Clausen was mainly interested in analyzing the reliability and consistency of methods used for time estimation and did not have assessment timing abilities in schizophrenia as a primary goal. However, several observations are warranted. First, in agreement with other investigations, Clausen found a strong inverse correlation between verbal estimation and reproduction/production. These results show that all three methods measure similar cognitive functions that are relatively independent of the length of the durations. Second, it is surprising that the surgical ablation of portions of the frontal lobes had such an insignificant impact on timing functions. Unfortunately, the lack of details with respect to the specific localization of the ablations prevents further speculation on this issue. Finally, the exclusion of a normal control group is a major limitation for the interpretation of results.

Lhamon and Goldstone (1956) studied the perception of time while attempting to exclude the interference of attentional and memory resources likely to mediate this process. For this purpose, they selected a 1s auditory signal. A patient sample (n= 37) was compared to normal controls (n= 41). Subjects were presented different auditory durations in a random fashion. There were 20 alternating ascending and descending intervals starting at 1s and subjects were required to verbally judge if the intervals were "more" or "less" than the standard duration. If the subjects reported "more" to the initial 1s presentation, the trials descended by 0.1s intervals until the subject reported "less" on three consecutive trials. The opposite procedure was used (i.e., ascending trials) if, at first, the subjects reported "less" to the initial 1s trial. Five feedback trials with

reinforcement durations of the standard interval were provided between the two testing sessions. Lhamon and Goldstone calculated the exact duration at which the subjects reported "more" and "less" 50% of the time, designated it as "second estimation point (SEP)," and considered that this point represented the duration that subjects believed to be a 1s clock time. The investigators found that both groups overestimated the 1s interval, indicating that intervals shorter than the standard duration were actually perceived as longer (i.e., stated "less" when the 1s standard interval was presented or, for example, agreed that a duration of 0.4s equaled the standard of 1s). Findings from this experiment suggest that subjective temporal units were larger than objective temporal units, possibly reflecting a slowed rate of the internal clock for very brief durations. Moreover, patients with schizophrenia were significantly more likely to overestimate the 1s interval (median SEP= 0.308) than comparable normal controls (median SEP= 0.538). The subjective perceived duration was relatively stable during the 10min required for the test procedure. With feedback, both groups were able to improve their performances. The SEP medians changed to 0.778 in normal controls and to 0.668 in the patient sample. Whereas with feedback the controls became more homogeneous as a group, the patients with schizophrenia exhibited greater variability. To conclude, these authors noted that a subsample of 16 patients was receiving chlorpromazine, with doses ranging from 100mg to 1600mg but they failed to find significant differences between medicated and unmedicated patients. Overall, the merit of this study is that it pioneered the isolation of time perception from other cognitive functions, like attention and memory. While it is apparent that the selection of a one second as the standard duration minimized the impact

of these functions, the clinical validity of such brief temporal processing is questionable. Moreover, the methodological procedure selected for this study is not frequently used in the literature, and hence, hampers helpful comparisons with other studies. Finally, despite the use of relatively large samples, the inclusion criteria were poorly defined. Mainly, the inadequate description of the diagnostic procedures and characteristics of the samples (i.e., IQ, education, duration of the illness and severity of the symptoms for the patient group) precludes from a comprehensive examination of the study.

Densen (1977) designed a time estimation task in which subjects were asked to provide a verbal estimation of elapsed time immediately after completing several distractor tasks involving four intervals 5s, 10s, 30s, and 120 s. For the 5s interval, participants were asked to trace their hand; for the 10s interval, the concurrent task was to arrange 20 pennies in four piles of five; for the 30s interval, subjects were required to divide a deck of cards by two colors; and for the 120s duration, participants were asked to cut out a picture. Densen compared a sample of 10 patients with chronic schizophrenia to 10 non-psychotic psychiatric patients, and to10 normal controls. Patients with schizophrenia demonstrated a significant verbal overestimation for all durations, except for the 120s interval, when compared to the other two samples. These findings suggest an overestimation of elapsed time in the schizophrenia subjects, with subjective temporal units smaller than objective ones, and presumably, an underlying faster rate of the internal clock compared to the external clock. For the 120s interval, there was a crossover effect. The sample of patients with schizophrenia exhibited the lowest mean (84s), compared to the non-psychotic and the normal control samples (means of 106.8s and 108.5s,

respectively), but these differences failed to reach significance. Based on these results, Densen hypothesized that time passes either too slowly or two quickly in patients with schizophrenia, a finding that could not be observed in the non-psychotic psychiatric population. This research study has several important limitations; including small sizes for all three samples, and inadequate characterization of the selection criteria (i.e., IQ, education, gender). Most important, the descriptions of the psychiatric populations are extremely limited, overlooking the explicit diagnoses of the non-psychotic patients as well as the medication status of both groups.

In 1983, Tysk designed a study to compare the perception of time in patients with schizophrenia and normal controls using a wide range of intervals (i.e., from 1s to 10min) and a variety of methods. This researcher selected a sample of 15 patients diagnosed with schizophrenia, based on the criteria of the Diagnostic Statistical Manual-Third Edition (DSM-III), and compared them to 60 normal controls. For the selected 1s duration, participants were asked to adjust an electronic metronome to the rate of one beat per second. This procedure is clearly a modified version of the classic method of production. For the verbal estimation method, Tysk selected three visual stimuli with durations of 7.5s, 17.5s, and 23.5s, respectively. For the method of production, participants were asked to produce three intervals of 10s, 20s, and 30s, by operating a stopwatch with a concealed dial. Finally, for the estimation of longer intervals, subjects were required to verbalize the elapsed time since they entered the room (i.e., between 5min and 10 min). Tysk controlled for possible effects of the circadian rhythm on the subjects' time estimation by performing all experiments at the same time of the day (i.e., between 9:00

am and 11:00 am). Interestingly, this author allowed the subjects to count to themselves while executing the tasks of verbal estimation and production. A comparison of the performances of the two groups using t-tests, yielded significant differences for all procedures and intervals measured, except for the verbal estimation of the time elapsed since entering the room (i.e., in the minutes range). Overall, patients with schizophrenia consistently overestimated standard durations in the seconds range, from 1s to 30s. These findings suggest that subjective temporal units that were smaller than objective temporal units characterize the patients' internal sense of time. This phenomenon is presumably associated with an accelerated rate of the internal clock compared to the rate of the external clock. Analysis of variance (ANOVA) revealed a greater variability among the patients for all methods and intervals, whereas normal controls exhibited a rather homogenous performance with nearly correct judgments for all intervals. Finally, Tysk used three variables (i.e., production of the 10s and 30s intervals, and metronome adjustment to 1s) for a stepwise discrimination analysis between patients and controls. This analysis was able to differentiate participants for each group with a degree of 90.5% accuracy. Despite the small sample size of the patients group, as well as the deficient control of their medication state, this research provided a most important contribution to this field. Methodologically, Tysk included an interesting spectrum of procedures and durations, while controlling for possible confounding variables (i.e., impact of the circadian rhythm in the internal clock). In addition, by allowing the participants to count, he minimized the possibility of increased distractibility during empty intervals and, therefore, ensured the participants' allocation of attention to the task, particularly for

longer intervals. Presumably, contrary to prior studies, it is the implement of this superior methodological design that is likely to account for the consistent overestimation of intervals across the 30s spectrum.

More recently, Rammsayer (1990), based on the assumption that a DA-mediated internal clock could be affected by various psychiatric disorders, attempted to replicate Tysk's findings by comparing different patients populations using durations in the range of ms. Rammsayer compared a sample of 80 normal controls with three patient samples, diagnosed according to DSM-III criteria. The patient population was composed of 27 patients with schizophrenia (disorganized, paranoid, and undifferentiated types), 33 patients with major depression with melancholic features, and 21 patients with dysthymic disorders. All patients with schizophrenia were treated with neuroleptics. All participants with depression with melancholic features and 12 with dysthymic disorders were receiving tricyclic antidepressant. Subjects participated in a temporal discrimination auditory task. Each session consisted of 100 forced-choice comparisons of durations ranging from 50ms to 98ms with ascending and descending steps of 3ms or 6 ms, depending on the duration of the interval. By pressing one of two computer keys, subjects were asked to indicate whether the first or the second interval was longer. After each trial, feedback was provided with a visual signal (i.e., "correct"/"false") in the computer monitor. Temporal discrimination in the ms range was significantly impaired for all patient samples, but particularly for the schizophrenia and the depression with melancholic features groups. These results led Rammsayer to assert that judgments in the rate of ms emerge as a more accurate measure than those using longer intervals to assess

time estimation in psychiatric disorders, including schizophrenia. According to this view, unlike estimations of durations in the seconds range, these judgments are reflections of pure timing functions. Indeed, this author proposes that, given the shortness of these kinds of intervals, it is improbable that other cognitive-processing deficits (i.e., attention, memory), frequent in these disorders, obscure the interpretation of results. Moreover, Rammsayer speculated that estimations of durations in the ms range could better mirror the nature of oscillatory mechanisms proposed for the DA-mediated internal clock (see Miall, 1992; 1996, discussed earlier in this chapter). Despite the innovative proposal by Rammsayer, this study failed to provide a substantial contribution to our knowledge in this field. While this author was able to document impaired timing functions in schizophrenia, the method selected for this study was inadequate to provide specific information with respect to the nature of these temporal deficits (i.e., under-versus overestimation). In addition, information regarding neuroleptic treatment is insufficient, and no pharmacological manipulations were included. Therefore, all references by Rammsayer to dopaminergic-mediated mechanisms of the internal clock in the study of these samples are decidedly speculative.

Results of these research studies have been summarized in Table 2.

Table 2

Summary of Relevant Studies on Time Estimation in Schizophrenia

Author	Method and Durations	Results
Clausen (1950)	Reproduction, Verbal Estimation, and Production of 5s, 10s, and 15s (filled and empty intervals)	Subjective temporal units smaller than objective ones Internal clock faster than external clock
Lhamon & Goldstone (1956)	Verbal Estimation ("more/less") of ascending/descending intervals compared to standard of 1s	Subjective temporal units larger than objective ones Internal clock slower than external clock
Densen (1977)	Verbal estimation of 5s, 10s, 30s, and 120s with four distractor tasks	Subjective temporal units smaller than objective ones Internal clock faster than external clock Crossover effect for the 120s interval
Tysk (1983)	Production of 1s Verbal Estimation of 7.5s, 17.5s, and 23.5s Production of 10s, 20s, and 30s Verbal estimation of elapsed time in the room (5min to 10min)	Subjective temporal units smaller than objective ones Internal clock faster than external clock No significant findings for durations in the minute range
Rammsayer (1990)	Temporal discrimination (forced choice comparisons) range between 50ms and 98ms	Impaired discrimination No information about the characteristics of the subjective time sense

Other research studies on time estimation in schizophrenia allude to this issue in a peripheral manner while focusing on the role of attention and memory in this function (Tracy et al., 1998).

In the face of the compelling evidence as to the importance of time estimation in

schizophrenia, the number of less-than-satisfactory research studies during the last five decades is staggering. Our current understanding of the neurobiology of temporal cognition in animal models and in neurological and other psychiatric disorders (i.e., PD, depression) far exceeds our current knowledge of basic aspects of timing in schizophrenia. The study of essential cognitive and neurobiological aspects involved in time estimation in patients with schizophrenia remains an important challenge for future neuropsychological research.

D. TIME ESTIMATION AND IMPULSIVE BEHAVIOR

Introduction

Despite the broad use of the concept of impulsiveness in the personality and psychiatry literature, it remains an elusive and controversial notion that encompasses different behavioral dimensions. As defined by Buss and Plomin (1975), impulsiveness is "the tendency to respond quickly rather than inhibiting the response" (p. 8). Furthermore, these authors assume "two main components: (1) resisting versus giving into urges, impulses, or motivational states; and (2) responding immediately and impetuously to a stimulus versus lying back and planning before making a move" (p. 8).

As pointed out early by Barratt and Patton (1983), most definitions of impulsiveness include "both quickness of response and short-term rewards versus long-term rewards" (p. 97). These researchers consider that internal time sense is an essential aspect of the concept of impulsiveness and speculate that "within the cognitive sphere, estimation of brief time intervals as well as "perceived" time zone measurements

involving broader periods of life span would relate to impulsivity" (Barratt and Patton, 1983, p. 97).

Human Studies: Contradictory Findings

The assumption that an accelerated internal time sense is likely to underlie impulsive behavior appears consistent with most definitions of impulsiveness. However, a review of the literature on the association between impulsiveness and time estimation (Bachorowski & Newman; 1985; Barratt, 1967, Barratt, Patton, Olsson, & Zucker, 1981; Lennings & Burns, 1998; Standford and Barratt, 1996) indicates contradictory results, which may be due to the inconsistency of the methods chosen to investigate time estimation. For example, Barratt (1967) pioneered this area of research by using a reaction time (RT) paradigm to measure time estimation. During the performance of this task, participants were required to hold a key down for different durations (i.e., 1000ms, 600ms, and 20ms) and were asked to release it "as quickly as possible" after the elapsed interval. In this experiment, a first auditory signal prompted the subjects to start pressing the key, while a second auditory signal indicated them to rapidly release the key. Results of these RT experiments revealed that highly impulsive subjects, as measured by the Barratt Impulsivity Scale (BIS) (Barratt, 1965), responded slower than low impulsive subjects in the 1000ms condition, contrary to Barratt's prediction that high impulsive subjects would have a faster RT. In the 600ms condition, results were less conclusive. However, in the 20ms condition, as expected, highly impulsive subjects showed a faster reaction time than low impulsive subjects. Barratt

interpreted these results to indicate that the response provided by highly impulsive subjects was slower during the longest interval (i.e., 1000ms) because these individuals had enough time to afford the slowing of an automatic set of motor responses. Despite the association found between impulsiveness and timing of responses, the method selected by Barratt to investigate time estimation was clearly inadequate.\ In a later study, Barratt, Patton, Olsson, & Zucker (1981) again attempted to study the relationship between time estimation and impulsiveness. The accuracy of paced tapping at a given rhythm was selected to measure time estimation, while the Matching Familiar Figures Test (MFFT) (Kagan, Rosman, Day, Albert, & Phillips, 1964) was used to characterize impulsive behavior. When analyzing their results, Barratt et al. reported a significant inverse relationship between high scores on impulsiveness on the MFFT and the accuracy of paced tapping. Again, although rhythm tasks are frequently used to study time estimation, the actual measurement of timing abilities is performed in a tangential fashion (i.e., participants are not required to produce, reproduce, or estimate elapsed durations in time units but rather synchronize a motor activity to an external pace) and thus, the validity of the estimation measurements appears highly questionable.

More recently, Standford and Barratt (1996) once more analyzed the relationship between time estimation and impulsiveness in a sample of 155 male adolescents. For this study, these authors selected the method of reproduction of two time intervals (i.e., 60s versus 120s). Participants were required to observe the experimenter press a key for the duration of each interval, and were later asked to reproduce the duration presented by the examiner. Standford and Barratt used the BIS and the MFFT to measure impulsiveness.

These authors found that no correlation between the BIS scores and estimation of both time intervals. However, they reported a modest positive correlation between MFFT scores, the 60s interval (r=.20), and the 120s interval (r=.25). Using Principal Components Analysis, a factor labeled as "cognitive tempo" (Standford and Barratt, 1996, p. 39) emerged as a first-order factor, with both measures of impulsiveness loading positively on this factor (MFFT, r=.51; BIS, r=.38). Despite the selection of a superior method to assess time estimation (i.e., reproduction), these contradictory results highlight the elusive nature of the conceptualization and measurement of impulsiveness and its impact on all attempts to study the relationship between this notion and the ability to estimate time.

In 1998, Lennings & Burns designed two experiments to approach this relationship. In a sample of 69 college students, these authors used the Schalling Impulsivity Scale (Schalling, Edman, & Asberg, 1983) to measure three aspects of impulsive behavior: (1) acting "on the spur of the moment" without planning; (2) rapid decision making and preference for speed rather than carefulness; and (3) a sense of being carefree without planning into the future. To assess the ability to accurately estimate time, Lennings and Burns asked participants to provide the amount of time elapsed during the completion of the Block Design of the Wechsler Adult Intelligence Scale (WAIS) (Wechsler, 1955). Half of the sample was told beforehand that they would be required to estimate the duration of the task (i.e., proactive condition), while the rest of the participants were only asked to provide their estimations after the completion of the Block Design (i.e., retroactive condition). Scores were computed as error scores (i.e., the

difference between the actual time and the participant's estimations). No significant correlations were found between impulsiveness and time estimation in either of these conditions (i.e., retroactive or proactive). Subsequently, Lennings, & Burns designed a second experiment in a sample of 77 college students that included two measures of time estimation. First, subjects were asked to estimate when an interval of 30s had elapsed while being instructed to "clear their minds, to think of nothing and not to attempt to count out the elapsed time" (Lennings, & Burns, 1998, p. 374). Similar to the first experiment, subjects were requested to determine the amount of time taken to complete the Picture Arrangement subtest of the WAIS, only using the retrospective method. Once again, these authors failed to find a relationship between impulsiveness and both time estimation tasks.

Finally, Bachorowski & Newman (1985) explored the relationship between impulsiveness, as measured by the BIS, motor inhibition (MI), and time estimation. These authors designed a MI task in which they instructed subjects to trace two circles "as slowly as possible" (Bachorowski & Newman, 1985, p. 134). In order to assess time estimation, these researchers used a verbal estimation task of three intervals (i.e., 5s, 15s, and 25s), with the beginning and the end of the durations indicated by the click of a stopwatch. A significant correlation was found between the BIS scores and the MI task, such that high impulsive subjects obtained smaller scores (i.e., less inability to slow down motor behavior) compared to low impulsive subjects. When analyzing the relationship between impulsiveness and time estimation, these researchers failed to report significant findings. However, the correlation between scores in the MI task and the 5s and 25s

intervals reached significance ($p<.025$), indicating that low scores in the MI task (i.e., greater inability to inhibit motor behavior) correlated with overestimations of elapsed time (i.e., subjects perceived time as passing slowly compared to objective time). Bachorowski & Newman concluded that the MI task appeared to exhibit a greater sensitivity than personality measures of impulsiveness to determine the degree of accuracy in the ability to estimate the passage of time in the seconds range.

Overview and Conclusions: A Challenge for Future Research

As described above, the vagueness of the conceptualization of impulsiveness in the literature, despite its ample use in personality and psychiatric research, coupled with the variability of methods to measure it, and the unsatisfactory selection of tasks to assess time estimation, have rendered past research in this area equivocal.

However, the appeal and almost natural conceptualization that impulsive behaviors are likely to be regulated by an accelerated time sense invites further research of this relationship with improved measures of time estimation and a better characterization of impulsiveness.

E. TIME ESTIMATION AND SUICIDAL BEHAVIOR

Early Experimental Confirmation of Phenomenological Observations

The idea that the subjective experience of the passage of time is distorted among individuals that attempt suicide appears intuitively correct. However, the literature on this subject is extremely limited. Early reports (Brockopp and Lester, 1970; Greaves, 1971), based on surveys with suicidal individuals, provided anecdotal data indicating that this

group has a subjective perception of time that is slower than chronological time.

Neuringer and Levenson (1972) pioneered the experimental research in this area by using widely accepted procedures to assess time perception. These researchers used verbal estimation of four empty intervals, two in the "short" range (i.e., 30s and 60s) and two in "long" range (i.e., 180s and 300s). The experimenter indicated the start and the end of the interval with a signal and, at the end of each interval, participants were asked to estimate the elapsed duration. A sample of hospitalized suicide attempters (n=15) was compared to geriatric patients (n=15), and non-psychiatric inpatient normal controls (n=15). Subjects in these last two groups were screened for psychopathology and suicidal behavior. Investigators controlled for length of hospitalization, age, and IQ. The results of this study indicate that both geriatric and suicidal individuals provided significantly greater mean estimations for the short intervals (i.e., 30s and 60s) than controls. However, for the long intervals the suicidal group tended to overestimate durations to a much greater degree (i.e., mean estimations of 301s for 180s and 441.7s for 300s interval) than the geriatric (i.e., mean estimations of 235.2s and 321.7s, respectively) and control groups (i.e., mean estimations 203.3s and 330s for each duration). Neuringer and Levenson interpreted this overestimation of elapsed time by the suicidal group as an experimental confirmation of the slowed perception of time that was reported in previous literature. Indeed, these authors suggested that this temporal overestimation is likely to explain the subjective experience of changeless present and unattainable future that is frequently associated with feelings of hopelessness reported among suicidal individuals (i.e., Beck, 1963; Kovacs, Beck & Weissman, 1975). Furthermore, based on the differences obtained

between short and long intervals, these authors speculated that the perception of time among suicidal individuals is experienced increasingly slower as more chronological time elapses.

Neuringer and Harris (1974) were interested in investigating the impact of the imminence of death on the perception of time among populations exposed to death. To test this idea, they replicated the same procedure used for the previous experiment, and compared the performance of groups of male suicidal inpatients, geriatric inpatients, and non-psychiatric normal inpatients on a verbal estimation task. For this study, they also included a fourth group of terminally ill inpatients that were aware of their terminal status. There were 15 participants in each group. The method of verbal estimation and the length of the intervals (i.e., 30s, 60s, 180s, and 300s) were identical to the ones used in their prior study. Results indicated that the suicidal patients, closely followed by the geriatric patients, overestimated time intervals to a significantly greater extent than normal controls and terminally ill patients. Again, suicidal individuals and, to a lesser degree geriatric patients, perceived objective time as passing slowly. Based on these results, Neuringer and Harris speculated that the comparison between suicidal and terminally ill individuals suggests that the significantly slower perception of time by the suicidal group appears to be triggered by factors other than the close relationship to death.

Despite the promising findings reported by these two studies, no further research has been done to systematically investigate this topic. A tentative explanation for such lack of research includes the fading interest in studying time estimation in populations other than neurological samples and overlooking psychiatric groups. Another explanation

resides in the cumbersome nature of most time estimation tasks which require participants to pay attention to empty durations to track the passage of time. This assignment could be difficult to achieve by patients that are mainly preoccupied with death.

Risk Factors for Suicidal Behavior: Time Estimation in the Neuropsychological Profile of Suicidal Patients With Schizophrenia

Research on indicators for suicidal risk mostly focus on identifying biological (i.e., Mann, Oquendo, Underwood & Arango, 1999; Matsubara, Arora & Meltzer, 1991; Stanley & Mann, 1983), social (i.e., Daly, Conway & Kelleher, 1986; Maris, 1997), as well as psychological and psychiatric factors (i.e., Apter et al., 1991; Beautrais, et al., 1996; Beck, Steer, Kovacs & Garrison, 1985; Pokorny, 1983) or, at best, combining them in clinical models (i.e., the stress-diathesis model of suicidal behavior proposed by Mann, Waternaux, Hass & Malone, 1999).

While some research has been done among various suicidal populations to examine specific cognitive deficits, such as cognitive rigidity and mental inflexibility (i.e., Neuringer, 1964; Pollock & Williams, 1998; Schotte & Clum, 1987), it has only been recently that several studies reported findings on overall neuropsychological functioning of suicide attempters (i.e., Bigler, 1989; Ellis, Berg & Franzen, 1992; Keilp et al., 2001). However, a remarkable lack of steady research has characterized the field of the neuropsychology of time perception in suicidal populations, and in fact, no investigation on this topic has been done among suicidal patients with schizophrenia.

Suicide has been reported to be the primary cause of premature death in

schizophrenia (Sartorious et al., 1987). It is estimated occur at a rate between 20 to 23 times higher than in the general population (see Caldwell & Gottesman, 1990; Verdoux, 1998, for a more detailed discussion on this issue). The prevalence of completed suicides among individuals with schizophrenia ranges between 10% and 13%, while the rate of attempts during the course of the illness is estimated to be between 20 and 40% (see Caldwell & Gottesman, 1990; Drake, Gates, Whitaker & Cotton, 1985; Miles, 1977, for a extensive review on this issue).

While cognitive dysfunction is well documented in schizophrenia (see Green, Kern, Braff & Mintz, 2000, for a review), the impact of neuropsychological deficits and their interactions with other factors in suicidal risk in this population remains unclear.

Based on early reports that indicate that both suicide attempters and individuals with schizophrenia tend to experience a subjective overestimation of the passage of time, it appears highly appealing to examine the perception of time in a population that displays the overlap of both disorders, as is the case of individuals with schizophrenia that attempted suicide. This research could contribute to a better knowledge of the neuropsychological profile of subjects at risk and increase the sensitivity and specificity of neurocognitive factors that trigger suicidal behavior, like a distorted perception of time.

F. CONCLUSION: STATEMENT OF THE PROBLEM AND IMPLICATIONS OF THE STUDY

During the last three decades, there has been significant progress in research on

the neuropsychology of time perception. However, there has been a lack of systematic research on time perception in schizophrenia and only five such studies (Clausen, 1950; Densen, 1977; Lhamon & Goldstone, 1956; Rammsayer, 1990; Tysk, 1983) have been published since 1950. Despite methodological flaws, these studies suggest that patients with schizophrenia have a subjective overestimation of elapsed time.

In this project, we proposed to study the perception of time in patients with schizophrenia while controlling for potential confounding variables (i.e., age, gender, medication status, length of illness) that were ignored in prior research.

In recent years, there has been growing data provided by drug manipulations in animal and clinical samples that suggest that timing mechanisms are mediated by DA. The neurochemical profile of schizophrenia is characterized by hyperdopaminergia, while that of PD is characterized by hypodopaminergia. Moreover, in terms of time estimation, these two disorders appear at the opposite poles of the spectrum. While PD patients are reported to underestimate the passage of chronological time, patients with schizophrenia appear to overestimate elapsed durations. Thus, timing deficits observed in both disorders seem to rely on DA dysregulation. The study of PD patients off and on levodopa (Artieda, Pastor, Lacruz & Obeso, 1992; Malapani et al., 1998; Pastor, Artieda, Jahanshahi & Obeso, 1992; Pastor, Jahanshahi, Artieda & Obeso, 1992) yielded findings that contributed to a better understanding of biological mechanisms underling time perception deficits in this neurological disorder. In light of these results, we proposed a similar approach to examine time estimation in patients with schizophrenia. Thus, we studied their ability to estimate durations both off and on antipsychotic medication.

Despite the longstanding debate on the specific mechanisms of action of atypical antipsychotics, the dopaminergic system still maintains a predominant role, directly or indirectly, in the mediation of pharmacological effects of these agents, mainly on positive symptoms. In the current project it was expected that antipsychotics would affect both positive symptoms and time estimation abilities, such that after medication there would be a reduction in both positive symptomatology and in the length of estimates corresponding to intervals. No specific relationship was posited between negative symptoms and time estimation abilities after neuroleptic medication. Furthermore, it was expected that the change in positive symptoms would be positively correlated with the change in estimation of time intervals while being on antipsychotics.

Most definitions of impulsive behavior include a timing component associated with rapid responses. It was our particular interest to investigate a possible association between time estimation and impulsiveness Given that no prior research has been published to examine this relationship in patients with schizophrenia, we proposed to study this relationship to determine whether internal time sense constitutes a crucial element in impulsive behaviors in this psychiatric population. It was proposed that highly impulsive individuals would exhibit longer estimates compared to less impulsive individuals.

Finally, based on early research studies that reported that suicide attempters tend to experience a subjective overestimation of the passage of time, it appeared reasonable to examine the perception of time in patients with schizophrenia because this population exhibits a high prevalence of suicide. Therefore, it was expected that time estimation

would be related to suicidal behavior, and that attempters would estimate longer intervals than to non-attempters.

Historically, it was believed that the processes involved in the perception of time are in the essence of all psychological phenomena, permeating most activities and behaviors. While other information crucial for the adequate management of our daily lives (i.e., "who," "when," and "how") has proven to be relatively more accessible for the study by psychologists and neuropsychologists, the subjective nature of the perception of time has posed methodological difficulties. Recently, some progress in this field has shed light on the cognitive and neurobiological mechanisms underlying this complex function. In view of the fragmented and, at times, contradictory information regarding cognitive, psychological, and biological mechanisms of schizophrenia, it seemed compelling to examine the issue of the duration of time (i.e., "how long?") in patients with this puzzling disorder. A better understanding of how individuals with schizophrenia experience the passage of time in their surrounding worlds eventually open a new perspective on the understanding of their inner worlds. A careful study of the processing of time in this patient population could mark the early stages of a reconceptualization of some core clinical aspects of this disorder (i.e., cognitive and behavioral impulsiveness, perseveration, blocking, motor retardation).

III. METHODS

A. INTRODUCTION

For nearly three decades there has been considerable animal and human research focused on the perceptual, cognitive, and physiological mechanisms involved in the estimation of time durations (e.g., Block, George & Reed, 1980; Fraisse, 1984; Freeman et al., 1996; Gibbon, Malapani, Dale & Gallistel, 1997; Haaland & Knight, 1998; Hicks, Miller & Kinsbourne, 1976; Ivry, 1996; Ivry and Keele, 1989; Lejeune et al., 1997; Macar et al., 2002; Malapani et. al, 1998; Maquet et al., 1996; Maricq & Church, 1983; Meck, 1986, 1996; Nichelli, Alway & Grafman,1996;O'Boyle, Freeman & Cody, 1996; Pastor, Artieda, Jahanshahi & Obeso, 1992; Pastor, Jahanshahi, Artieda & Obeso, 1992; Tracy et al., 1998; Zakay, Nitzan & Glicksohn, 1983; Zakay & Tsal, 1989). Most of these studies were designed to assess the organism's accuracy in predicting the length of time intervals without the aid of an external timepiece.

Research in the field relies on some analogy to a clock. Based on this analogy, the main variable to be assessed is the rate of a hypothesized internal, subjective clock in comparison to the rate of an external, objective and real clock.

In general, experiments designed to explore time estimation require subjects to measure and compare relative durations, usually a "standard" duration provided by the experimenter and a "judgment" duration produced by the subject. At first glance, this design probably appears simple, and yet the findings in the field of time perception are often obscured by the use of different estimation methods as well as inconsistent terminology across studies. These factors frequently impede comparisons among investigations and therefore, restrict generalization of results.

An early review by Bindra and Waksberg (1956) described the prevalent use of three methods in experiments of time perception: 1) verbal estimation; 2) production; and 3) reproduction. These methods require different cognitive processes, which are partially indicated by the inconsistency of results obtained across studies.

For verbal estimation, the subject is required to provide a verbal judgment in seconds to minutes of a standard duration provided by the experimenter. This process entails an indirect mechanism of translation of the subject's internal experience of the elapsed duration, which is by definition free of measurement in arbitrary time units, into conventional clock units. For example, a subject may be instructed to estimate the amount of time elapsed (i.e., in clock units) of a standard duration (i.e., 8s) indicated by two beeps. This estimate is made in conventional time units that could be precise (i.e., 8s), or could be a source of inconsistency if the subject responds by rounding the estimate up (e.g., 10s). Moreover, it is assumed that this process is accomplished through different cognitive mechanisms by different individuals (e.g., counting versus not counting) and that this is likely to generate further variability.

Time production involves the examiner stating a duration in conventional units of seconds or minutes and the experimental subject being asked to operatively delimit, usually by holding down a key, an interval that is judged to be equal to the stated interval. It is generally agreed that this method, similar to verbal estimation, has the disadvantage of being indirect because it assumes that conventional clock units will be applied to delimit the subjective experience of the elapsed duration.

For time reproduction, the experimenter presents an operatively delimited interval and the subject is asked to reproduce the same duration, frequently by pressing down a key. Here,

the important consideration is that neither the examiner nor the subject are allowed to mention the actual elapsed time in conventional units like seconds or minutes. It is assumed that the reproduction method relies solely on a comparison of two perceived experiences, one external and one internal, without the mediation of any translation mechanisms. A variation of the method of reproduction is the method of comparison, where the examiner presents the experimental subject with two successive intervals. The subject is required to compare their relative duration and decide which interval was longer or shorter. As with the method of reproduction, the cognitive strategies underlying this procedure include the perception of a standard interval, either through an auditory or visual signal, and the comparison of this predetermined duration to the subject's internal experience of elapsed time. In general, the experimental subject's responses are verbal (i.e., "shorter" or "longer") and they assume a reliable translation mechanism from a subjectively experienced duration to an objectively labeled response.

For more than five decades, the results of time estimation studies have been described in contradictory and, at times, fairly confusing ways. Terms such as "overestimation or underestimation of the standard" (Woodrow, 1951), "underestimation or overestimation of the elapsed time" (Eson & Kafka, 1952; Falk & Bindra, 1954), "relative speed of the 'internal' and 'external' clocks" (Church, 1981), and "relative magnitude of subjective and objective temporal units" (Hoagland, 1933) have been coined in the literature and used alternatively by researchers in the field. "Elapsed time" (Eson & Kafka, 1952; Falk & Bindra, 1954) is ordinarily described as temporal durations measured by standard, objective, and external clocks.

As previously mentioned, a hypothetical internal clock model is frequently used to describe the underlying mechanism posited for time estimation. Its rate appears as a core feature in the measurement of duration. In this same line of thought, the term "subjective temporal units" (Hoagland, 1933) refers to internally perceived magnitudes, in the range of seconds to minutes, which are posited to be intrinsically related to the rate of the internal clock. As shown in Table 3, Bindra and Waksberg (1956) successfully summarized the analogous relationships that are likely to be drawn for the different terminology, depending upon the method used to research the topic. As diverse as the methods and the terminology used to study time perception have become, some consensus exists concerning the empirical consequences that should be expected from the reliable use of these methods. If the hypothesized rate of the internal, subjective clock is likely to vary from one subject to another, it is expected that the rate should remain constant within subjects across different methods. Moreover, a nearly perfect reciprocal linear relationship is predicted for within-subjects analysis for results obtained with the methods of verbal estimation and production (Carlson & Feinberg, 1968), without completely overlapping functions because both methods measure slightly different aspects of time estimation. The rationale for such assumption is that both methods involve similar underlying cognitive functions but in reverse order (auditory or visual perception of a standard duration translated into a linguistic motor output of the judgment duration, for verbal estimation, versus linguistic auditory or visual perception of the standard interval translated into a motor response to signal the experienced duration, for production).

Table 3

Relationship Between Research Terminology and Methods Used For Time Estimation

	VERBAL ESTIMATION	PRODUCTION	REPRODUCTION
Judgment larger than the standard duration	Overestimation of elapsed time	Underestimation of elapsed time	Not applicable (judgment and standard are simultaneous)
	Overestimation of standard duration	Overestimation of standard duration	Overestimation of standard duration
	Internal clock faster than external clock	Internal clock slower than external clock	Internal clock slower than external clock
	Subjective temporal units smaller than objective temporal units	Subjective temporal units larger than objective temporal units	Subjective temporal units larger than objective temporal units
Judgment smaller than the standard duration	Underestimation of elapsed time	Overestimation of elapsed time	Not applicable (judgment and standard are simultaneous)
	Underestimation of standard duration	Underestimation of standard duration	Underestimation of standard duration
	Internal clock slower than external clock	Internal clock faster than external clock	Internal clock faster than the external clock
	Subjective temporal units larger than objective temporal units	Subjective temporal units smaller than objective temporal units	Subjective temporal units smaller than objective temporal units

Note. From "Methods and Terminology in Studies of Time Estimation," by D. Bindra and H. Waksberg, 1956, Psychological Bulletin, 53, p.157, Copyright 1956 by the American Psychological Association.

One longstanding controversy in time perception research has centered around the effectiveness of estimating durations by counting. As early as 1940, Gilliland and Martin addressed the advantage of counting by reducing the variability of the estimates to less than 30 percent, with the size of the errors being proportional to the length of the interval. These researchers showed that 82 percent of subjects from a college sample used

counting as a "natural" strategy to estimate durations in the range of 4s to 27s when no instructions were given. These authors argued that counting ensures the focusing of attentional resources to the time estimation task because it provides a convenient mental content for filling in the time of the interval. Also, counting appears more constant than other types of filling mental activities used in time estimation tasks and which, depending on the level of difficulty and the type of content, are likely to lengthen or shorten the apparent elapsed time of the intervals. In addition, Gilliland and Martin's study (1940) yielded interesting results about the differential impact of practice on counting versus non-counting time estimation trials. Subjects showed no significant improvement in the ability to estimate time if they lacked the knowledge of the amount and the direction of the error, even after eight trials in which they were allowed to count and three trials during which they were instructed not to count. However, when provided feedback about the extent and the direction of the errors, subjects significantly improved their accuracy in the estimation of durations when counting but no effect was found when subjects did not count. Moreover, using a college sample, these authors demonstrated that a considerable consistency is observed in a subject's ability to estimate time from one experiment to another, even if the experiment is repeated several days later.

For most theorists, the issue of explicit counting while estimating time durations has become critical. Fetterman and Killeen (1990) have addressed this issue by pointing out that most experiments in the field of time perception have attempted to capture the ability to perceive time in a pure fashion and avoid the interference of other cognitive abilities, like counting, by means of presenting durations with the use of explicit filling tasks. However, in many cases, the interpretation of results is obscured by the presence

of attentional factors that are likely to mediate the perception of filled durations. Killeen (1992) emphasized the importance of standard units generated by the "pacemaker-accumulator" described in the previous chapter. Essentially, in timing processes, the pacemaker generates pulses that are stored in the accumulator and this provides the basis for the perceived duration.

In the internal clock model, the switch is assumed to count temporal units and gate these pulses into the accumulator. As postulated by Church (1992), the switch could operate in the "run" mode by closing itself at the reception of the signal that marks the beginning of a temporal interval to be timed, and opening when the end of this interval is signaled. According to this model, Church posited that the switch is also likely to operate in the "event" mode by which, at each occurrence of a stimulus, the switch briefly closes and then opens. Thus, explicit counting by humans and keeping track of the number of events by animals are likely to occur when the switch is in the event mode. These two processes appear to involve different cognitive strategies (i.e., counting relies on an internally generated numerical cue, while keeping track of events depends on externally generated cues like a flash or a sound) but both seem to trigger the event mode of the switch as they constantly generate and register novel cues.

Fraisse (1984) has argued that the "psychological present" seems to range from 100ms to 5s. After this limit, as evidenced by the important role of explicit counting, it is feasible that keeping track of durations and time relies on working memory or even long-term memory processes. As it was well documented (Baddeley, 1986; 1995; Baddeley & Hitch, 1994), even a simple task like mental counting involves the articulatory loop that is likely to be activated through a subvocal rehearsal process, with a phonologically-

based store of working memory, and the priming of the most recently accessed numbers registered in long-term memory.

Overall, researchers in the field of time perception have traditionally adopted three methods to study perception of duration: verbal estimation, production, and reproduction. A review of the literature indicates that alternating and, at times, confusing terms have been used to label analogous results. However, a careful approach to the cognitive functions and the underlying mechanisms involved in timing, including explicit counting, allocation of attentional resources, and memory processes, emphasizes the importance of considering these factors while choosing a method to study the perception of time and during the analysis of the results.

B. PARTICIPANTS

Patients

The patient sample was recruited from the Schizophrenia Research Unit (SRU) at the New York State Psychiatric Institute (NYSPI). Patients were initially approached for a larger study ("Schizophrenia Research Unit Umbrella Protocol," Principal Investigator: Jack Gorman) and later recruited for another research protocol ("Suicidal behavior in schizophrenia: A prospective longitudinal study," Principal Investigator: Jill M. Harkavy-Friedman). Patients who underwent an antipsychotic-free period were enrolled in a third research protocol ("Imaging D1 receptors in patients with schizophrenia and healthy controls with (^{11}C) NNC112," Principal Investigator: Anissa Abi-Dargham). The SRU admits approximately 35 patients per year. Only patients who meet Diagnostic Statistical Manual-Version IV (DSM-IV) criteria for schizophrenia, schizoaffective disorder or

schizophreniform disorder are admitted to SRU. Patients were included in the present study based on inclusionary and exclusionary criteria discussed below.

Thirty-eight patients (25 males and 13 females) between the ages of 18 and 53 (mean=30.74; SD=11.08) were included. In terms of ethnicity, there were 12 Caucasians, 13 African-Americans, eight Hispanics, four Asians, and one other. With regard to cognitive functioning, the mean for the Wechsler Adult Intelligence Scale-Revised (WAIS-R) and the Wechsler Adult Intelligence Scale-Third Edition (WAIS-III) Vocabulary Subtest score was 9.5 (SD=3.61, range 3-17). In terms of educational attainment, the mean number of years was 13 (SD=2.69; range 8-20 years). The clinical course of this sample was characterized by a mean age of onset of 22 years (SD=7.54; range 8-53), a mean duration of illness of 10 years (SD=10.72; range 1-39 years), and a mean age at first mental health contact for emotional problems of 23 years (SD=7.95; range 10-53 years). The mean age of first psychiatric hospitalization was 23 years (SD=5.95; range 12-39 years), while the mean number of prior psychiatric hospitalizations was 4 (SD=4.51; range 0-16). The mean length of current psychotic episode was 416 weeks (SD=453.45; range 26-1664 weeks). In terms of diagnosis type, 17 patients were diagnosed with Schizophrenia, Undifferentiated Type, 14 with Schizophrenia, Paranoid Type, two with Schizophrenia, Disorganized Type, two with Schizoaffective, Bipolar Type, and three with Schizoaffective, Depressive Type. In this inpatient sample, the rate of past suicide attempts was 24% (9/38).

A subsample of 10 patients (6 males, 4 females) between the ages of 18 to 41 (mean=30, SD=9.09) was evaluated off and on antipsychotic medication with the same neuropsychological measures of time estimation and clinical ratings. There were no

significant differences between this subsample and the rest of the patients included in the study with regard to the demographic and clinical characteristics described above. In terms of ethnicity, there were two Caucasians, five African-Americans, two Hispanics, and one Asian. Regarding cognitive functioning, the mean for the WAIS-R/WAIS-III Vocabulary Subtest score was 8 (SD=4.14, range 3-15). In terms of educational attainment, the mean number of years was 13 (SD=2.08; range 10-16 years). The clinical course of this subsample was characterized by a mean age of onset of 22 years (SD=7.25; range 8-32), a mean duration of illness of 9 years (SD=9.39; range 1-32 years), and a mean age at first mental health contact for emotional problems of 24 years (SD=7.53; range 10-36 years). The mean age of first psychiatric hospitalization was 25 years (SD=7.89; range 12-39 years), while the mean number of prior psychiatric hospitalizations was 3 (SD=4.03; range 0-13). The mean length of current psychotic episode was 282 weeks (SD=251.38; range 26-780 weeks). In terms of diagnosis type, three patients were diagnosed with Schizophrenia, Undifferentiated Type, five with Schizophrenia, Paranoid Type, one with Schizophrenia, Disorganized Type, and one with Schizoaffective, Bipolar Type. Among this subsample, there were two suicide attempters.

Inclusion and Exclusion Criteria for the Patient Sample

As shown in Table 4, patients were selected on the basis of the following inclusion criteria: (a) a consensus diagnosis of DSM-IV Schizophrenia or Schizoaffective Disorder based on the Diagnostic Interview for Genetic Studies, version 2.0 (DIGS) (Nurnberger et. al, 1994) and the Structured Clinical Interview for the DSM-IV (SCID) (First, Spitzer, Gibbon & Williams, 1995); (b) age 18 or older; (c) English

speaking; and (d) capacity to provide consent to participate in research. Patients were not admitted to the research unit, and therefore not included in the present study, if a diagnosis of schizophrenia or schizoaffective disorder could not be made because of the presence of active/acute and significant medical problems, including neurological illnesses that were likely to impair language comprehension or mental retardation. Patients were not excluded for alcohol or substance abuse, except in cases of acute state of intoxication and/or withdrawal from alcohol or other substances of abuse.

Non-Patient Comparison Sample

Archival data collected for a research study ("Effect of repeated neuropsychological assessment on performance in normals," Principal Investigator: John Keilp) completed at the NYSPI was used for our non-patient comparison sample. The group included 47 subjects (18 males and 29 females) between the ages of 20 and 45 (mean=31.02; SD=7.36) who participated as non-patients for normative data collected. In terms of ethnicities, there were 27 Caucasians. 13 African-Americans, five Hispanics, and two Asians. With regard to cognitive functioning, the mean for the WAIS-R/WAIS-III Vocabulary Subtest score was 12 (SD=2.7, range 7-17). In terms of educational attainment, the mean number of years was 15 (SD=2.02; range 10-20 years).

Inclusion and Exclusion Criteria for the Non-Patient Comparison Sample

Participants in the non-patient comparison group were selected on the basis of the following inclusion criteria: (a) age 18 or older; (b) English speaking; (c) capacity to give informed consent. Subjects were excluded from the present study if they had a

current or past psychiatric history, chronic medical, and/or neurologic disease. Exclusionary criteria also included physical limitations, which could invalidate test results on any instrument (i.e., missing an index finger, blindness), a positive history of head injuries with loss of consciousness for greater than 10 minutes, and/or neurosurgical treatment. Current use of psychotropic medication, acute state of intoxication, and/or withdrawal from alcohol of substance abuse were also exclusionary criteria for this sample. Criteria for inclusion and exclusion for the non-patient comparison sample are presented in Table 4.

Table 4

Inclusion and Exclusion Criteria for Participation in the Study

PATIENTS

INCLUSION CRITERIA	**METHOD OF ASCERTAINMENT**
DSM-IV Diagnosis of Schizophrenia or Schizoaffective Disorder	Consensus diagnosis based on DIGS/SCID
Age 18 or older	Patient interview and chart review
Fluency in English	Patient interview
Capacity to give informed consent	Primary clinician's assessment
EXCLUSION CRITERIA	**METHOD OF ASCERTAINMENT**
Presence of active/acute and significant medical problems, neurological illnesses that are likely to impair language comprehension or mental retardation.	Patient interview, chart review, and physical exam
Acute state of intoxication, withdrawal from alcohol or other substances of abuse	Patient interview and chart review

NON-PATIENTS

INCLUSION CRITERIA	**METHOD OF ASCERTAINMENT**
Age 18 or older	Participant interview
Fluency in English	Participant interview
Capacity to give informed consent	Primary clinician's assessment
EXCLUSION CRITERIA	**METHOD OF ASCERTAINMENT**
Current or past psychiatric history, chronic medical, and/or neurologic disease	Participant interview
Physical limitations which would invalidate test results on any instrument	Observation, brief questioning
Positive history of neurosurgical treatment and/or history of head injuries with loss of consciousness >10 minutes	Participant interview
Current use of psychotropic medication, acute state of intoxication, withdrawal from alcohol or other substances of abuse	Participant interview

Demographics: Comparison between samples

As shown in Table 5, no differences were found between patients and the comparison group with respect to age (t=.14, p=.888), but the participants in the latter group achieved a significantly higher level of education (t=4.57, **p=.0001**). Patients also

scored significantly lower on the WAIS-R/WAIS-III Vocabulary Subtest Scale score (mean=9.5), used in this study as an estimate of intellectual functioning, compared to the non-patient group (mean=12.37). Table 6 describes that the groups differ significantly (p=.012) with respect to gender with more males in the patient group and more females in the non-patient group. The groups were comparable in terms of ethnicity (Chi^2 =7.25, p=.123). Gender was included our analyses to determine the effects of this variable on time estimation. The differences between patients with schizophrenia and non-patients on the WAIS-R/WAIS-III Vocabulary Subtest Score and educational attainment were expectable given the impact that the illness produces on both variables. The onset of schizophrenia may cause individuals to fall short of their educational potential. This issue is well-addressed in the literature as the "matching fallacy" (Meehl, 1970), a notion that suggests it would be inappropriate to equate individuals with schizophrenia and normal controls in number of years of education and current intellectual functioning. Therefore, WAIS-R/WAIS-III Vocabulary Subtest scores and educational level were excluded as covariates in analyses comparing the two groups. However, correlation analyses among WAIS-R/WAIS-III Vocabulary Subscale Scores, educational level, and time estimation were included in our Results section.

Characteristics of the Patient and Non-Patient Comparison Samples

	Patients (N=38) Mean (SD)	Non-Patients (N=47) Mean (SD)	t-value	df	p-value
Age (years)	30.74 (11.08)	31.02 (7.36)	.14	1	.888
WAIS-R/WAIS-III Vocabulary SS	9.50 (3.61)	12.36 (2.7)	4.19	81	.0001*
Total Years of Education	13.13 (2.69)	15.47 (2.02)	4.57	83	.0001*

Table 6

Gender and Ethnicity characteristics of the Patient and Non-Patient Comparison Samples

Variables	Patients (N=38)	Non-Patients (N=47)	Chi ^{2} value	df	p-value
GENDER	25 males (65.8%) 13 females (34.2%)	18 males (38.3%) 29 females (61.7%)	6.35	1	.012*
ETHNICITY			7.26	4	.123
Caucasian	12 (31.6%)	27 (57.4%)			
African-American	13 (34.2%)	13 (27.7%)			
Hispanic	8 (21.1%)	5 (10.6%)			
Asian	4 (10.5%)	2 (4.3%)			
Other	1 (2.6%)	--			

Clinical Characteristics: Comparison between Suicide Attempters and Non-Attempters

As shown in Table 7 and 8, patients who had attempted suicide did not differ significantly from non-attempters with respect to gender (Chi^2= .55, p=.459), WAIS-R/WAIS-III Vocabulary Subtest Scale score (t=.91, p=.372), age at first mental health contact (t= .25, p=.803), age of first psychotic symptom (t=-.31, p=.761), age at first psychiatric hospitalization (t=1.67, p=.104), diagnosis type (Chi^2=4.84, p=305), number of prior hospitalizations (t=.85, p=.400), and length of current psychotic episode in weeks (t=1.09, , p=.281). Attempters were significantly different in terms of ethnicity (Chi^2=10.80, p=.029). Also, this group was significantly older (t=2.18, p=.036), had more years of education (t=-2.55, p=.015), and had a longer duration of illness (t=-2.11, p=.042) compared to the group of non-attempters. A set of correlation analyses was conducted to establish whether age, education, ethnicity, and duration of illness were related to our variable of interest, time estimation. Ethnicity was not significantly correlated with time estimation abilities, thus it was excluded from all analyses. However, the remaining variables (i.e., age, education, and duration of illness) exhibited significant correlations with time estimation. Consequently, these were included as covariates in analyses comparing attempters and non-attempters.

Table 7

Gender, Ethnicity, and Diagnosis Type of the Patient Sample Based on Attempt Status

Variables	All Patients (N=38)	Attempters (N=9)	Non-Attempters (N=29)	Chi ^{2} value	df	p-value
GENDER	25 males (65.8%) 13 females (34.2%)	5 males (55.6%) 4 females (44.4%)	20 males (69%) 9 females (31%)	.55	1	.459
ETHNICITY				10.80	4	.029*
Caucasian	12 (31.6%)	5 (55.6%)	7 (24.1%)			
African-American	13 (34.2%)	--	13 (44.8%)			
Hispanic	8 (21.1%)	4 (44.4%)	4 (13.8%)			
Asian	4 (10.5%)	--	4 (13.8%)			
Other	1 (2.6 %)	--	1 (3.4%)			
DIAGNOSIS TYPE				4.84	4	.305
Schizophrenia, Undifferentiated	17 (44.7%)	3 (33.3%)	14 (82.4%)			
Schizophrenia, Paranoid	14 (36.8%)	3 (33.3%)	11 (37.9%)			
Schizophrenia, Disorganized	2 (5.3%)	--	2 (6.9%)			
Schizoaffective, Bipolar	2 (5.3%)	1 (11.1%)	1 (3.4%)			
Schizoaffective, Depressed	3 (7.9%)	2 (22.2%))	1 (3.4%)			

Table 8

Other Demographic and Clinical Characteristics of the Patient Sample Based on Attempt Status

Variables	All Patients (N=38) Mean (SD)	Attempters (N=9) Mean (SD)	Non-Attempters (N=29) Mean (SD)	t-value	df	p-value
Age	30.74 (11.08)	37.44 (11.35)	28.66 (10.32)	2.18	36	.036*
Number of Years of Education	13.13 (2.69)	15 (2.65)	12.55 (2.47)	2.55	36	.015*
WAIS-R/ WAIS-III Vocabulary SS	11.12 (3.38)	10.44 (3.00)	9.19 (3.78)	.91	34	.372
Age at First Mental Health Contact	22.63 (7.95)	23.22 (5.07)	22.45 (8.72)	.25	36	.803
Age at First Psychotic Symptom	22.24 (7.54)	21.56 (7.00)	22.45 (7.81)	-.31	36	.761
Age of First Psychiatric Hospitalization	23.29 (5.95)	26.11 (7.10)	22.41 (5.39)	1.67	36	.104
Duration of Illness	9.92 (10.72)	16.22 (12.35)	7.97 (9.57)	2.11	36	.042*
Total Number of Prior Psychiatric Hospitalizations	4.21 (5.95)	5.33 (4.72)	3.86 (4.47)	.85	36	.400
Length of Current Episode (Weeks)	416.89 (453.45)	560.89 (520.88)	372.21 (430.65)	1.09	36	.281

C. MEASURES

Overview

All participants in the patient and the non-patient comparison samples completed a neuropsychological assessment designed to evaluate time estimation, which included two tasks: (1) time perception and (2) time production. In addition, subjects in the patient sample received a comprehensive set of clinical measures, including diagnostic and symptom assessment, and history of suicidal behavior. Demographic data such as age, sex, highest level of education, as well as information on cognitive functioning from the WAIS-R/WAIS-III Vocabulary Subscale scores were used to describe both the patient and non-patient comparison group. Clinical history, including age of onset and duration of the illness, number of psychiatric hospitalizations, and age at first mental health contact were collected for all patients. The diagnostic measures including symptomatology, impulsiveness, and suicidal behavior were used to characterize the patient sample. Given that the current study used archival data and that impulsiveness was not a primary aim of research in the original study, ratings on impulsiveness were missing for the non-patient comparison group. Data gathered on symptomatology, impulsiveness, suicidal behavior, and time estimation were used to address the primary hypotheses of the study. Additional measures of past suicidal behavior, including number of attempts, suicidal ideation, lethality, and past suicide intent were used in secondary analyses to clarify the nature of differences between groups (attempters versus non-attempters). Table 9 summarizes the neuropsychological and clinical measures included in this study.

Table 9

Clinical and Neuropsychological Measures

CLINICAL MEASURES	
Clinical Diagnosis of Schizophrenia or Schizoaffective Disorder	Diagnostic Interview for Genetic Studies (DIGS)
Symptoms	Positive and Negative Syndrome Scale (PANNS)
Suicidal Behavior	Harkavy Asniss Suicide Survey I (HASS-I) Scale for Suicidal Ideation (SSI) Lethality Rating Scale Suicide Intent Scale (SIS)
Impulsiveness	Barratt Impulsiveness Scale, Version 11 (BIS-11)
NEUROPSYCHOLOGICAL MEASURES	
Time Estimation	Time Perception Task Time Production Task
Cognitive Functioning	WAIS-R/-WAIS-III Vocabulary Subscale score

Clinical Assessment

The current study used archival data on diagnoses and clinical measures (i.e., symptoms, suicidal behavior, history of suicide attempts, suicidal ideation, physical damage, suicidal intent, and impulsiveness). These data were gathered by clinical raters recruited for two of the protocols included in this study ("Schizophrenia Research Unit Umbrella Protocol," Principal Investigator: Jack Gorman, and "Suicidal behavior in schizophrenia: A prospective longitudinal study," Principal Investigator: Jill M. Harkavy-Friedman).

Diagnosis

The Diagnostic Interview for Genetic Studies (Numberger et. al, 1994), version 2.0 (DIGS) is a structured interview used to assess lifetime history of psychopathology on a symptom and syndromal basis. This polydiagnostic interview allows for DSM-III-R and DSM-IV diagnoses of Somatization Disorder, Major Depression, Mania, Alcohol and Substance Abuse and Dependence; Schizophrenia, Schizoaffective Disorder, Panic Disorder, Phobic Disorders, Obsessive-Compulsive Disorder and Antisocial Personality Disorder. It was developed as part of the National Institute of Mental Health Genetics Initiative. The DIGS has several advantages for studies in schizophrenia. First, it is symptom based and permits a full evaluation of specific psychotic symptoms (i.e. specific types of delusions and hallucinations). It is not tied to one specific criteria system, and diagnoses using the DSM-III-R, DSM-IV, Research Diagnostic Criteria (RDC) and most other diagnostic systems can be made from the DIGS. Second, the DIGS investigates the potential overlap between affective and psychotic syndromes, strengthening the reliability of the diagnosis of schizophrenia and schizoaffective disorder. Third, the DIGS was developed from previously existing instruments and the SCID (First, Spitzer, Gibbon & Williams, 1995) can be extrapolated from the DIGS without requiring any interpretation of the data. The interview takes approximately 3-4 hours. The DIGS has demonstrated good reliability (.73 to.95) (Nurnberger et al., 1994) and adequate sensitivity and specificity for diagnoses (Faraone et al., 1996).

Symptoms

The Positive and Negative Syndrome Scale (PANSS) (Kay, Opler & Fiszbein, 1992) was used to assess the presence and severity of schizophrenia symptoms among the patient sample. The PANSS was selected because it has clinical subscales that contribute significantly to understanding clinical symptoms in schizophrenia. This scale is a 30-item, 7-point rating instrument utilizing 18 items from the Brief Psychiatric Rating Scale (Overall & Gorham, 1962) and 12 items from the Psychopathology Rating Schedule (Singh & Kay, 1975). Each item is accompanied by a complete definition and anchoring criteria in a 7-point format, ranging from 1= absent to 7 = extreme. The scale distinguishes three symptomatic dimensions: (1) 7 items constitute a positive symptoms subscale; (2) 7 items constitute a negative symptoms subscale; and (3) 16 items constitute a general psychopathology subscale. The PANSS has well-established psychometric properties, including good interrater reliability (Kay, Opler & Lindenmayer, 1988), adequate construct validity (Kay, Fiszbein & Opler, 1987; Kay, Opler & Lindenmayer 1988), high internal reliability (Kay, Fiszbein & Opler, 1987), and external validity (Kay, Fiszbein & Opler, 1987; Kay & Singh, 1989). It is currently used extensively in clinical and therapeutic trials.

This scale was administered during a fixed-dose period of antipsychotic medication. For the subsample of patients followed off and on antipsychotic medication, the scale was administered during the off antipsychotic state and repeated during the fixed-dose period of antipsychotic medication.

Neuropsychological Assessment of Time Estimation: Description of Tasks

The assessment of time estimation was carried out with a computerized test developed by Keilp (2001, unpublished data) for a Macintosh laptop computer that involved a time perception task followed by a time production task. In both, subjects were instructed to keep track of time by counting the number of elapsed seconds. The tasks were administered in this same order to every subject, including those repeatedly assessed off and on medication. After completion of the first task, time perception, participants were told that they would be asked to estimate time again for the second task, time production.

Participants completed both tasks without interruption or discontinuation. Each task took about 15 minutes to complete. Selected durations of 5s, 10s, 15s, 20s, 35s, 40s, 55s, 60s, 85s, and 90s were included.

For both tasks, subjects were tested in a quiet room where all clocks, watches, or external pieces (i.e., metronomes) that aid with the tracking of time were removed. Subjects were informed that there would be a total of 15 intervals presented to them and that the intervals would last "anywhere from a few seconds to a few minutes." They were instructed to "count seconds like a clock in their heads" starting from one. Counting was specifically required to be "internal." Thus, subjects were forbidden from tapping their hands or feet, moving their lips while counting, or from relying on any external source that helped them regulate time or rhythm in order to preclude auditory or propioceptive input. By instructing the participants to count, the experimenter decreased the probability of distractibility during intervals, particularly the long ones (i.e., 60s and 90s), and

reduced random guessing. The participants did not receive any feedback regarding their performance on each interval or each task.

For both tasks, each duration was presented three times in a random order to generate a total of 15 intervals. The three absolute values corresponding to each interval were averaged to calculate the respective means and standard deviations. These were used to obtain the total mean and standard deviation for the task. These absolute values were transformed into percent deviations and collapsed for each task into a single overall average percent deviation score. Thus, the overall performance was characterized as the percent deviation of the subject's estimate, in terms of overestimation (i.e., "+") and underestimation (i.e., "-"), from the actual length of the interval that was judged. The total of the 15 interval estimates for each task were summarized as an overall average percent deviation.

In the statistical analyses included in this study, percent deviations from each of the five individual intervals as well as the overall percent deviation for the task were used appropriately.

Time Perception Task

This task involved the presentation of two computer-generated beeps, separated by a specified interval of time. In order to reinforce the auditory signal, the examiner made a specific visual sign with each of both beeps. After each interval, the participants told their estimate to the examiner, who entered it into the computer. After each interval, participants were instructed to reset their counting to one. A minimum of two practice trials with durations of two seconds were administered before the 15 test trials. The

practice trials were repeated until the participants demonstrated a satisfactory understanding of what they were expected to do during the task. The time intervals chosen were built around durations of 5s, 15s, 35s, 55s, and 85s. However, at each repeat, 2s or 4s was added and prorated to the original duration in order to prevent subjects from anticipating interval lengths (i.e., presentation of 7s and 9s for the 5s interval; 17s and 19s for the 15s interval; 37s and 39s for the 35s interval; 57s and 59s for the 55s interval; and 87s and 89s for the 85s interval).

As described above, the overall performance was characterized as overestimation (i.e., "+") and underestimation (i.e., "-") from the actual length of the interval in terms of percent deviations. The total of the 15 interval estimates for each task were summarized as an overall average percent deviation.

Time Production Task

For this second task, subjects were informed that the duration of each interval would be shown on the computer screen (i.e., "Press the zero key, XX seconds after the beep"). The visual instruction was accompanied by the same instruction in a verbal form by the examiner, including the repetition of the length of the interval, in order to ensure the patient's comprehension. As in the perception task, participants were presented with at least two practice trials with durations of two seconds. These practice trials were repeated until the examiner ensured the participants' comprehension of what they were expected to do for the task.

Each trial, subjects were instructed to reset their counts, starting at 1s. At the beginning of each interval, the computer generated a beep that was meant to alert

participants to start counting. Participants pressed a computer key (i.e., the "zero" key) when they judged that the specified amount of time had elapsed.

Fifteen trials were presented in three blocks to ensure that the five trial lengths (10s, 20s, 40s, 60s, and 90s) were each repeated three times in a random order. For this task, the intervals were not altered upon repetition.

Again, performance was characterized as the percent deviation of the subject's estimate, in terms of overestimation (i.e., "+") and underestimation (i.e., "-"), from the actual length of each interval. The total of the 15 interval estimates for the production task were summarized as an overall average percent deviation.

Interpretation of the Time Perception and Time Production Scores

Analyses included the average percent deviations for each of the 10 selected intervals, five for the time perception task (i.e., 5s, 15s, 35s, 55s, and 85s), five for the time production task (i.e., 10s, 20s, 40s, 60s, and 90s), and average percent deviations for each task. For both tasks, positive values in percent deviations indicate larger estimates compared to the target time intervals. For example, a percent deviation of .15 indicates that the subject's estimate was 15% larger than the target interval and it is consistent with an overestimation of the standard interval for both tasks. However, the interpretation of this value is different based on each task. For the time perception task, a positive percent deviation indicates an internal time sense that is faster than the objective time. For the time production task, a positive value in percent deviation suggests an internal time sense that is slower than the objective time. Contrarily, negative values in the percent deviations designate smaller estimates compared to the target duration. For example, a

percent deviation from the target of -.15 indicates that the subject's estimate was 15% smaller than the target interval. This result indicates an underestimation of the standard duration. For the time perception task, such deviation is interpreted as an internal time sense that is slower than the objective time. For the production task, a negative value in the percent deviation indicates an internal sense of time that is faster than the objective time.

Psychometric Properties of the Time Estimation Tasks

The tasks of time perception and time production have been shown to have high internal consistency and reliability in a normative study (Keilp, unpublished data, 2001). Interval estimated correlate very highly with actual time (r's>.95, across all subjects).

For a one-week period, test-retest reliability was excellent. The time perception task yielded a Spearman correlation coefficient of .87. The scores were normally distributed (skewness=1.46) with scores attenuated for those with smaller estimates. For the time production task, the Spearman correlation coefficient was .92. The distribution of scores was superior (skewness=.47) than for the time perception task. Moreover, in this same sample, the overall average percent deviations for both tasks were strongly correlated across subjects (r=.88) in a reciprocal fashion (i.e., a subject whose internal sense of time moved rapidly would tended to have higher estimates on perception and lower estimates on production), thus sharing approximately 70% of the variance. Factor analyses of deviations at each interval revealed a single factor explaining variance across the intervals, with each approximately equally weighted. Based on these analyses, estimates were collapsed for each task into a single overall average percent deviation

score. In this normative study, the average percent deviation in estimates in both perception and production centered around zero, but varied both above and below real time (1 SD equals ~40% deviation).

Furthermore, time estimation measures were associated with a number of clinical characteristics in a pilot study comparing normal controls and depressed patients. Time production demonstrated a moderate correlation with the cognitive impulsiveness scale score of the Barratt Impulsivity Scale ($r\ [56] = .32$, $p < .05$), and self-rated hostility in the Buss-Durkee Hostility Inventory ($r\ [56] = .31$, $p < .05$) in both samples. Among a sample of depressed suicide attempters, both time perception ($rho = .71$, $p = .021$) and time production ($rho = .68$, $p = .031$) correlated with lethality of past attempts.

Cognitive Functioning

Vocabulary level is widely used as an estimate of general cognitive functioning and is frequently used alone or in test batteries designed to assess overall mental ability (Lezak, 1995). This subtest requires participants to provide definitions of words presented on a stimulus card (WAIS-R) or a stimulus booklet (WAIS-III). Words are organized with increased difficulty, and the administration is suspended when the participant is unable to provide five correct definitions in a row, or when the list is finished. While the WAIS-R includes 35 words, the WAIS-III has a list of 33 words. Between both versions, some of the scoring and questioning criteria were changed. However, the correlation coefficient between the WAIS–R and WAIS–III for the verbal scale is still high (.94) (Wechsler, 1997). Education appears to have a significant effect on Vocabulary scores, particularly for older subjects with less years of education (Lezak,

1995). The psychometric properties of this subtest are well-established in the literature (Wechsler, 1981; 1997).

Suicidal Behavior

The measures of suicidal behavior have demonstrated adequate reliability and validity and are customarily used for research into suicidal behavior. Clinical interviewers were provided supervision and reliability training at the NYSPI, insuring consistent and reliable administration of the scales. The advantage of the choice of measures described below is that both categorical and dimensional information would be available. More specifically, attempter status was defined categorically (attempter vs. non-attempter) while medical damage, suicidal intent and current suicidal ideation were measured dimensionally. This facilitated the tests of the hypotheses by: (1) providing an in-depth assessment of suicidality; and (2) expanding the options for statistical analysis.

History of Suicide Attempts

The Harkavy Asnis Suicide Survey I (HASS-I) (Harkavy-Friedman & Asnis, 1989) was used to measure lifetime and current suicidal behavior. The HASS-I was developed to measure past history of suicidal behavior using survey and interview techniques. It has been adapted for the study of suicidal behavior in schizophrenia to assess the overlap between suicidal behavior and psychosis, affective illness and substance abuse. The HASS-I is an interview that assesses past history of suicidal behavior and the details surrounding that behavior. This instrument has been used in other studies of psychiatric patients (Harkavy-Friedman, et al., 1999; Asnis et al., 1993)

and has demonstrated good reliability between self-report and interview formats (Kaplan, Asnis, Sanderson, Keswani, De Lecuona, Joseph, 1994).

Patients were asked about prior suicide attempts. Those who reported past suicide attempts received a categorical rating to identify the method of each attempt. The categories for suicide include use of firearms, immolation, drowning, cutting, jumping, hanging, drug overdose with sedatives, and drug overdose with non-sedative medications. Suicide attempt is defined as a self-injurious act committed with at least some intent to die. Suicide attempts for each patient were weekly discussed in consensus among raters at the NYSPI. Medical records were reviewed for all participants to verify attempter status. Non-attempters who had evidence of a suicide attempt in their medical records were re-approached. If information regarding the attempt could not be obtained from the patient, the patient was not included in the present study. For schizophrenia, the HASS has been shown to have adequate sensitivity (67%), specificity (84%), and positive predictive value (67%) when compared to medical records.

For this study, the presence/ absence of prior attempts was used to characterize the patients. The total number of prior attempts was included in our analyses.

Current Suicidal Ideation

The Scale for Suicidal Ideation (Beck, Kovacs & Weissman, 1979) (SSI) was used to assess current suicidal ideation at the time of the assessment. This 19-item scale has three factors (active suicidal desire, specific plans for suicide, and passive suicidal desire). Items assess suicidal ideation during the past week, including the extent and characteristics of suicidal thoughts and the patient's attitude towards them, the desire to

attempt suicide, details of planning, potential deterrents from an active attempt, and the internal sense of control in relation to a proposed attempt. The interviewer completes the scale based on the patient's responses during a semistructured interview. Each item includes three related statements ranging in intensity from 0 to 2. This scale was administered to both attempters and non-attempters at the time of admission to the SRU, during a period of fixed-dose of antipsychotic medication, and prior to discharge from the hospital. The psychometric properties for this scale reported by Beck, Kovacs, and Weissman (1979) in their original publication done on a sample of 90 inpatients, including patients with depression and schizophrenia, indicated good reliability, high internal consistency (alpha=.89) and validity. A more recent study (Beck, Brown & Steer, 1997), carried out on a sample of 4063 outpatients, replicated findings with regard to the psychometric properties of the scale.

For the purpose of the present study, the total score on the SSI obtained during the fixed-dose of medication was used in statistical analyses.

Lethality

The Lethality Rating Scale (Beck, Morris & Beck, 1979) was used with attempters to assess the extent of actual physical damage of each suicide attempt. Clinicians rated the lethality of each attempt on a scale ranging from 0 (no harm) to 8 (death). The latter was not applicable to our sample because there were no reported completed suicides. Research has demonstrated that this measure is reliable (ICC=.72), tends to escalate with each subsequent attempt, and correlates with serotonin deficiency

(Mann & Malone, 1997; Mann at al., 1996). In this study, we included the score corresponding to the most lethal attempt.

Suicidal Intent

The Suicide Intent Scale (Beck, Schuyler & Herman, 1974) was used with attempters to assess the level of intent for the most severe and the most recent suicide attempt. It is important to distinguish physical damage from intent, as these are distinct aspects of suicidal behavior. That is, one might have strong intent but select a less lethal method, or one might have weak intent but select an extremely damaging method. In fact, an early study (Beck, Beck & Kovacs, 1975) done on a sample of 227 patients admitted after a suicide attempt, reported a low correlation (r=.19) between suicidal intent and lethality. The Suicide Intent Scale allows for a dimensional rating of suicide intent. It is a 15-item instrument that provides an assessment of the circumstances surrounding a suicide attempt, including plans, preparation, communication to others, and the individual's assumptions regarding the lethality of the method he/she selected. Adequate reliability and validity of the instrument have been demonstrated (Beck, Morris & Beck, 1974; Beck, Schuyler & Herman, 1974). Researchers identified two factors for this scale: (1) objective planning; and (2) subjective intent (Mieczkowski et al., 1993). The interrater reliability coefficients in the NYSPI research group are greater than .70.

Total scores on this scale for the most lethal and the most recent attempts were used in the present study.

Impulsiveness

Barratt Impulsiveness Scale, Version 11 (BIS-11)

Patients were administered this 30-item self-report measure of impulsiveness (Barratt, 1965). The BIS-11 measures frequency of impulsive behavior using a four-point Likert scale (Rarely/Never, Occasionally, Often, Almost Always/Always). This scale directs questions to the respondent's usual style (e.g., "I am self-controlled," "I change jobs," "I buy things on impulse," "I finish what I start"). The BIS-11 measures three domains of impulsiveness: motor impulsiveness, non-planning impulsiveness, and cognitive impulsiveness. The BIS-11 is the most well validated self-report measure of impulsiveness. Similarly to other measures of aggression, it is assumed that scores on this scale reflect a "usual behavior" independent of clinical state. This instrument has demonstrated good psychometric properties (Barratt, 1965; Patton, Standford & Barratt, 1995).

For the purpose of the present study, BIS-11 total scores were included in analyses.

D. PROCEDURES

Clinical Assessments

Clinical research interviewers conducted all clinical assessments. Interviewers read all self-report measures to each participant to avoid difficulties that might emerge from medication side effects such as blurred vision, avolition and akathesia. The rating scale for each question was presented in large print on a separate piece of paper to facilitate reading. The diagnostic interviews, clinical symptoms, suicidality, and

impulsiveness required approximately 5 to 8 hours of direct interview time with patients and several hours for medical record reviews. All evaluations were scheduled with the patients according to the procedures followed on the SRU. A senior psychologist at the NYSPI conducted training, supervision, and interrater reliability of these assessments. Interviewers demonstrated a satisfactory reliability (at least .70) on all measures.

Overview of Procedures for the Patient Sample

As previously mentioned, patients initially participated in the larger study "Schizophrenia Research Unit Umbrella Protocol" (Principal Investigator: Jack Gorman) or the other protocol "Suicidal behavior in schizophrenia: A prospective longitudinal study" (Principal Investigator: Jill M. Harkavy-Friedman). Those patients who participated in imaging studies which involved a antipsychotic-free period were enrolled in the research protocol "Imaging D_1 receptors in patients with schizophrenia and healthy controls with (^{11}C) NNC112" (Principal Investigator: Anissa Abi-Dargham). Upon admission to the SRU, researchers and treating clinicians discussed potential candidates for these studies. If patients were considered appropriate, clinicians approached them and asked if they could be approached by a study investigator. The investigator discussed the study with the participant and obtained written informed consent. The participant's clinician attested to capacity to participate. Subsequently, clinical measures (i.e., PANSS) and neuropsychological testing (i.e., time estimation) were assessed during the fixed-dose period of medication. These assessments were also done during the off antipsychotic period for the subsample of 10 patients. Impulsiveness and suicide ratings

were obtained when the patients were stable enough to provide reliable information. These procedures are further described below.

Patient and Non-Patient Comparison Samples: Informed Consent

All three protocols discussed above had approval from the Institutional Review Board at the NYSPI.

Data on the non-patient comparison group was gathered for normative purposes in an ongoing research protocol at the NYSPI ("Effect of repeated neuropsychological assessment on performance in normals," Principal Investigator: John Keilp).

The Institutional Review Boards at the NYSPI and Queens College approved the use of archival data for a secondary analysis for the present study from patients who participated in the above-mentioned protocols. All diagnostic measures, clinical ratings, neuropsychological and time estimation measures were obtained from data already collected under these protocols.

Patients and Non-Patient Comparison Samples: Recruitment and Screening Procedures

Patients were recruited from the emergency room and inpatient services at New York Presbyterian Hospital, other psychiatric hospitals, mental health clinics and clinicians, as well as advocacy groups and local National Association for the Mentally Ill chapters for admission to the SRU. Participants in the non-patient comparison group were recruited by advertisement postings.

Prior to admission to the 12-bed SRU-NYSPI unit, patients were screened for diagnosis of schizophrenia or schizoaffective disorder. Subjects were specifically

recruited to the SRU for the purpose of participating in research. Information about research participation was provided throughout the admission, beginning early in the screening process. At the SRU screening meeting, capacity to understand the procedures and risks involved during the overall research process, as well as the patient's knowledge of the voluntary participation and alternatives to participation were assessed. Capacity to comprehend the specific procedures involved in each protocol was independently assessed for each study.

Antipsychotic-Free Period

A subsample of 14 patients was assessed while free of antipsychotics. Before being reevaluated during a fixed dose period of psychotropic medication, four patients dropped from the study. Thus, the remaining 10 patients were repeatedly assessed on time estimation off and on medication.

After admission, patients were tapered off medications according to accepted clinical guidelines for medication withdrawal. This antipsychotic-free period was used clinically to underscore the effects and impact of medication, to aid in symptom identification, and to discriminate medication-induced symptoms from symptoms of illness (i.e., akinesia from depression). No patient was withdrawn from medication to participate in this study.

These 10 patients were maintained free of psychotropic medication for a period of at least three weeks and no more than four weeks before testing and clinical evaluations. In the standard sequence, there was a two-week period until the patients were tapered off antipsychotic medication, followed by four weeks antipsychotic-free, prior to

antipsychotic medication. Lorazepam 1 to 2 mg, intramuscularly or orally, would have been given in cases of severe agitation, anxiety, and/or insomnia to a maximum of 8 mg per day. In weeks three and four, patients completed the two time estimation tasks and clinical ratings. No placebo medication was given during this period.

Antipsychotic Treatment Period

All 38 patients included in this sample were treated with antipsychotic medication for at least six weeks. For at least the first two weeks of this period, the dose of the medication was adjusted according to the clinical response, as determined by the treating psychiatrist. During the last four weeks of the period, patients remained on a "fixed" dose of antipsychotic medication, based on the physician's assessment of the treatment response. Different patients were treated with different doses of medication. For the purpose of the present study, daily dosage of neuroleptic medication was converted to chlorpromazine mg equivalents (CPZE), in order to allow adequate comparisons among subjects. Table 10 illustrates CPZE of currently used neuroleptics, including those used to treat this patient sample (AstraZeneca, 2002; Drug Facts and Comparisons, 2003; Jibson & Tandon, 1998; Schizophrenia Patient Outcome Research Team (PORT), 2002; Schatzberg, Cole, DeBattista, 1997; Schatzberg, DeBattista, Overman & Ereshefsky, 1998).

Occasionally, the fixed-dose of medication was not restricted exclusively to neuroleptics but could include other medications (i.e., serotonin agonists, anticholinergics, tranquilizers, anticonvulsants, and beta-blockers). This was the case in which the treating physician considered that the combination of neuroleptics with other

drugs contributed to the enhancement of patients' clinical response. Likewise, lorazepam could have been administered, as outlined above, for severe agitation, anxiety, and/or significant insomnia. For the purpose of this study, the effect of non-antipsychotic medications was briefly assessed and analyzed.

During the fourth week on the fixed-dose of antipsychotic medication, patients included in this study completed the two time estimation tasks. Clinicians obtained clinical ratings including diagnosis, impulsiveness, and suicidal behavior. This was also the case for the subsample of 10 patients assessed during the off antipsychotic period.

Table 10

Drug Potency: Chlopromazine Equivalents for Antipsychotic Medications

Generic Name	CPZE (*)	CPZE Multiplier (**)
Chlorpromazine	100	1
Haloperidol	2	50
Haloperidol Decanoate (converted to daily dosage of Haloperidol)	2	50
Fluphenazine	2	50
Fluphenazine Decanoate (converted to daily dosage of Fluphenazine)	2	50
Clozapine	50	2
Olanzapine	4	25
Risperidone	1	100
Quetiapine	80	1.25

Note: (*) Approximate dose to achieve therapeutic efficacy of 100 mg of chlorpromazine

(**) This number multiplied by the dose of antipsychotic medication results in the CPZE dose

E. DATA ANALYSIS

To compare between and within group time estimation performance, all analyses included average percent deviations from the target duration. When deemed appropriate, analyses included percent deviations for the 10 selected intervals, five corresponding to the time perception task (i.e., percent deviations from 5, 15, 35, 55, and 85 seconds) and five for the time production task (i.e., percent deviations from 10, 20, 40, 60, and 90 seconds), as well as overall average percent deviations for each task.

It was established that to obtain an acceptable power of .80 for the correlations and t-tests with an effect size of 0.3-0.4 (Keppel, 1991) and alpha =. 05, a minimum of 30 patients was required.

There were three major components to the statistical analyses conducted. First, since there were several subgroups (i.e., patients and non-patients; attempters and non-attempters), Chi ^{2} and t-tests were used to determine significant differences in demographic, cognitive, and clinical variables among these groups (refer to Tables 5, 6, 7 and 8; pp. 89, 91 and 92). Second, Pearson Product Moment Correlations were used to determine whether these variables were related to the variables of interest (i.e., overall percent deviations for the time perception and time production tasks). If any of these variables were related to time estimation performance, they were included as covariates for group comparisons. Correlation analyses between CPZE and both time estimation tasks were also conducted to determine whether CPZE would be included as a covariate in the comparison of time estimation performance off and on antipsychotic.

Third, within and between groups comparisons (i.e., off and on antipsychotic, attempters versus non-attempters) were performed using paired samples t-tests or

Analyses of Covariance (ANCOVA), as deemed appropriate. Mixed Analysis of Variance (ANOVA) were conducted to examine possible interactions between variables (i.e., gender, group, and interval length).

Finally, Pearson Product Moment Correlations were performed to examine the relationship between average percent deviations for both time estimation tasks and variables of interest such as Positive and Negative symptoms scores on the PANSS subscales and impulsiveness as measured by the BIS-11 total score. Within the subsample of suicide attempters, correlations between average percent deviations for both time estimation tasks and variables related to suicidal history including number of prior suicide attempts, lethality scores as well as total scores on the SSI for the most recent and the most lethal attempts were also examined.

Scatter plots were used to interpret all correlations.

Given the exploratory nature of the present study as well as the inclusion of relatively small sample sizes, the Bonferroni procedure was not used to correct for the number of analyses. It was considered that lowering the alpha level and adopting a more stringent criterion of statistical significance could eliminate potentially theoretically meaningful findings.

1) Hypothesis I: Patients with schizophrenia would exhibit deficits in their ability to accurately estimate time, as compared to non-patients.

To test this hypothesis, percent deviations for estimates on the two time estimation tasks, time perception and time production, served as dependent measures. Since patients and non-patients differed significantly in gender, a three-way Group (2) by

Gender (2) by Interval (5) mixed ANOVA was conducted independently for both time estimation tasks. Patients and non-patients also exhibited significant differences in WAIS-R/WAIS-III Vocabulary Subscale scores and educational attainment. The correlations between these two cognitive variables and time estimation performance were analyzed. However, both the WAIS-R/WAIS-III Vocabulary Subscale scores and educational level were excluded as covariates based on the "matching fallacy" (Meehl, 1970) which conveys the inadequate approach of equating individuals with schizophrenia and normal controls in educational level and current intellectual functioning. Independent samples t-tests were used to compare the performance of all groups across different intervals. Finally, ANCOVA controlling for CPZE were conducted.

2) Hypothesis II: In patients with schizophrenia, time estimates would be differentially associated with the severity of positive and negative symptoms such that:

a. Positive symptoms would be positively correlated with estimates of time intervals on the perception task, and negatively correlated with estimates of time intervals on the time production task.

b. There would be no direct relationship between the estimation of time intervals and negative symptoms.

Pearson Product Moment Correlations were used to investigate the correlation between scores on the respective subscales of the PANSS and the overall percent deviations for time estimates of the two tasks. Exploratory analyses on gender and medication effects were conducted with Pearson Product Moment Correlations.

3) Hypothesis III: Patients on a fixed-dose of medication would have lower estimates on time perception and higher estimates on time production tasks as compared to their performance when unmedicated.

Paired t-tests were used to compare overall percent deviations of time estimates of patients on and off antipsychotic. In this case, the independent variable was antipsychotic status and, again, the dependent variable was performance on each time estimation task, as evidenced by overall percent deviations. Correlations between the daily dosages of antipsychotic medication at the time of neuropsychological assessment, converted to CPZE, and both time estimation tasks yielded not significant results. Therefore, this variable was excluded as a covariate. To eliminate possible effects of medications other than neuroleptics (i.e., serotonin agonists, anticholinergics, tranquilizers, anticonvulsants, and beta-blockers) received during the fixed-dose period of medication, independent sample t-tests were conducted to analyze the time estimation performance of the subsamples of patients receiving adjunctive medications. Exploratory analyses to examine the effect of adjunctive medications and anticonvulsants on gender differences were performed with two-way ANOVA.

4) Hypothesis IV: There would be a relationship between time estimation and the change in symptoms in patients with schizophrenia after treatment with antipsychotic medication. It was hypothesized that:

a. The change in positive symptoms from the off medication to the on medication state, which should be in the direction of lower values, would be correlated with change in time estimation, such that it would be

positively correlated with change in estimates of the perception task and negatively correlated with change in estimates on the production task;

b. No specific relationship was posited between change in negative symptoms and change in time estimates on both tasks after neuroleptic medication.

Paired t-tests were used to compare scores on the PANSS in the off and on medication states and to demonstrate change in the hypothesized direction. Pearson Product Moment correlations were used to investigate the relationship between the on and off medication change in scores in the PANSS and the change in overall percent deviations for the two time estimation tasks.

5) Hypothesis V: For patients with schizophrenia, impulsivity would be positively correlated with estimates in time perception and negatively correlated with estimates in time production. More specifically, patients with high total scores on the BIS-11 would exhibit larger estimates of time intervals on the time perception task and lower estimates of time intervals on the time production task when compared to patients with low total scores on the BIS-11.

Pearson Product Moment Correlations were conducted between total impulsiveness scores on the BIS-11 and overall percent deviations for time estimates on the perception and the production tasks. Exploratory analyses on gender differences and CPZE in impulsiveness scores were also conducted with Pearson Product Moment Correlations.

6) Hypothesis VI: Among patients with schizophrenia, suicide attempters would exhibit higher estimates of time intervals on the perception task and lower estimates of time intervals on the production task compared to non-attempters.

Suicide attempters and non-attempters were compared on overall percent deviations for time estimates on both tasks using analysis of covariance and controlling for age, education, and duration of illness given that all three variables were significantly correlated with time estimation performance. No significant correlations were found between ethnicity and overall percent deviations on both time estimation tasks. Thus, this variable was excluded as a covariate. Exploratory analyses to examine gender differences and the effect of CPZE were conducted with ANCOVA. Pearson Product Moment Correlations were used to investigate the relationship between time estimation and current suicidal ideation, as measured by total scores on the SSI. Supplementary analyses with Pearson Product Moment Correlations were performed on the subsample of attempters to study the relationship between time estimates and remote measures assessing characteristics of prior attempts, including suicide intent, number of attempts, and lethality of the most lethal attempt.

IV. RESULTS

To facilitate interpretation of the results presented in this section, the term "fast" is used when the internal sense of time of the participants passed subjectively more rapidly than the objective time (i.e., higher numbers), as measured by responses to the intervals included in each task. On the contrary, the term "slow" is operatively used to characterize an internal time sense that passed subjectively more slowly for the participants than the objective time (i.e., lower numbers), as measured by performance during the target durations. While most participants were consistently fast or slow across both tasks, a few demonstrated an inconsistent performance (i.e., were slow in time perception and fast in time production, or vice versa). However, the correlation between performance on the time perception and time production tasks was strong in the entire sample (r=-.80), the non-patient comparison group (r=-.80), and in the patient group (r=-.81) when assessed during the fixed-dose of medication. During the medication-free period, the correlation between both tasks was still moderate to strong (r= -.54). The correlation across individual intervals for both tasks was also moderately high in the entire sample (range between r= -.70 and -.79), the non-patient comparison group (range between r=-.68 and -.82), and in the patient group while medicated (range between r=-.65 and -.77). During the off medication period, the correlations were weak to moderate (r= between -.17 to -.62). These correlations support the reliability of both tasks in the measurement of time estimation. Nevertheless, their correlation coefficients are not high enough to indicate duplication. Moreover, the change in the relationship between these tasks under different conditions (i.e., off and on antipsychotic medication) suggests that

the time perception and time production tasks might be assessing overlapping but, at the same time, distinctive time estimation functions.

1) Hypothesis I: Patients with schizophrenia would be different from the non-patient comparison group in their ability to accurately estimate time. More specifically, the patient group would exhibit a faster internal time sense as indicated by larger positive percent deviations in the time perception and larger negative percent deviations in the time production task compared to the non-patient comparison participants.

Comparison between Patients and Non-Patients

First, analyses examining the relationship between demographic and clinical variables and time estimation were conducted. Correlations among WAIS-R/WAIS-III Vocabulary Subtest scores, educational level, and percent deviations for the time perception and production tasks were obtained for the overall sample and within each group. Patients differed significantly from the non-patient comparison group on several variables that may be related to time estimation, including gender (Chi^2= 6.35, p=**.012**), level of education (t=4.57, p=**.0001**), and WAIS-R/WAIS-III Vocabulary Subscale scores (t=4.19, p=**.0001**). For the time perception task, data on a female participant in the non-patient comparison group is missing.

a. Gender

Gender was included in analyses comparing patients and non-patients. A three-way Group (2) by Gender (2) by Interval (5) repeated measures ANOVA was conducted

independently for the time perception and time production tasks. As shown in Figure 2 and Table 11, in the time perception task there was a marginally significant main effect for Group (F=3.70, p=.058) such that subjects in the patient group provided larger estimates across all intervals, suggesting a faster internal sense of time compared to the non-patient group. There was a marginally significant main effect for Gender (F=3.72, p=.057) such that females in both groups, patients and non-patients, provided estimations larger than the targets across all intervals indicating a faster internal time sense. A significant Interval main effect (F=21.54, p=**.0001**) was observed. There was no significant Group x Gender interaction (F=.11, p=.741). However, significant Group x Interval (F=21.54, p=**.0001**) and Gender x Interval (F=3.23, p=**.013**) interactions were observed. Also, a trend Group x Gender x Interval (F=.081, p=.081) was detected.

Figure 2. Gender Effects Based on Groups: Time Perception

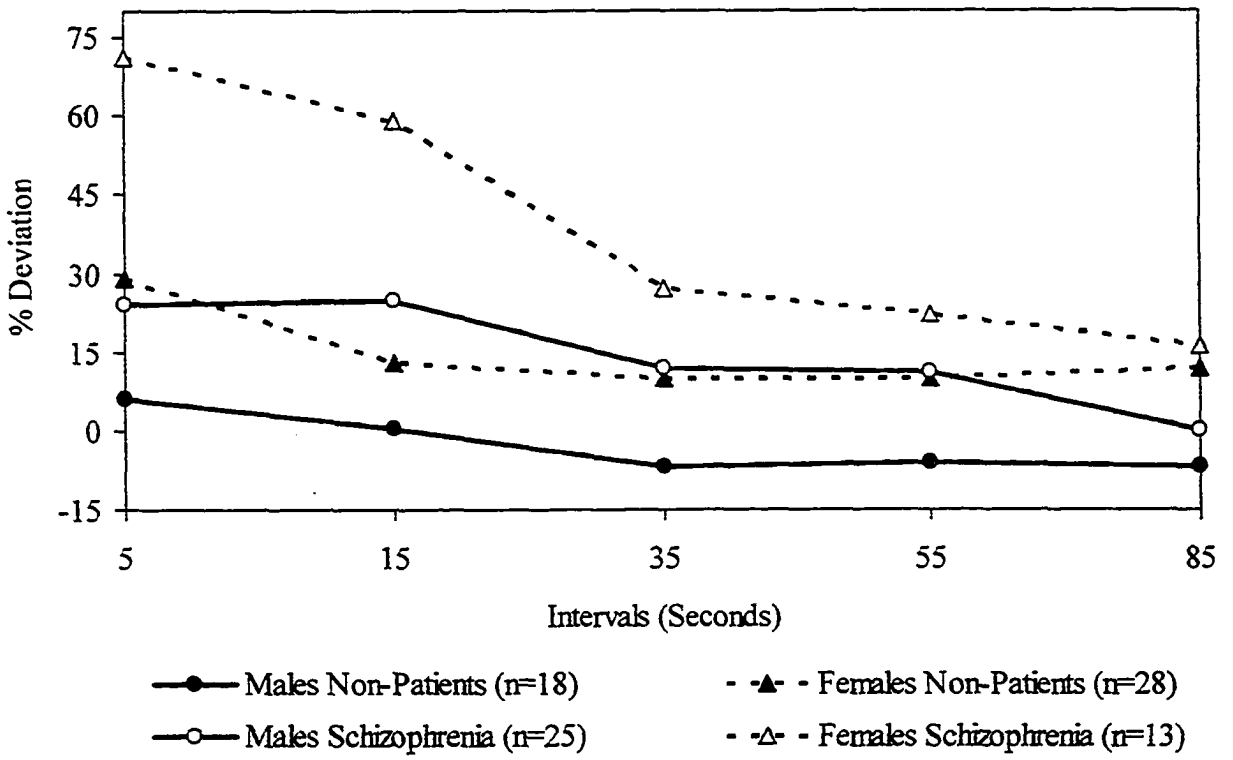


Table 11

Time Perception: Effects of Group and Gender across Intervals

Interval (Seconds)	Non-Patient Males (N=18) Mean (SD)	Non-Patient Females (N=28) Mean (SD)	Patient Males (N=25) Mean (SD)	Patient Females (N=13) Mean (SD)
5	.056 (.405)	.287 (.687)	.240 (.672)	.711 (.723)
15	.002 (.303)	.131 (.528)	.248 (.712)	.592 (.619)
35	-.067 (.266)	.103 (.506)	.122 (.477)	.265 (.390)
55	-.058 (.334)	.095 (.464)	.107 (.508)	.223 (.394)
85	-.066 (.431)	.117 (.512)	-.012 (.407)	.162 (.298)

Variable	F-value	df	p-value
Patient	3.70	1	.058
Gender	3.72	1	.057
Interval	21.54	4	.0001*
Group x Gender	.11	1	.741
Group x Interval	5.92	4	.0001*
Gender x Interval	3.23	4	.013*
Group x Gender x Interval	2.09	4	.081
Corrected df		80	

As shown in Tables 12 and 13, independent samples t-tests were conducted to compare the performance of the four groups across individual intervals. Male patients and non-patients did not exhibit significant differences across intervals. However, females in the patient group exhibited a significantly faster sense of the passage of time for the 15s interval compared to non-patient females. Similarly, a marginally significant difference for the 5s interval was observed, such that female patients demonstrated a

faster internal time sense compared to females in the non-patient group for this duration. No significant differences were observed between males and females in the non-patient comparison group. A marginally significant difference was found between males and females in the patient group for the 5s interval, such that females exhibited a faster sense of the passage of time.

Table 12

Performance on Time Perception across Intervals by Gender

Interval (Seconds)	Non-Patient Males (N=18) Mean (SD)	Patient Males (N=25) Mean (SD)	t-value	df	p-value
5	.056 (.405)	.240 (.672)	-1.04	41	.306
15	.002 (.303)	.248 (.712)	-1.38	41	.175
35	-.067 (.266)	.122 (.477)	-1.51	41	.138
55	-.058 (.334)	.107 (.508)	-1.20	41	.238
85	-.066 (.431)	-.012 (.407)	-.60	41	.551
Interval (Seconds)	Non-Patient Females (N=28) Mean (SD)	Patient Females (N=13) Mean (SD)	t-value	df	p-value
5	.287 (.687)	.711 (.723)	-1.81	39	.078
15	.131 (.528)	.592 (.619)	-2.47	39	.018*
35	.103 (.506)	.265 (.390)	-1.02	39	.314
55	.095 (.464)	.223 (.394)	-.87	39	.393
85	.117 (.512)	.162 (.298)	-.29	39	.774

Table 13

Performance on Time Perception across Intervals by Group

Interval (Seconds)	Non-Patient Males (N=18) Mean (SD)	Non-Patient Females (N=28) Mean (SD)	t-value	df	p-value
5	.056 (.405)	.287 (.687)	-1.29	44	.204
15	.002 (.303)	.131 (.528)	-.94	44	.354
35	-.067 (.266)	.103 (.506)	-1.31	44	.198
55	-.058 (.334)	.095 (.464)	-1.20	44	.235
85	-.066 (.431)	.117 (.512)	-1.26	44	.216
Interval (Seconds)	Patient Males (N=25) Mean (SD)	Patient Females (N=13) Mean (SD)	t-value	df	p-value
5	.240 (.672)	.711 (.723)	-1.99	36	.053
15	.248 (.712)	.592 (.619)	-1.47	36	.149
35	.122 (.477)	.265 (.390)	-.93	36	.359
55	.107 (.508)	.223 (.394)	-.72	36	.475
85	-.012 (.407)	.162 (.298)	-1.17	36	.249

For the time production task, a significant main effect for Group (F=6.23, p=**.015**) was observed such that individuals in the patient group provided estimations smaller than the target durations across all intervals, suggesting a faster internal time sense than participants in the comparison group. Also, a significant main effect for Gender (F=5.60, p=**.020**) was identified such that females in both groups provided estimations that were significantly smaller than the standard durations across intervals. This result indicates a faster internal time sense across intervals compared to males. No significant interactions were found. These findings are shown in Figure 3.

Figure 3. Gender Effects Based on Groups: Time Production

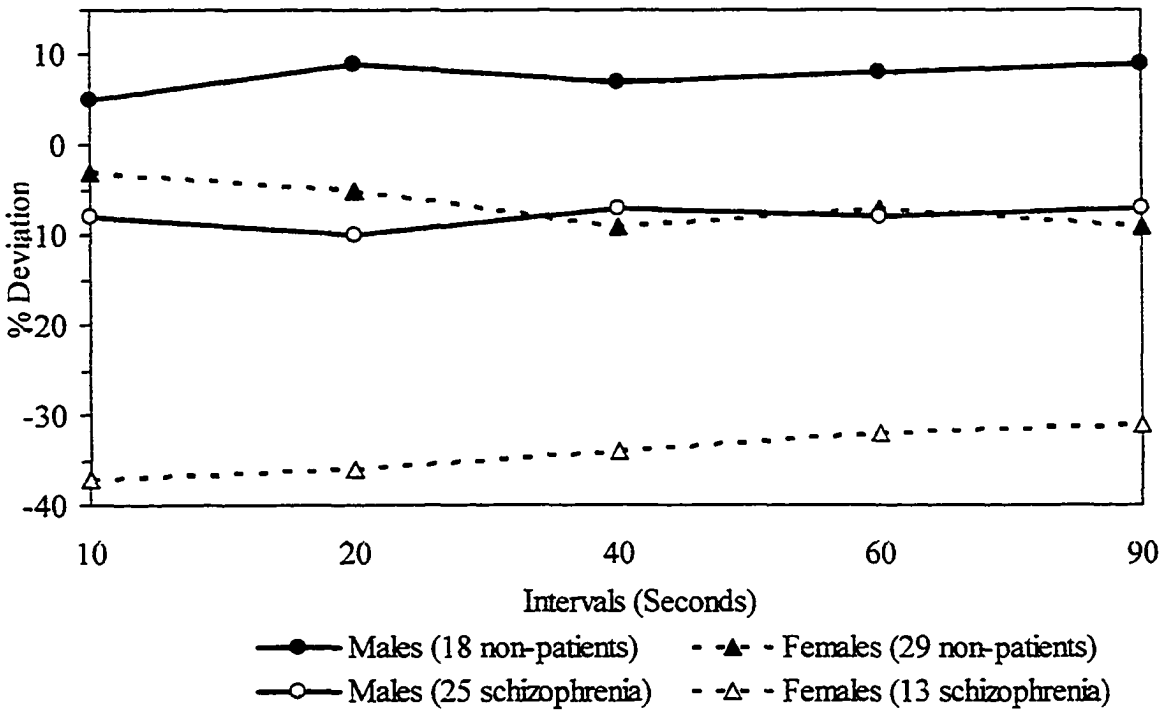


Table 14 illustrates the results corresponding to main effects and interactions described above. Independent samples t-tests were conducted to examine group differences across individual intervals. For the time production task, no significant differences were observed between males in both groups. However, significant differences were observed between female patients and non-patients for the 10s and the 20s intervals, such that females in the patient group exhibited a significantly faster internal time sense compared to females in the non-patient group. Similarly, marginally significant differences were found between these two groups for the 40s, 60s, and 90s interval, suggesting that female patients exhibited a faster sense of the passage of time also for longer intervals. Between group analyses indicate that there were no significant differences between males and females in the non-patient group. On the contrary, females

in the patient group exhibited a significantly faster sense of the passage of time for the 10s interval compared to male patients. Similarly, marginally significant differences for the 20s and the 40s intervals were observed, such that female patients demonstrated a faster internal time sense compared to males in this same group. Overall, female patients were faster than male patients across all intervals. These results are shown in Tables 15 and 16.

Table 14

Time Production: Effects of Group and Gender across Intervals

Interval (Seconds)	Non-Patient Males (N=18) Mean (SD)	Non-Patient Females (N=29) Mean (SD)	Patient Males (N=25) Mean (SD)	Patient Females (N=13) Mean (SD)
10	.054 (.204)	.-.033 (.410)	-.082 (.410)	-.374 (.315)
20	.086 (.310)	-.050 (.419)	-.097 (.449)	-.361 (.283)
40	.072 (.277)	-.092 (.452)	-.067 (.472)	-.341 (.257)
60	.078 (.315)	-.073 (.448)	-.079 (.467)	-.320 (.242)
90	.092 (.325)	-.092 (.397)	-.070 (.465)	-.312 (.234)

Variable	F-value	df	p-value
Group	6.23	1	.015*
Gender	5.60	1	.020*
Interval	.23	4	.922
Group x Gender	.34	1	.493
Group x Interval	1.23	4	.297
Gender x Interval	.26	4	.901
Group x Gender x Interval	1.35	4	.250
Corrected df		81	

Table 15

Performance on Time Production across Intervals by Gender

Interval (Seconds)	Non-Patient Males (N=18) Mean (SD)	Patient Males (N=25) Mean (SD)	t-value	df	p-value
10	.054 (.204)	-.082 (.410)	1.29	41	.205
20	.086 (.310)	-.097 (.449)	1.50	41	.142
40	.072 (.277)	-.067 (.472)	1.12	41	.271
60	.078 (.315)	-.079 (.467)	1.24	41	.223
90	.092 (.325)	-.070 (.465)	1.27	41	.212
Interval (Seconds)	Non-Patient Females (N=29) Mean (SD)	Patient Females (N=13) Mean (SD)	t-value	df	p-value
10	-.033 (.410)	-.374 (.315)	2.66	40	.011*
20	-.050 (.419)	-.361 (.283)	2.43	40	.020*
40	-.092 (.452)	-.341 (.257)	1.85	40	.072
60	-.073 (.448)	-.320 (.242)	1.87	40	.069
90	-.092 (.397)	-.312 (.234)	1.85	40	.072

Table 16

Performance on Time Production across Intervals by Group

Interval (Seconds)	Non-Patient Males (N=18) Mean (SD)	Non-Patient Females (N=29) Mean (SD)	t-value	df	p-value
10	.054 (.204)	-.033 (.410)	.83	45	.410
20	.086 (.310)	-.050 (.419)	1.19	45	.240
40	.072 (.277)	-.092 (.452)	1.38	45	.173
60	.078 (.315)	-.073 (.448)	1.25	45	.219
90	.092 (.325)	-.092 (.397)	1.65	45	.106
Interval (Seconds)	Patient Males (N=25) Mean (SD)	Patient Females (N=13) Mean (SD)	t-value	df	p-value
10	-.082 (.410)	-.374 (.315)	2.25	36	.031*
20	-.097 (.449)	-.361 (.283)	1.92	36	.063
40	-.067 (.472)	-.341 (.257)	1.94	36	.060
60	-.079 (.467)	-.320 (.242)	1.74	36	.091
90	-.070 (.465)	-.312 (.234)	1.76	36	.087

b. WAIS-R/WAIS-III Vocabulary Subscale Score and Educational Level

The patient and non-patient comparison group exhibited significant differences in the WAIS-R/WAIS-III Vocabulary Subscale score and in educational level. As expected, an examination of the correlation between educational level and the WAIS-R/WAIS-III Vocabulary Subtest was significant both for the non-patients (r=.53, p=**.0001**) and for the patients (r=.59, p=**.0001**). These results suggest that both variables tend to measure abilities that are moderately interrelated.

Overall correlations for the entire sample were not significant between WAIS-R / WAIS III Vocabulary score and time perception (r= -.19, p=.083) or time production (r=.16, p=.147). Similarly, no significant correlation was observed between educational attainment and the time perception (r=-.11, p=.318) or the time production tasks (r=.04, p=.733).

As shown in Table 17, within group correlations between these two variables and both time estimation tasks yielded conflicting results.

In the non-patient comparison sample, the WAIS-R/WAIS-III Vocabulary Subscale score was significantly correlated with performance on both the time perception task (r=.-47, p=**.0001**) and the time production task (r=.45, p=**.0001**). These results indicate that, for both tasks, high scores in this WAIS-R/WAIS-III are associated with an internal sense of the elapsed time that is slower than the objective time.

In addition, within the non-patient comparison group, there was a significant negative correlation between level of education and average percent deviations from the target durations in the time perception task (r=-.38, p=**.009**), such that individuals with high level of education provided overall estimations that were smaller than the target durations, thus suggesting a slow internal time sense. Analyses of the correlation between level of education and the time production task for this same group indicate a trend for significance for a positive correlation (r=.26, p=.075), such that individuals with a high level of education provided estimations larger than the standard durations, also suggesting a sense of the passage of time that is slower than the objective time.

Within the patient sample, no significant correlations were found between WAIS-R/ WAIS-III Vocabulary Subscale and the percent deviations for time perception (r=.16,

p=.351) or time production (r=-.24, p=.168). Similarly, there was no significant association between educational attainment and overall percent deviation in the time perception task (r=.23, p=.157) for this group. However, contrary to the non-patient group, a significant negative correlation was found between level of education and time production (r= -.33, p=**.042**). As explained in greater detail below, it is possible that this relationship is spurious in nature because, in many cases, the onset of schizophrenia truncated the patients' academic achievement.

Table 17

Correlations between WAIS-R/WAIS-III Vocabulary Subtest Score, Educational Level and Both Time Estimation Tasks in the Non-Patient and the Patient Groups

	Non-Patients		Patients	
Variable	Time Perception r (p)	Time Production r (p)	Time Perception r (p)	Time Production r (p)
WAIS-R/ WAIS-III Vocabulary	-.47 (.001)*	.45 (.001)*	.16 (.351)	-.24 (.168)
Educational Level	-.38 (.009)*	.26 (.075)	.23 (.157)	-.33 (.042)*

The significant differences between patients with schizophrenia and non-patients in the WAIS-R/WAIS-III Vocabulary Subscale score and educational attainment are expected given the impact that the presence of the illness produces on both variables. The onset of schizophrenia may cause individuals to fall short of their educational potential. Given that education and the WAIS-R/WAIS-III Vocabulary Subscale score are strongly correlated with each other, it would be inappropriate to equate individuals with schizophrenia and normal controls in number of years of education and current

intellectual functioning. This issue is well-addressed in the literature as the "matching fallacy" (Meehl, 1970). Therefore, these variables will not be used as covariates.

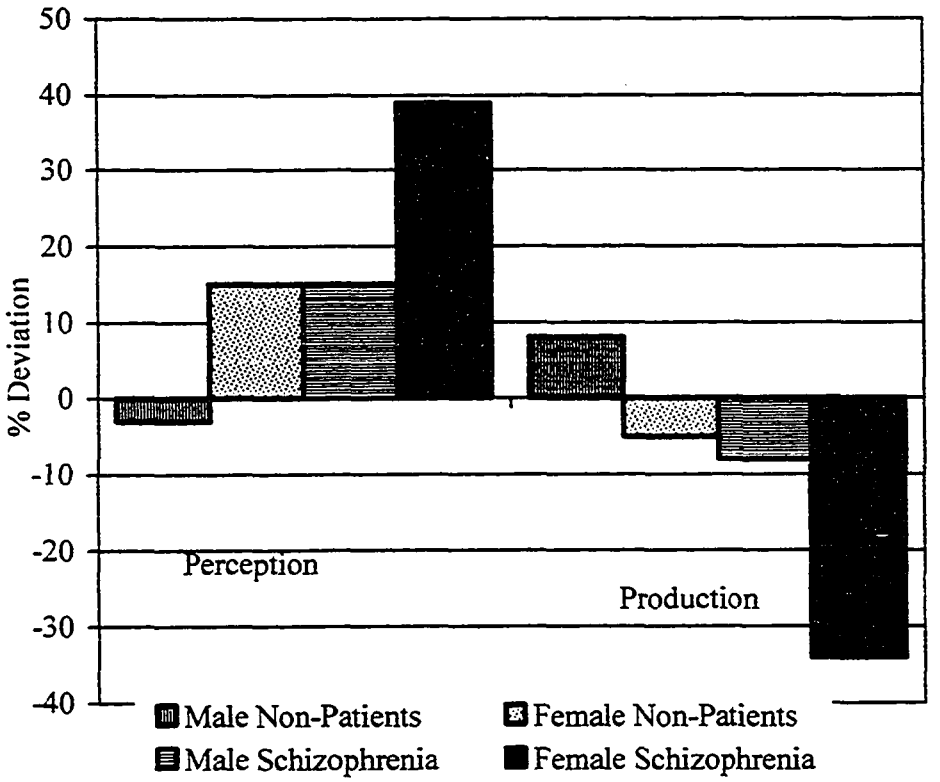
Hypothesis I: Summary of Findings

The findings described above suggest that patients exhibited an overall faster internal time sense compared to non-patients. Figure 6 summarizes the total percent deviations for time perception and time production. While main effects were significant for the time production task, they were not significant for the time perception task. As shown in Figures 4 and 5, females in both groups exhibited an overall faster internal time sense compared to males. However, while female patients were significantly faster than male patients and female non-patients across several intervals, this latter group did not exhibit significant differences across intervals from male non-patients. Overall, females in the patient group exhibited the fastest internal time sense for both time perception and production, while males in the non-patient comparison group showed the slowest internal time sense.

In view of these results, a careful examination of the male/female distribution within the groups (females comprised 62% of the non-patient group and 24% of the patient group) suggests that larger differences between the groups on time perception and production were eliminated due to this disproportion.

A caveat must be mentioned in relation to the outcome of these analyses. In view of findings related to a significant medication effect obtained in our Hypothesis III, these results will be revisited later in this chapter.

Figure 4. Overall Performance on Time Estimation by Gender



2) Hypothesis II: Among patients, time estimates would be differentially associated with the severity of positive and negative symptoms such that:

a. Positive symptoms would be positively correlated with estimates of time intervals on the perception task and negatively correlated with estimates of time intervals on the production task.

b. There would be no direct relationship between the estimation of time intervals and negative symptoms.

As shown in Table 18, Pearson Product Moment Correlations did not yield any significant correlations between positive symptoms, as measured by the total score on the

positive symptoms scale of the PANSS, and average percent deviations obtained by the patient group in either the time perception (r= -.11, p=.509) or the time production (r=.14, p=.394) tasks. As predicted, no significant correlation was found between negative symptoms, as measured by the total score on the negative scale of the PANSS, and the average percent deviations obtained by the patients in the time perception (r=.12, p=.480) and in the time production (r=-.02, p=.900) tasks.

Table 18

Correlations between Average Percent Deviations in the Time Perception and the Time Production Tasks and Positive and Negative Symptoms Scores in the PANSS

Time Estimation Task	Positive Symptoms (PANNS) r (p)	Negative Symptoms (PANSS) r (p)
Time Perception	-.11 (.509)	.12 (.480)
Time Production	.14 (.394)	-.02 (.900)

Given the gender differences on time estimation reported previously in this section, we reexamined these correlations separately for males and females. As shown in Table 19, both groups did not differ in their mean scores on the PANSS positive symptoms scale (t=-.40, p=.693). However, males exhibited a significantly higher (t=2.32, p=**.026**) mean score on the negative symptoms scale than females.

Table 19

Mean Scores on the PANSS Positive and Negative Symptoms Scales

Patients	Males Mean (SD)	Females Mean (SD)	t-value	df	p-value
Positive Symptoms	12.44 (5.46)	13.16 (4.81)	-.397	36	.693
Negative Symptoms	19.56 (5.26)	15.31 (5.57)	2.32	36	.026*

Independent correlations based on gender were conducted between performance on the time perception and production tasks and PANSS scores. These results are shown in Table 20. Among females, the overall percent deviation on the time perception task exhibited a moderate positive correlation (r=.37, p=.221) with the total score on the negative symptoms scale, and a weak negative correlation (r=-.20, p=.522) with the total score on the positive symptoms scale. Also in this group, a marginally significant positive correlation (r=.54, p=.055) was observed between positive symptoms and the overall percent deviation on the time production task. Although not significant, a modest inverse correlation (r=-.46, p=.116) was observed between the total score for negative symptoms and the time production task. These findings suggest that, among females, higher scores on the positive symptoms scale are associated with a slower internal time sense, while higher scores on the negative symptoms scales are correlated with a faster sense of the passage of time. No significant correlations were found between these variables among males. However, an inspection of the correlations shown in Table 20, suggests that a similar trend also exists in the subgroup of males. Evidently, these results contradict the direction of findings predicted in our hypothesis.

Table 20

Gender Correlations between Average Percent Deviations in the Time Perception and the Time Production Tasks and Positive and Negative Symptoms Scores in the PANSS

Time Estimation Task	Positive Symptoms (PANNS) r (p)		Negative Symptoms (PANSS) r (p)	
	Males (N=25)	Females (N=13)	Males (N=25)	Females (N=13)
Time Perception	-.11 (.608)	-.20 (.522)	.13 (.547)	.37 (.221)
Time Production	.08 (.715)	.54 (.055)	-.06 (.765)	-.46 (.114)

3) Hypothesis III: Patients on a fixed-dose of medication would have lower estimates on time perception and higher estimates on time production tasks as compared to their performance when unmedicated.

Time Estimation Off and On Antipsychotics: CPZE as a Potential Covariate

Since patients were placed on a four-week period of fixed-dose neuroleptic medication with different dosages, daily antipsychotic medication doses were converted into chlorpromazine equivalents (CPZE) (AstraZeneca, 2002; Drug Facts and Comparisons, 2003; Jibson, & Tandon, 1998; Schizophrenia Patient Outcome Research Team (PORT), 2002; Schatzberg, Cole, DeBattista, 1997; Schatzberg, DeBattista, Overman, & Ereshefsky, 1998) for the entire patient sample. The mean dosage of CPZE in the entire sample was 711mg (SD=354.54; range 250-1700). In the subsample of 10 patients tested off and on antipsychotic medication the mean was 535 mg (SD=279.93; range 250-1000). Correlation analyses were conducted to examine the relationship between CPZE dosage and both time estimation tasks for all patients. There were no

correlations between levels of CPZE and time perception (r=-.07, p=.691) and production (r=.150, p=.370) tasks in the entire sample. Similar results were obtained within the subsample of patients repeatedly tested off and on medication for the correlations between CPZE, time perception (r=.11, p=.769), and time production (r=-.14, p=.710). Therefore, CPZE was eliminated as a potential covariate.

Time Estimation Off and On Antipsychotics: Primary Analyses

Paired samples t-tests were conducted to examine the effects of the four-week period of fixed-dose neuroleptic medication on time estimation abilities. A subsample of patients (N=10) was repeatedly tested off and on neuroleptic medication using both time estimation tasks. As shown in Table 21, a significant difference was observed in the average percent deviation for the time perception task (t=-3.59, p=**.006**). During on antipsychotics testing for the time perception task, average percent deviations from the target intervals showed significantly larger values than those obtained for this same task during the antipsychotics-free period. Contrary to our hypothesis, while medicated, patients demonstrated a significantly faster internal time sense compared to the off antipsychotics state. The mean difference between average percent deviations off and on antipsychotics (-.37), suggests that, while medicated, patients were 37% faster compared to the off antipsychotics period. Given the small sample size, a marginally significant difference was observed for the time production task (t=1.82, p=.103). A careful observation of the means corresponding to the off antipsychotics (.17) and on antipsychotics (-.26) testing, indicates that, contrary to our prediction, the internal time sense of medicated patients was 43% faster compared to their testing off antipsychotics.

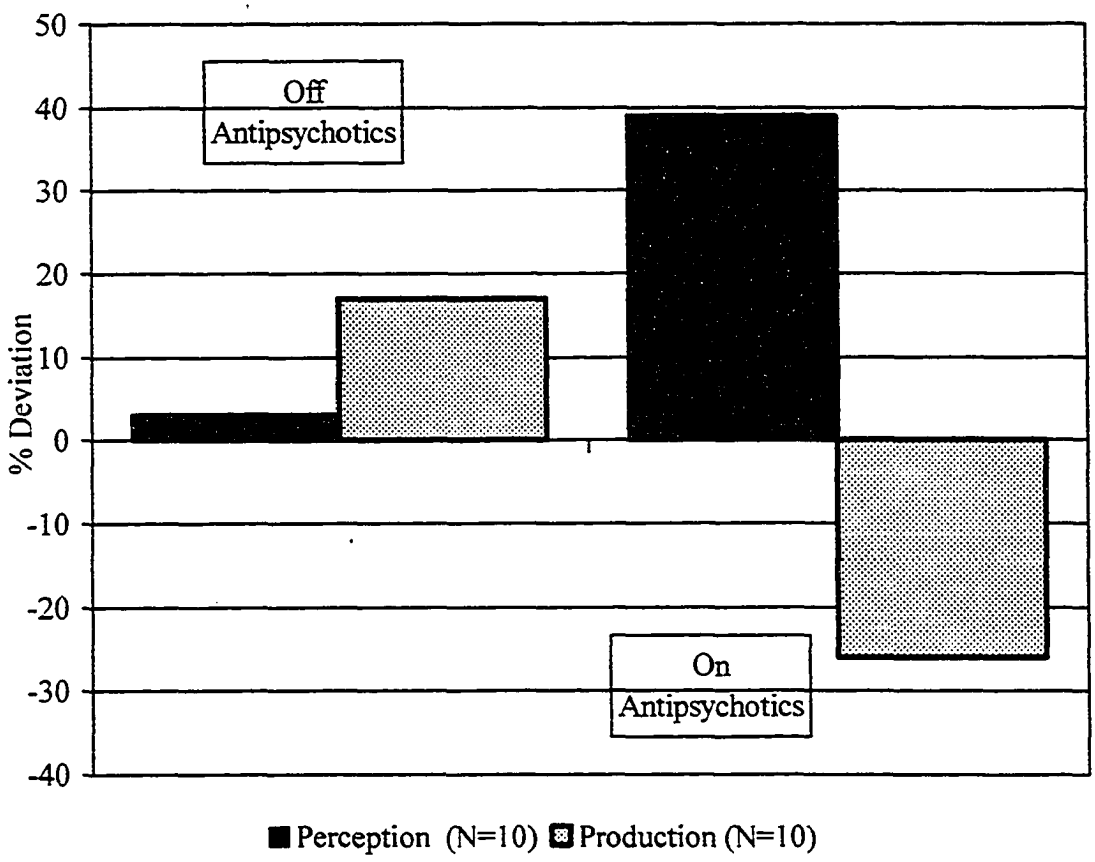
Results obtained for both tasks off and on antipsychotics consistently indicate that patients' internal sense of the passage of time becomes faster after a four-week period of fixed-dose antipsychotic medication. These results are illustrated in Figure 5.

Table 21

Performance on both Time Estimation Tasks Off and On Antipsychotics

Time Estimation Task	Off Antipsychotics (N=10) Mean (SD)	On Antipsychotics (N=10) Mean (SD)	Paired Differences Mean (SD)	t-value	df	p-value
Perception	.029 (.313)	.395 (.572)	-.366 (.322)	-3.59	9	.006*
Production	.171 (.783)	-.262 (.305)	.432 (753)	1.82	9	.103

Figure 5. Time Estimation Off and On Antipsychotics



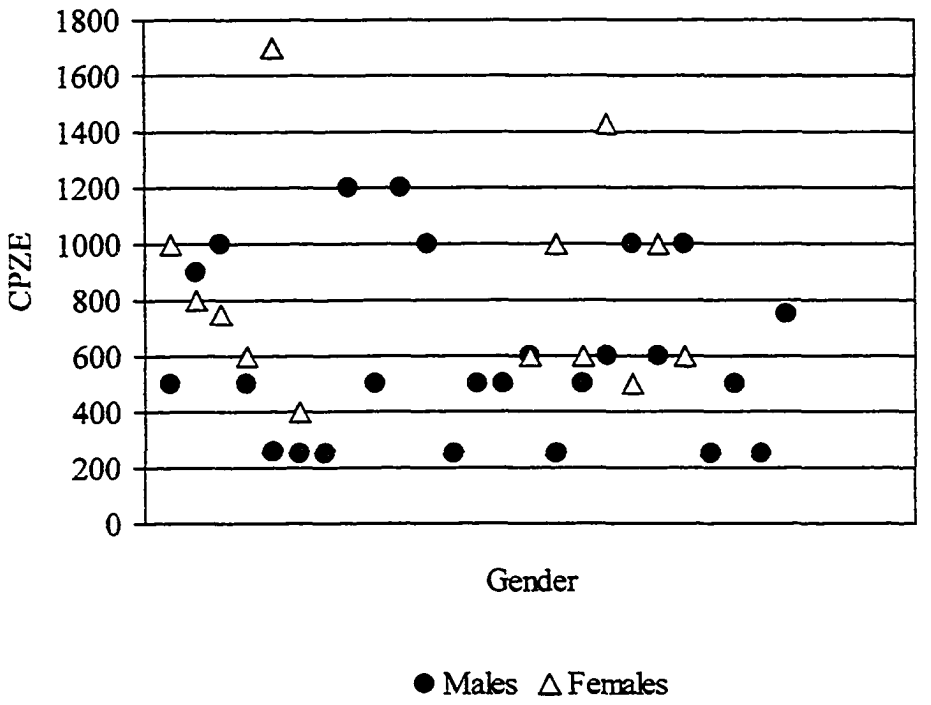
The Effect of Neuroleptics on Time Estimation: Exploratory Analyses and Reexamination of Hypothesis I

Given the systematic differences observed between males and females on time estimation, as well as the significant effect of neuroleptic medication on this cognitive function, we examined CPZE levels in both groups. Females received higher doses of antipsychotics (mean=.642, SD=.328; range 400-1700) than male patients (mean=.844, SD=.377; range 250-1200). However, these differences failed to reach significance (t=-1.71, df=36, p=.096).

As shown in Figure 6, two females were on particularly high doses (i.e., 1700 mg and 1425 mg, respectively) while males received doses equal or less than 1200 mg. Seventeen males (68%) were receiving CPZE doses of 600 mg or less, while all female patients received doses of CPZE that were at least 400 mg.

No significant correlations were found between CPZE and time perception (r=-.15, p=.485) or time production (r=.16, p=.454) for males. On the other hand, among female patients, a significant positive correlation was observed between CPZE and the time perception task (r=.56, p=**.046**). Although not significant, a modest negative correlation was also found between this variable and the time production task (r=-.39, p=.185). Both results suggest that, among female patients, a high dose of CPZE is associated with a fast internal sense of the passage of time.

Figure 6. Neuroleptic Dosages in CPZE by Gender



In view of the different dosages of CPZE between males and females, Analyses of Covariance (ANCOVA) were performed to compare these two groups on time estimation controlling for CPZE dose. For the time perception task, the main effect for Gender ($F=1.37$, $df=1$, $p=.251$) and the interaction CPZE x Gender ($F=1.96$, $df=2$, $p=.156$) were not significant. These results indicate that after controlling for CPZE, males and females did not exhibit significant differences in the overall percent deviations for time perception. In addition, the effect of CPZE dosage on performance for this task was similar for males and females. Similarly, ANCOVA for the time production task yielded a non-significant main effect for Gender ($F=.09$, $df=1$, $p=.769$). Thus suggesting, after adjusting for differences in CPZE, male and female patients did not exhibit significant differences on the overall percent deviations for the time production task. In addition, the

interaction Gender x CPZE (F=.759, df=2, p=.476) was not significant on this task. This latter result indicates that the effects of CPZE dosage on time production performance did not differ based on gender. The raw and adjusted means for both time estimation tasks were used for post-hoc comparisons using the Bonferroni procedure. As shown in Table 22 and Figure 7, the effect of adjusting for CPZE based on gender was modest for the time perception and was even smaller for time production since the differences between adjusted means were slightly attenuated in the latter task.

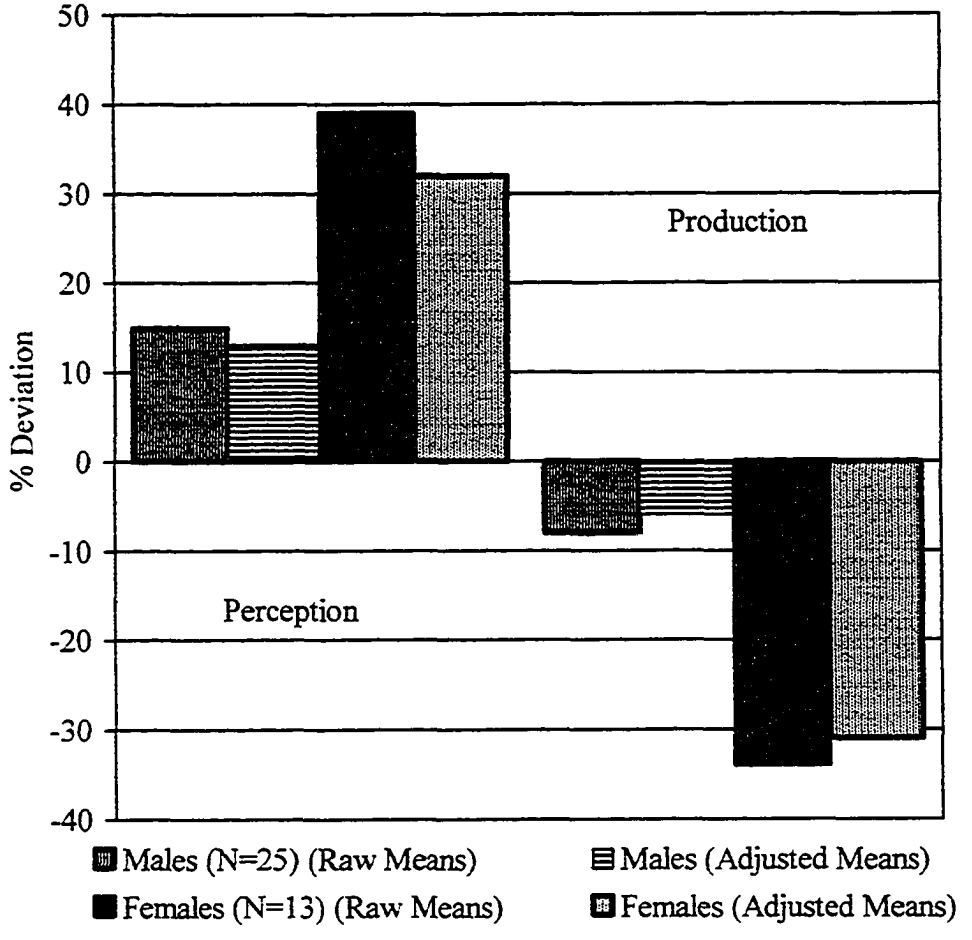
In summary, these results indicate that although female patients exhibited an overall, yet non-significant, faster internal time sense compared to male patients, the gender effect was eliminated when differences in CPZE dosage were adjusted.

Table 22

Raw and Adjusted Means for Time Perception and Time Production by Gender

	PERCEPTION		PRODUCTION	
	Uncorrected Mean (SD)	Adjusted Mean (SE)	Uncorrected Mean (SD)	Adjusted Mean (SE)
Male Patients (N=25)	.146 (.508)	.130 (.098)	-.079 (.446)	-.064 (.081)
Female Patients (N=13)	.391 (.449)	.302 (.141)	-.342 (.255)	-.306 (.117)
Mean Difference (SE)	.245 (.167)	.172 (.171)	-.263 (.134)	-.242 (.142)
df	1	1	1	1
p-value	.152	.323	.058	.097

Figure 7. Raw and Adjusted Means on Time Estimation after Adjusting for CPZE by Gender



Other Medications during Fixed-Dose: Further Analyses

During the four-week period of fixed dose of medication, 14 patients (37%) were taking exclusively antipsychotics. Nine were taking Clozapine, 3 Olanzapine, and 2 Risperidone. In some cases, other drugs were added when the treating clinician considered that such combination contributed to the enhancement of patients' clinical response. As such, 16 patients (42%) were receiving a combination of neuroleptics and a single additional medication, including 5 patients with anticholinergics (i.e., Benztropine), 6 with tranquilizers (5 with Lorazepam, and 1 with Clonazepam), 3 with

anticonvulsants (1 with Topiramate, and 2 with Valproic Acid), and 2 with serotonin agonists (i.e., Paroxetine). Six patients (16%) were on a combination of neuroleptics and two additional medications, including 3 patients with tranquilizers and anticonvulsants (1 with Clonazepam and Carbamazepine, 1 with Lorazepam and Topiramate, and 1 with Lorazepam and Valproic acid), 2 with Lorazepam and serotonin agonists (1 with Citalopram and 1 with Sertraline), and 1 with Valproic Acid and Citalopram. One patient was medicated with a combination of neuroleptics (i.e., Olanzapine), and three other drugs including Benztropine, Sertraline, and Atenolol. Finally, one patient was treated with neuroleptics (i.e., Fluphenazine) and four additional medications (i.e., Benztropine, Trihexyphenidyl, Lorazepam, and Valproic Acid). With regard to neuroleptics dosages, the means were 15mg (SD=7.1) for Haloperidol, 21mg (SD=5.3) for Fluphenazine, 495mg (SD=106.6) for Clozapine, 6mg (SD=1.7) for Risperidone, 16mg (SD=6.2) for Olanzapine, and 500mg for Quetiapine. The mean dosages for anticonvulsants were 1250mg (SD=847.7) for Valproic Acid, 350mg (SD=70.7) for Topiramate, and 1400mg for Carbamazepine. The mean dosages for tranquilizers were 1.9 (SD=.9) for Lorazepam, 3mg (SD=0) for Clonazepam, while for serotonin agonists were 40 mg for Citalopram, 188mg (SD=17.7) for Sertraline, and 50mg (SD=14.1) for Paroxetine. Finally, Benztropine had a mean dosage of 1.7mg (SD=.49), while the doses for Atenolol and Trihexyphenidyl were 75mg and 2mg, respectively.

Time Estimation: Possible Effects and Interactions among Medications

We conducted several exploratory analyses to investigate the role of psychotropic medications administered in combination with neuroleptics during the four-week period

of fixed dose. Independent samples t-tests were conducted to assess the separate effects of four types of medications (i.e, serotonin agonists, anticholinergics, tranquilizers, and anticonvulsants) on time estimation among subsamples of patients. Given that only one patient received a beta-blocker (i.e., Atenolol), no t-tests were conducted in this case.

Table 23

Effect on Time Perception of Non-Antipsychotic Medications Included in Fixed-Dose

Medication Type		N (%)	Time Perception Mean (SD)	t-value	df	p-value
Serotonin Agonists	Yes	6 (16)	.100 (.236)	-.69	36	.495
	No	32 (84)	.254 (.531)			
Anticholinergics	Yes	7 (18)	.313 (.469)	.49	36	.628
	No	31 (82)	.211(.508)			
Tranquilizers	Yes	12 (32)	.263 (.559)	.27	36	.785
	No	26 (68)	.214 (.477)			
Anticonvulsants	Yes	8 (21)	.487 (.563)	1.69	36	.099
	No	30 (79)	.161 (.464)			

Table 24

Effect on Time Production of Non-Antipsychotic Medications Included in Fixed-Dose

Medication Type		N (%)	Time Production Mean (SD)	t-value	df	p-value
Serotonin Agonists	Yes	6 (16)	-.187 (.180)	-.12	36	.905
	No	32 (84)	-.165 (.439)			
Anticholinergics	Yes	7 (18)	-.177 (.359)	-.06	36	.955
	No	31 (82)	-.167 (.423)			
Tranquilizers	Yes	12 (32)	-.156 (.410)	.13	36	.895
	No	26 (68)	-.175 (.414)			
Anticonvulsants	Yes	8 (21)	-.386 (.322)	-1.75	36	.089
	No	30 (79)	-.111 (.412)			

As shown in Tables 23 and 24, no significant differences were observed on time estimation between subsamples of patients with and without these four types of medications. However, there was a trend for mood stabilizers both for the time perception (t=1.69, df=36, p=.099) and the time production task (t=-1.75, df=36, p=.089). Patients who were medicated with Carbamazepine, Topiramate, or Valproic Acid exhibited a faster internal sense of time (i.e., 33% for time perception; 28% time for production) than patients who were not receiving these types of medications.

Given that the subsamples of patients receiving different combinations of medications were extremely small, we decided to increase our statistical power by comparing time estimation performance of patients exclusively on neuroleptics (N=14) with those on neuroleptics and other medications (N=24). No significant differences were found between these two groups in the overall percent deviations for the time perception (t=-.92, df= 36, p=.366) and the time production (t=.507, df=36, p=.615) tasks. Furthermore, a two-way Gender (2) by Medication Type (2) ANOVA was executed to determine gender differences on time estimation based on these two subgroups of medications. No significant main effects for Gender (F=1.68, df=1, p=.204) and Medication Type (F=.416, df=1, p=.523) were observed for time perception. Similarly the interaction Gender x Medication Type was not significant (F=.175, df=1, p=.679) in this task. With regard to time production, no significant main effect was observed for Medication Type (F=.66, df=1, p=.421). The interaction Gender x Medication Type (F=.18, df=1, p=.677) was also not significant. However, a trend for significance was found for Gender (F=4.01, df=1, p=.053) in which females had a faster internal time

sense than males for the time production task regardless of the medication type. Table 25 presents the mean values for these analyses.

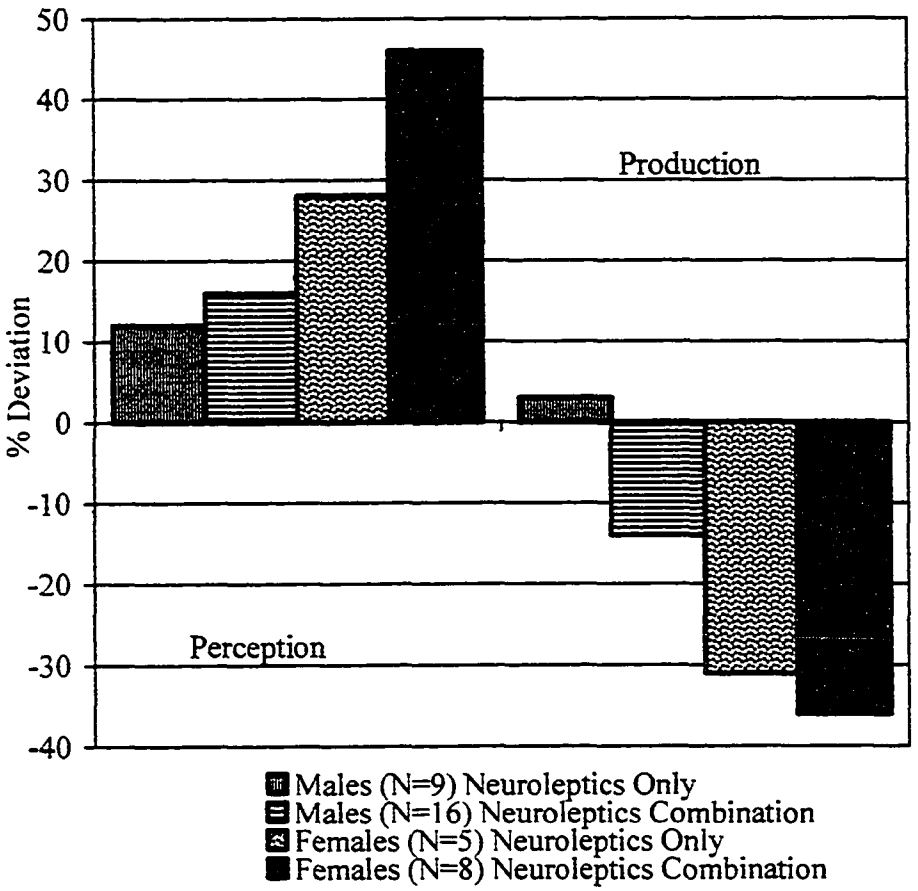
Table 25

Time Estimation: Effects of Neuroleptics and Combination of Neuroleptics and Additional Medications

TIME PERCEPTION			
Neuroleptics Only Mean (SD)		Neuroleptics and Combination Mean (SD)	
Subsample (N=14) .176 (.514)		Subsample (N=24) .261 (.495)	
Males (N=9) .120 (.641)	Females (N=5) .275 (.134)	Males (N=16) .160 (.441)	Females (N=8) .463 (.565)
TIME PRODUCTION			
Neuroleptics Only Mean (SD)		Neuroleptics and Combination Mean (SD)	
Subsample (N=14) -.090 (.475)		Subsample (N=24) -.215 (.365)	
Males (N=9) .032 (.555)	Females (N=5) -.308 (.150)	Males (N=16) -.141 (.376)	Females (N=8) -.363 (.311)

As shown in Figure 8, despite the lack of significant differences, the combination of neuroleptics with other drugs appears to have a greater impact on the acceleration of the internal time sense of females and males in both tasks than antipsychotics alone.

Figure 8. Time Estimation: Effect of Neuroleptics and Other Medications by Gender



With these results in conjunction with the trend for significant differences evidenced for anticonvulsants (refer to Tables 23 and 24; p. 140), we examined differences on time estimation performance based on the presence of Valproic Acid, Topiramate, and Carbamazepine. Once more, to increase our statistical power, the patient sample was divided in only two groups despite the multiple combinations of medications (refer to pp.138-139). One subsample included patients who were exclusively on neuroleptics or on neuroleptics with medications other than anticonvulsants. The second subsample was comprised by patients who, in addition to neuroleptics, were on anticonvulsants alone or on anticonvulsants with other drugs. Independent samples t-tests

were conducted between these two groups. A trend for significant differences was observed both for time perception (t=-1.69, df=36, p=.099) and time production (t=1.75, df=36, p=.089). Patients treated with neuroleptics and anticonvulsants were faster than those medicated exclusively with antipsychotics or with antipsychotics and medications other than anticonvulsants. A two-way Gender (2) by Medication Type (2) ANOVA was performed to examine gender differences on time estimation based on the presence of anticonvulsants in the patients' psychotropic treatment. Table 26 presents the mean values for these analyses.

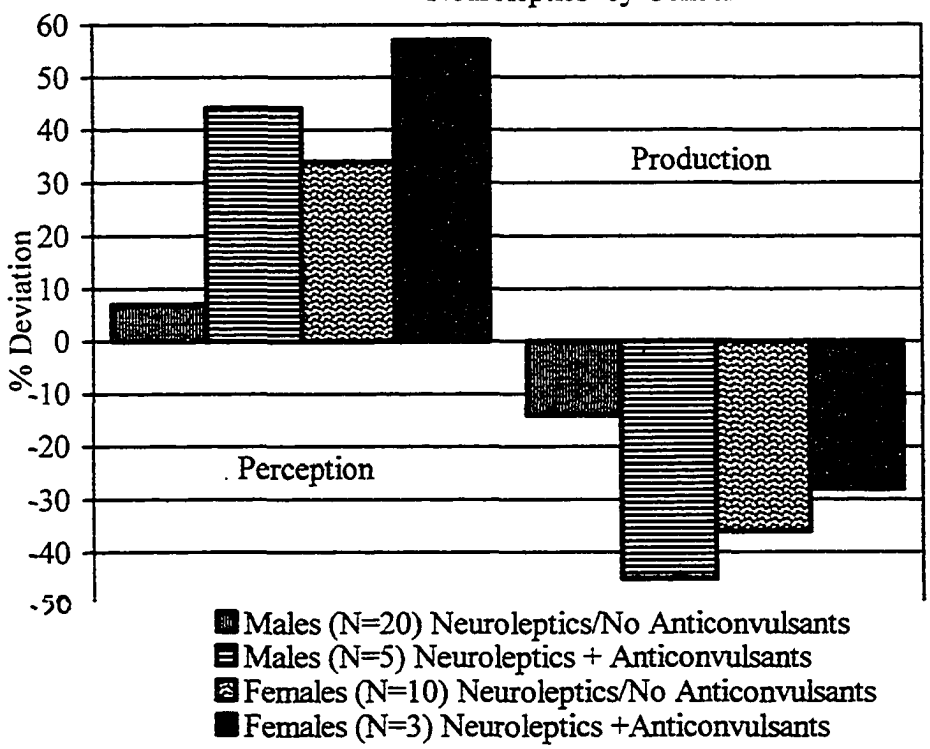
Table 26

Time Estimation: Effects of Anticonvulsants and Neuroleptics

TIME PERCEPTION			
Neuroleptics Alone or in Combination (No Anticonvulsants) Mean (SD)		Neuroleptics with Anticonvulsants Mean (SD)	
Subsample (N=30) .161 (.464)		Subsample (N=8) .487 (.563)	
Males (N=20) .073 (.501)	Females (N=10) .337 (.334)	Males (N=5) .438 (.475)	Females (N=3) .569 (.802)
TIME PRODUCTION			
Neuroleptics Alone or in Combination (No Anticonvulsants) Mean (SD)		Neuroleptics with Anticonvulsants Mean (SD)	
Subsample (N=30) -.111 (.412)		Subsample (N=8) -.386 (.322)	
Males (N=20) -.014 (.444)	Females (N=10) -.360 (.170)	Males (N=5) -.449 (.206)	Females (N=3) -.282 (.503)

No significant main effects for Gender (F=.98, df=1, p=.330) or Medication Type (F=2.23, df=1, p=.145) were observed for the time perception. Similarly, the interaction Gender x Medication Type was not significant (F.112, df=1, p=.740) for this task. With regard to the time production task, no significant main effects for Gender (F=.452, df=1, p=.506) or Medication Type (F=1.58, df=1, p=.218) were found. Nevertheless, a trend for a significant interaction (F=3.11, df=1, p=.087) was observed such that males on anticonvulsants had a faster internal sense of the passage of time than males off anticonvulsants. Conversely, females on anticonvulsant medication had a slower internal time sense compared to females off anticonvulsants. Despite the exploratory nature of these analyses, the presence of anticonvulsants appears to change the relationship between gender differences in the perception of the passage of time. This is more evident for the time production task. These findings are illustrated in Figure 9.

Figure 9. Time Estimation: Effect of Anticonvulsants and Neuroleptics by Gender



4) Hypothesis IV: There will be a relationship between time estimation and the change in symptoms in patients with schizophrenia after treatment with antipsychotic medication. It was hypothesized that:

a. The change in positive symptoms from the off antipsychotics to the on medication state, which should be in the direction of lower values, would be correlated with change in time estimation, such that it would be positively correlated with change in estimates of time intervals of the perception task and negatively correlated with change in estimates of time intervals on the production task;

b. No specific relationship was posited between change in negative symptoms and change in time estimates on both tasks after neuroleptic medication.

Change in Positive and Negative Symptoms Off and On Antipsychotics

First, we examined whether the total scores on the subscale for the positive and negative symptoms on the PANSS was associated with performance on time perception and time production. Table 27 shows that no significant association was found between these measures both in the entire patient sample and in the subsample of 10 patients during the fixed dose of medication. Although not significant given the small sample size, a moderate inverse relationship ($r=-44$, $p=.206$) was observed between total scores for positive symptoms and time perception during the antipsychotic-free phase.

Table 27

Relationship between PANSS Scores and Time Estimation

PANSS Scores	Patient Sample On Antipsychotics (N=38) r (p)		Subsample Off Antipsychotics (N=10) r (p)		Subsample On Antipsychotics (N=10) r (p)	
	Perception	Production	Perception	Production	Perception	Production
Positive Symptoms	-.11 (509)	.14 (.394)	-.44 (.206)	-.03 (.940)	.06 (878)	.05 (.888)
Negative Symptoms	-.12 (.480)	-.02 (.900)	-.30 (.399)	-.36 (.304)	.20 (.956)	.05 (.889)

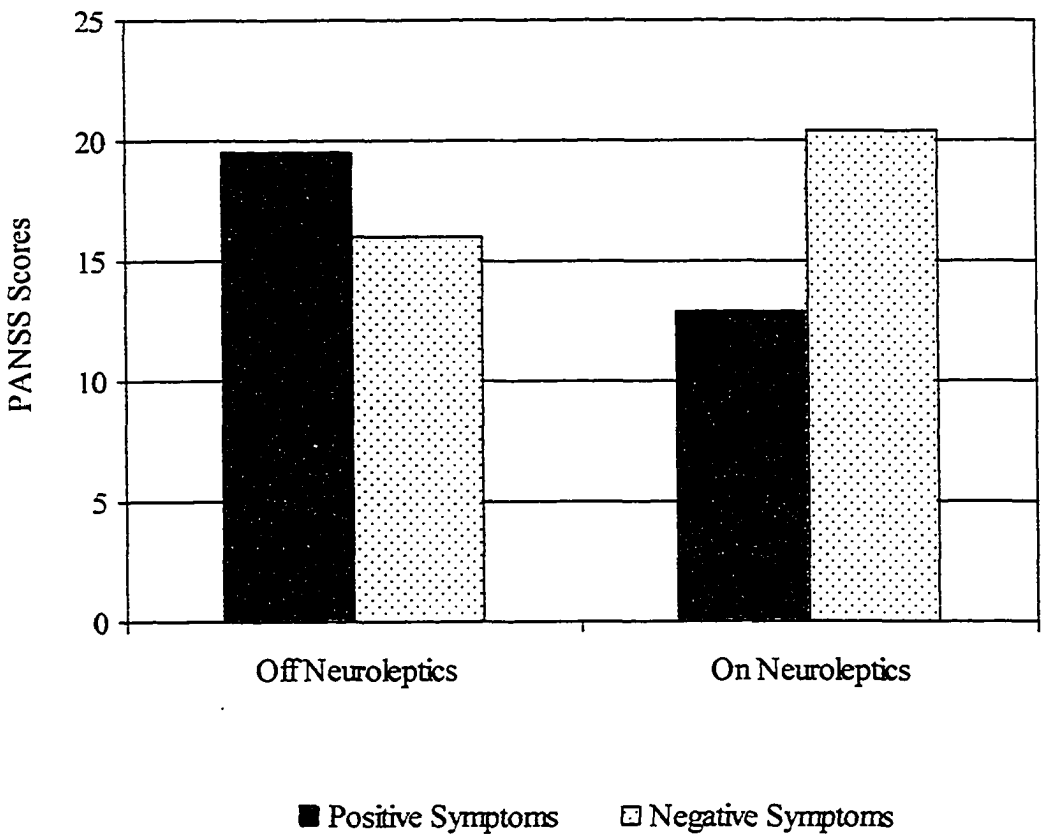
Second, to evaluate the change in positive and negative symptoms in response to medication, paired sample t-tests were conducted. As shown in Table 28, there was a significant change in the total score on the positive symptom subscale on the PANSS (t=-2.60, p=**.029**). The mean difference (-6.70) was obtained by subtracting the total score obtained on this subscale during the off antipsychotics assessment from the on-antipsychotics one. As expected, the mean score for positive symptoms in the PANSS during the antipsychotic-free phase was higher than the mean score during the fixed-dose of medication, indicating an improvement of positive symptomatology. In addition, medication led to a significant change in PANSS scores for negative symptoms (t=2.46, p=**.036**) with a mean difference between on and off antipsychotic scores of 4.40. These results indicate a significant worsening in negative symptomatology after the four-week period of fixed dose medication compared to the off-antipsychotics phase. These results are illustrated in Figure 10.

Table 28

Change in PANSS scores for Positive and Negative Symptoms Off and On Antipsychotics

PANSS Scores	Off Antipsychotics (N=10) Mean (SD)	On Antipsychotics (N=10) Mean (SD)	Paired Differences Mean (SD)	t-value (df)	df	p-value
Positive Symptoms	19.50 (7.605)	12.80 (4.158)	-6.70 (8.17)	-2.60	9	.029*
Negative Symptoms	16.00 (5.754)	20.40 (5.754)	4.40 (5.67)	2.46	9	.036*

Figure 10. Change in PANSS Symptoms Off- and On-Neuroleptics



As shown in Table 29, the correlations between the change in the total scores for the positive and negative symptoms subscales on the PANSS and the change in the percent deviations for the time perception and production tasks, each measured off and on antipsychotics, did not reach significance in this small sample. However, consistent with our hypothesis, a moderate positive relationship was observed between the change in positive symptoms and the change in percent deviations for time perception. After the fixed-dose period of neuroleptic medication, patients who demonstrated an improvement in positive symptomatology also exhibited a slower internal time sense compared to when unmedicated.

A moderate negative correlation was found between the change in negative symptoms and the change in percent deviations for the time perception task. No significant correlations were observed between negative symptoms and the time production task.

Table 29

Correlations between change in PANSS scores and change in Time Estimation Off and On Antipsychotics

Time Estimation Task (N=10)	Change in Positive Symptoms r (p)	Change in Negative Symptoms r (p)
Change in Perception	.43 (.212)	-.42 (.233)
Change in Production	-.03 (.934)	.19 (.596)

5) Hypothesis V: For patients with schizophrenia, impulsivity would be positively correlated with estimates in time perception and negatively correlated with estimates in time production. More specifically, patients with high total scores on the BIS-11 would exhibit larger estimates of time intervals on the time perception task and lower estimates of time intervals on the time production task when compared to patients with low total scores on the BIS-11.

Pearson Product Moment Correlations were conducted between total impulsiveness scores as measured by the BIS-11 and overall percent deviations for both time estimation tasks in the entire patient sample. Contrary to the anticipated outcome, no significant correlations were found between impulsiveness scores and the time perception ($r = -.14$, $p=406$) or the time production tasks ($r=.20$, $p=.240$).

Time Estimation and Impulsiveness: Exploratory Analyses on Gender Differences

Given the systematic differences observed in time estimation among female and male patients, we separately examined the correlation between BIS-11 total scores and time estimation for both genders. Among males, no correlation was found between impulsiveness and the time perception ($r=-.05$, $p=.981$) or the time production ($r=.12$, $p=.589$) tasks. Among females, although non-significant, a modest negative correlation ($r=-.45$, $p=.119$) was found between BIS-11 total scores and overall percent deviations for the time perception task. As such, females who provided lower scores on this scale demonstrated a faster internal time sense. Consistently, total scores on the BIS-11 showed a significant positive correlation with estimates on the time production task ($r=.64$,

p=.019). Thus, female patients with lower scores on impulsiveness demonstrated a faster internal sense of the passage of time.

Although we did not anticipate gender differences in our hypothesis, these findings contradict our prediction.

When examining the possible effect of antipsychotic medication in these findings, no association was found between CPZE and BIS-11 total scores for male (r=.15, p=.484) and female (r=-.19, p=.545) patients.

6) Hypothesis VI: Among patients, suicide attempters would exhibit higher estimates of time intervals on the perception task and lower estimates of time intervals on the production task when compared to non-attempters.

Potential Covariates

Attempters and non-attempters differed significantly in demographic and clinical characteristics (refer to Tables 7 and 8, pp. 88-89) such as age, ethnicity, duration of illness, and number of years of education. Pearson Product Moment Correlations were used to examine their association to percent deviations in the time perception and production tasks. To evaluate the effect of ethnicity on time estimation, a one-way ANOVA was conducted. No significant group differences were found for the time perception (F=.36, df=4, p=.834) or the time production tasks (F=.04, df=4, p=.997). Therefore, ethnicity was excluded as a covariate in all analyses comparing attempters and non-attempters. As shown in Tables 30 and 31, within group correlations yielded contradictory results. No significant correlation was found between age and overall

percent deviation in the time perception task (r=.23, p=.238), while this relationship was marginally significant for the time production task (r=-.35, p=.062) in the non-attempter group. This variable was significantly correlated with both time perception (r=.69, p=**.040**) and time production (r=-.90, p=**.001**) in the attempter group. Education was not significantly correlated with percent deviations in the time perception (r=.06, p=.741) and the time production (-.27, p=.157) task within the group of non-attempters. Still, education was significantly correlated with time perception (r=.74, p=.024) and time production (r=-.69, p=**.038**) in the subsample of attempters, such that attempters with high level of education exhibited a fast internal sense of time. Finally, no significant correlation was found between duration of illness and overall percent deviations on both the time perception (r=.09, p=.658) and the time production (r=-.19, p=.325) tasks in the non-attempter group. Given the small sample size, the moderate positive correlation between this variable and the time perception task (r=.48, p=.188) was not significant within the attempter group. Duration of illness exhibited a strong negative correlation with time production (r=-.74, p=.024) such that this variable was significantly associated with a fast internal time sense among suicide attempters. Clearly, the tables detailed below indicate that attempt status has a significant effect in the correlation among these demographic and clinical variables and the ability to accurately estimate the passage of time.

Table 30

Correlations between Age, Educational Level, Duration of Illness and Both Time Estimation Tasks in the Non-Attempter Group (N=29)

Variable	Time Perception r (p)	Time Production r (p)
Age	.23 (.238)	-.35 (.062)
Educational Level	.06 (.741)	-.27 (.157)
Duration of Illness	.09 (.658)	-.19 (.325)

Table 31

Correlations between Age, Educational Level, Duration of Illness and Both Time Estimation Tasks in the Attempter Group (N=9)

Variable	Time Perception r (p)	Time Production r (p)
Age	.69 (.040)*	-.90 (.001)*
Educational Level	.74 (.024)*	-.69 (.038)*
Duration of Illness	.48 (.188)	-.74 (.024)*

Time Estimation in Attempters and Non-Attempters

As described above, age, educational level, and duration of illness were significantly correlated with time estimation within the subsample of non-attempters. Given that age was highly interrelated with education (r=.60, p=**.0001**) and duration of illness (r=.86, p=**.0001**), we only selected the latter two variables as covariates to increase our statistical power. Duration of illness was chosen as a covariate instead of age because it appears to be more representative and unique to this disorder than age. Therefore, suicide attempters and non-attempters were compared on overall percent deviations for both timing tasks using ANCOVA controlling for education and duration of illness. As

shown in Table 32, no significant differences were detected between these two groups for the time perception task (F=.41, p=.527). However, a trend for significant differences was found for the time production task (F=2.99, p=.093) such that, contrary to our prediction, attempters exhibited a slower internal sense of time compared to non-attempters.

Table 32

Comparison of Suicide Attempters and Non-Attempters on Both Time Estimation Tasks

Time Estimation Task	Attempters (N=9) Mean (SD)	Non-Attempters (N=29) Mean (SD)	F-value (df)	p-value
Perception	.244 (.590)	.225 (.476)	.41 (1)	.527
Production	-.117 (516)	-.185 (.377)	2.99 (1)	.093

To examine whether the performance of both groups was uniform across interval length, a two-way Group (2) by Interval (5) repeated measures ANCOVA controlling for education and duration of illness was conducted for both time estimation tasks. Results for these analyses are illustrated in Figures 11 and 12.

Figure 11. Attempters and Non-Attempters: Time Perception

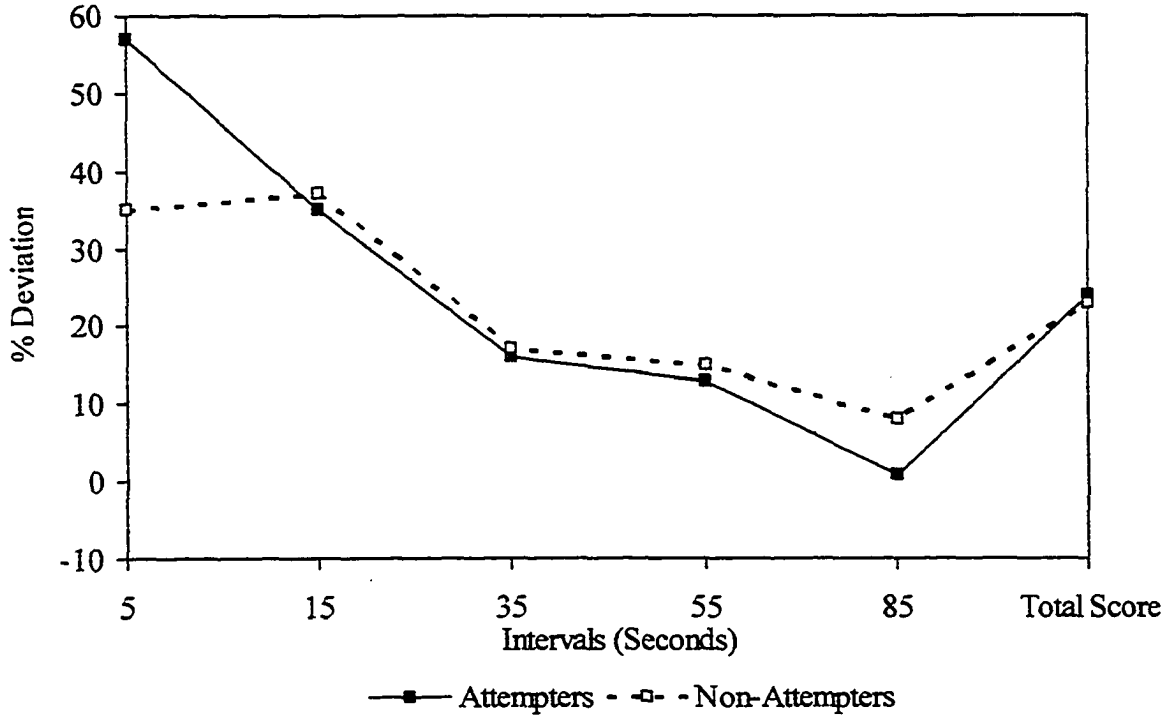
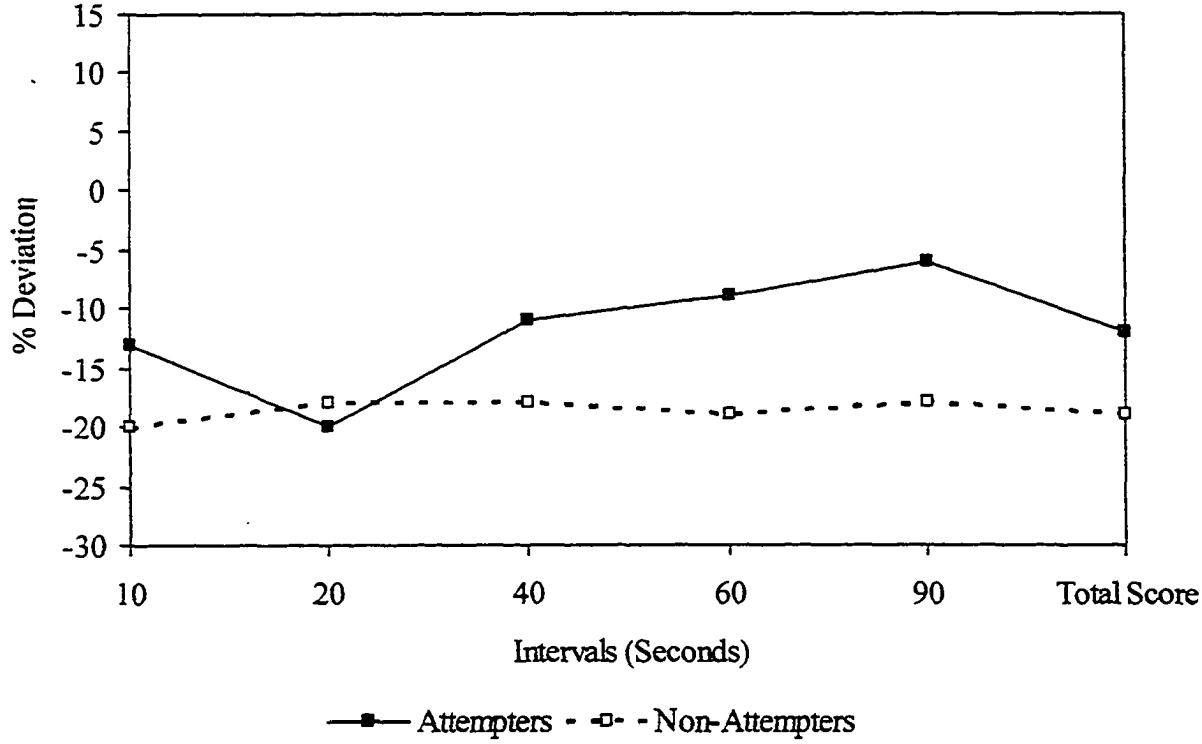


Figure 12. Attempters and Non-Attempters: Time Production



No significant main effects were observed for Group (F=.51, df=1, p=.527), Interval (F=.64, df=1, p=.634), education (F=1.53, df=1, p=.274) and duration of illness (F=.54, df=1, p=.444) for the time perception task. Similarly, there were no significant interactions Group x Interval (F=.27, df=4, p=.889), Interval x Education (F=1.79 df=4, p=.135) and Interval x Duration of Illness (F=.154, df=4, p=.961). With regard to the time production task, a trend for a significant main effect for Group (F=2.99, df=1, p=.093) was observed such that attempters exhibited a slower internal time sense compared to non-attempters. Similarly, a trend for a significant main effect was found for education (F=3.26, df=1. p=.080). No other significant main effects were found. Also, there were no significant interactions Group x Interval (F=1.8, df=4, p=.131), Interval x Education (F=.307, df=4, p=.873), and Interval x Duration of Illness (F=.633, df=4, p=.640) for the time production task.

Time Estimation and Attempt Status: Exploratory Analyses of Gender Differences

Since there were gender differences in time estimation, we examined the performance of attempters and non-attempters based on gender across interval length. Therefore, a three-way Group (2) by Gender (2) by Interval (5) repeated measures ANCOVA controlling for education and duration of illness was conducted for both time perception and production. No significant main effects for Group (F=.169, df=1, p=.684), Gender (F=2.52, df=1, p=.122), Interval (F=.002, df=4, p=.969), education (F=.56, df=1, p=.459), and duration of illness (F=.41, df=1, p=.526) were found for time perception. A marginally significant interaction for Group x Gender (F=3.21, df=1, p=.085) was found,

such that female attempters exhibited a faster internal time than the other groups, while male attempters demonstrated a slower internal time sense compared to the other three groups. No other interactions were significant. With regard to the time production task, no significant main effects were found for Group (F=2.47, df=1, p=.126), Interval (F=1.01, df=4, p=.322), education (F=1.08, df=1, p=.126), and duration of illness (F=2.77, df=1, p=.106). However, a significant main effect for Gender was observed (F=4.61, df=1, p=**.039**), such that both female attempters and non-attempters demonstrated a significantly faster internal time sense compared to males in both groups. There were no significant interactions, except for a marginally significant Group x Gender (F=4.54, df=1, p=.065), which suggests that female attempters exhibited a faster internal time sense on time production compared to the other groups. Male attempters demonstrated a slower sense of time than patients in the remaining three groups. Results for these analyses are illustrated in Figures 13 and 14.

Figure 13. Time Perception: Attempters and Non-Attempters Based on Gender

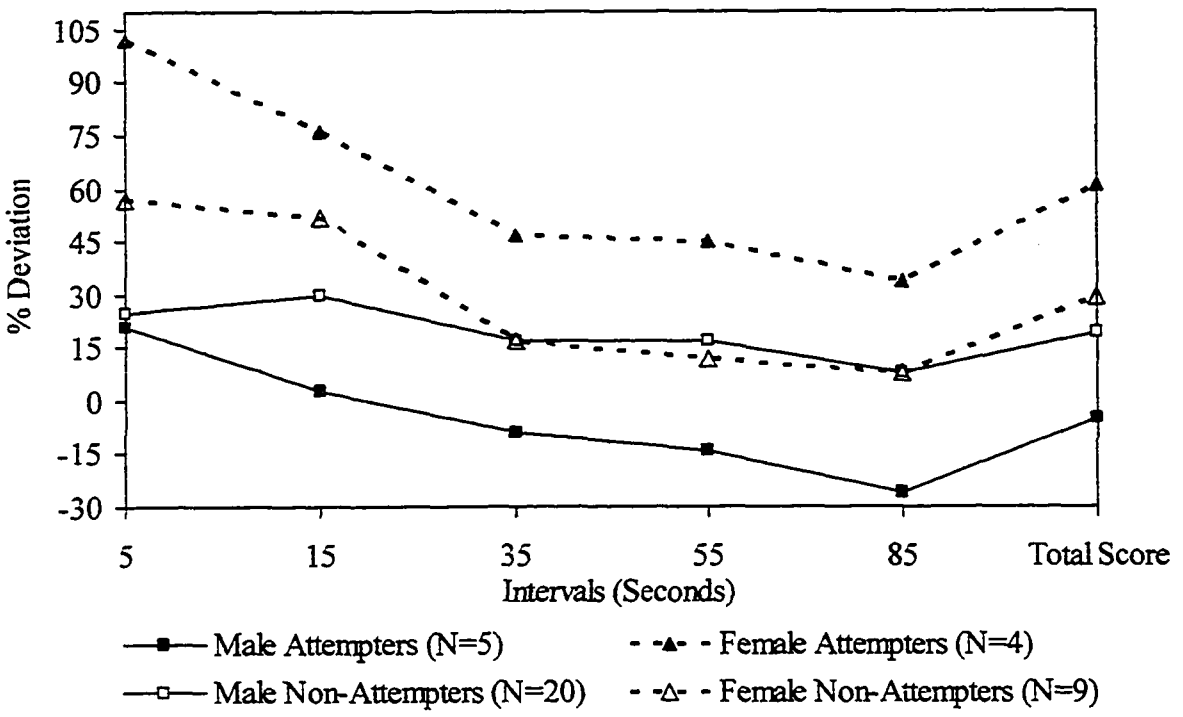
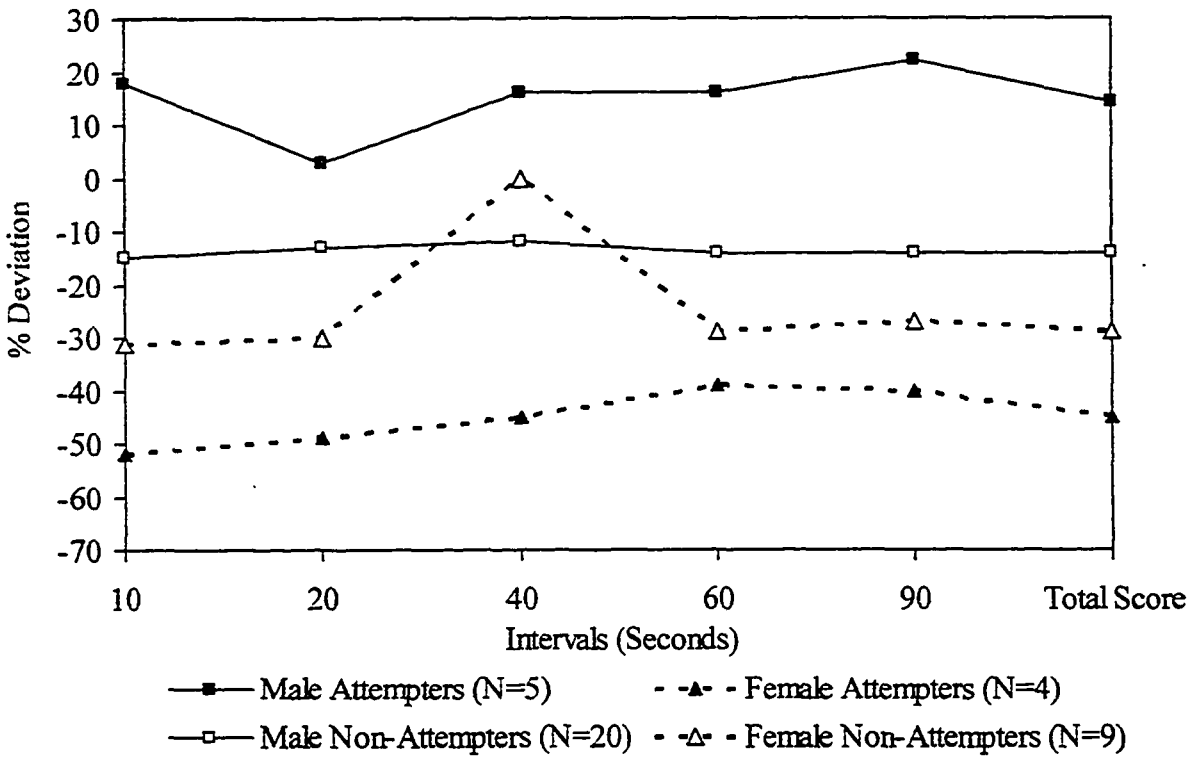


Figure 14. Time Production: Attempter and Non-Attempters Based on Gender



Exploration of Medication Effects on Time Estimation in Attempters

Given the effect of neuroleptic medication on time estimation, we conducted further exploratory analyses to examine the CPZE levels in attempters and non attempters. Attempters were on higher doses of antipsychotics (mean=797, SD=337.83; range 400-1425) than non-attempters (mean=684, SD=361.08; range 250-1700). However, these differences failed to reach significance (t=.830, df=36, p=.412). Among attempters, males were on average on higher doses of neuroleptics (mean=830, SD=263.63; range 600-1200) than females (mean=756, SD=455.7; range 400-1425). These differences failed to reach significance (t=.306, df=7, p=.768). Within the subgroup of non-attempters, females were on higher doses of antipsychotics (mean=883, SD=360.56; range 500-1700) compared to males (mean=595, SD=332.02; range 250-1200). These differences were significant (t=-2.108, df=27, p=**.044**).

In view of the different dosages of CPZE between males and females, we conducted an ANCOVA to compare attempters and non-attempters (Group) based on gender, uniquely controlling for CPZE dose. For the time perception task, the main effects for Group (F=.2, df=1, p=.900) and CPZE (F=.37, df=1, p=.371) were not significant. However, a trend for significance was observed for Gender (F=3.39, df=1, p=.075) such that, after controlling for CPZE, females in both groups exhibited a faster internal time sense compared to males in both groups. The interaction Gender x Group (F=2.66, df=1, p=.112) was not significant. Consistently, ANCOVA for the time production task yielded non-significant main effects for Group (F=.195, df=1, p=.662) and CPZE (F=.80, df=1, p=.779). However, there was a significant main effect for Gender (F=5.71, df=1, p=**.023**) thus suggesting, after adjusting for differences in CPZE,

that females in both groups exhibited a faster internal time sense on this task compared to male attempters and non-attempters. The interaction Group x Gender was not significant ($F=2.11$, $df=2$, $p=.156$) for time production.

Suicidal Ideation: Exploratory Analyses

Pearson Product Moment Correlations were used to investigate the relationship between percent deviations on both timing tasks and current suicidal ideation, as measured by the total score on the Scale of Suicidal Ideation (SSI) for the entire patient sample. A trend for a significant negative correlation was detected between scores on the SSI and overall percent deviation for the time perception task ($r=-.30$, $p=.064$), such that patients with scores of zero or with low scores on the SSI within the week of the assessment exhibited a fast internal time sense while those with high scores on the SSI had a slow sense of time. Consistently, in the production task, there was a significant positive correlation ($r=.34$, $p=.035$) between scores on the SSI and the overall percent deviation in the time production task. Patients with scores of zero or with low scores on the SSI within the week of the assessment exhibited a fast internal time sense, while patients with high scores on the SSI exhibited a slow internal sense of the passage of time on the production task. Within the attempter group, the negative correlation between scores on the SSI and the time perception task was not significant but was still moderate ($r=-.49$, $p=.180$). Scores on the SSI had a marginally significant positive correlation ($r=.61$, $p=.084$) with the overall percent deviation on the time production task. Both results suggest that suicide attempters with scores of zero or with low scores on the SSI during the week of the assessment

exhibited a fast internal time sense, while those attempters with high scores on the SSI exhibited a slow internal time sense.

Time Estimation and Suicide History

Supplementary analyses in the subsample of attempters were performed to further investigate the relationship between time estimation and measures assessing characteristics of past suicidal behavior, including number of prior attempts (mean=3.56, SD=4.82), lethality of the most lethal attempt (mean=1.78, SD=1.64), and scores on the Suicide Intent Scale (SIS) for the most recent (mean=14, SD=4.72) and the most lethal attempt (mean=14.44, SD=4.30). A significant positive correlation (r=.79, p=**.010**) was detected between average percent deviations in the time perception task and the number of prior suicide attempts. Given the small sample size, a modest negative correlation (=-.41, p=.276) was found between this variable and time production. Both results suggest that attempters with a higher number of suicide attempts exhibited a faster internal sense of time than those with lower number of attempts. No correlations were found between lethality for the most lethal attempt and time perception (r=-.20, p=.603) and time production (r=-.070, p=.857). A trend for significant negative correlations (r=-60, p=.091) were observed between scores on the SIS for the most lethal and most recent (r=-.59, p=.093) attempts and average percent deviations for the time perception task. Consistently, modest positive correlations were observed between SIS for the most lethal (r=.64, p=.064) and most recent (r=.55, p=.126) attempts and average percent deviations for time production. Thus, attempters who scored higher on their intent for both the most

lethal and the most recent attempt exhibited a slower sense of time than attempters who exhibited lower scores on the SIS.

Additional exploratory analyses

As shown in Table 33, Pearson Product Moment Correlations between percent deviations for the time perception and the time production tasks and clinical indicators of severity suggested that a fast internal time sense was significantly associated with duration of illness, age at first psychotic symptom, age at first mental health contact, and length of current psychotic episode in the entire patient sample.

Table 33

Correlation between Time Estimation Performance and Clinical Indicators of Severity

Indicators of Clinical Severity	Time Perception r (p)	Time Production r (p)
Age at First Psychotic Symptom	.37 (.024)*	-.26 (.116)
Age at First Mental Health Contact	.42 (.009)*	-.32 (.049)*
Length of Current Psychotic Episode	.29 (.082)*	-.33 (.045)*

Summary of Findings

To facilitate discussion, results are summarized in Tables 34, 35, 36, and 37.

Table 34

Summary of Findings Based on Groups

Groups	PERCEPTION	PRODUCTION	Internal Time Sense (Compared to Objective Time)
PATIENTS	⬆	⬇⬇	Fast
Females	⬆	⬇⬇	Fast
Males	⇧	⇩	Fast
ATTEMPTERS	⇧	⬆	Slow
Males	⬇	⬆	Slow
Females	⬆	⬇	Fast
NON-ATTEMPTERS	⇧	⬇	Fast
Males	⬆	⬇	Fast
Females	⬆	⬇	Fast
NON-PATIENTS	↕	↕	Accurate
Females	⬆	⬇⬇	Fast
Males	↕	↕	Accurate

⬆⬆ = Estimates Significantly Larger than Standard Durations

⬇⬇ = Estimates Significantly Smaller than Standard Durations

⬆ = Trend for Significance for Estimates Larger than Standard Durations

⬇ = Trend for Significance for Estimates Smaller than Standard Durations

↕ = Estimates Close to Standard Durations

⇧ = Estimates Larger than Standard Durations-Not Significant

⇩ = Estimates Smaller than Standard Durations-Not Significant

Table 35

Summary of Correlations Based on Demographic and Clinical Variables

Demographic and Clinical Variables	**Correlations with**	
	PERCEPTION	**PRODUCTION**
NON-PATIENTS		
Educational Level	Negative/ Strong	Positive/ Weak
Vocabulary Score	Negative/ Strong	Positive/ Strong
PATIENTS		
Educational Level	None	Negative/Strong
Vocabulary Score	None	None
ATTEMPTERS		
Age	Positive/ Strong	Negative/ Strong
Educational Level	Positive/ Strong	Negative/ Strong
Duration of Illness	Positive/ Moderate	Negative/ Strong
NON-ATTEMPTERS		
Age	None	Negative/ Moderate
Educational Level	None	None
Duration of Illness	None	None

Table 36

Summary of Findings Based on Clinical Variables

Clinical Variables	**PERCEPTION**	**PRODUCTION**	Internal Time Sense (Compared to Objective Time)
Effects of Neuroleptics	⇑⇑	⇓	Fast
Effects of Neuroleptics and Additional Drugs	⇧	⇩	Fast
Effects of Anticonvulsants	⇑	⇓	Fast

⇑⇑ = Estimates Significantly Larger than Standard

⇓⇓ = Estimates Significantly Smaller than Standard Durations

⇑ = Trend for Significance for Estimates Larger than Standard Durations

⇓ = Trend for Significance for Estimates Smaller than Standard Durations

⇧ = Estimates Larger than Standard Durations-Not Significant

⇩ = Estimates Smaller than Standard Durations-Not Significant

Table 37

Summary of Correlations Based on Clinical Variables

Clinical Variables	Correlations with	
	PERCEPTION	**PRODUCTION**
PANSS SYMPTOMS		
Entire Patient Sample		
Positive Symptoms	None	None
Negative Symptoms	None	None
Males		
Positive Symptoms	None	None
Negative Symptoms	None	None
Females		
Positive Symptoms	Negative/ Weak	Positive/ Moderate
Negative Symptoms	Positive/ Moderate	Negative/ Moderate
CHANGE IN PANSS		
Positive Symptoms	Positive/ Moderate	Negative/ Moderate
Negative Symptoms	None	Positive/ Weak
IMPULSIVENESS		
Entire Sample	None	None
Males	None	None
Females	Negative/ Moderate	Positive/ Strong
SSI		
Entire Sample	Negative/ Moderate	Positive/ Strong
Attempters	Negative/Moderate	Positive/Moderate
ATTEMPTERS		
Number of Prior Attempts	Positive/ Strong	Negative/ Moderate
Lethality (Most Lethal)	Negative/ Moderate	Positive/ Moderate
Lethality (Most Recent)	Negative/ Moderate	Positive/ Moderate
PATIENT SAMPLE		
Age at First Psychotic Symptom	Positive/ Strong	Negative/ Moderate
Age at First Mental Contact	Positive/ Strong	Negative/ Strong
Length of Current Episode	Positive/ Strong	Negative/ Strong

V. DISCUSSION

Overview and Background

The overarching aim of this research was to extend the neuropsychological understanding of the perception of time in patients with schizophrenia. Given the heterogeneous presentation of this psychiatric illness, a better comprehension of this cognitive function could provide an insight into the etiology and underlying brain functioning of schizophrenia. Moreover, since time has a major impact on the regulation of daily behaviors, understanding the neuropsychology of its perception could contribute to the reconceptualization of some core cognitive and clinical characteristics of schizophrenia. As such, timing deficits could potentially be reflected in attention and working memory difficulties, disorganized speech and behavior, motor retardation, perseveration, and impulsiveness. Therefore, research into time perception may well have important clinical implications for effective interventions on cognitive and behavioral symptoms affecting patients with this disorder.

Studies of time estimation in schizophrenia were published over several decades (Clausen, 1950; Densen, 1977; Lhamon and Goldstone, 1956; Rammsayer, 1990; Tysk, 1983). However, this research was frequently flawed by methodological limitations. Small samples and inadequate control of potential confounding variables for comparisons with normal controls including age, education, and intellectual functioning were some of the limitations. In addition, in some cases, a comprehensive description of inclusion criteria and research procedures for the studies (i.e., diagnostic and clinical instruments, medication status of the patients) was absent. Thus, replication was unfeasible. Despite

these flaws, investigators reported quite consistently that patients with schizophrenia bear an internal sense of the passage of time that is faster than the objective time.

In view of these considerations, our primary focus was to examine the perception of time by patients with schizophrenia while attempting to overcome common limitations encountered by prior studies. Therefore, we carefully examined the relationship between several demographic (i.e., age, gender, and ethnicity), cognitive (i.e., level of education and WAIS-R/WAIS-III Vocabulary Subscale score), and clinical (i.e., duration of illness, age of onset, age at first mental health contact, length of current psychotic episode, number of prior hospitalizations, and age at first psychiatric hospitalization) variables and time estimation. Contrary to prior literature, this study analyzed and controlled, when indicated, the impact of these variables on the ability to accurately perceive the passage of time. In this sense, our findings contribute significantly to the field. Moreover, our research is the first that controlled the medication status of the patients included in the sample. Indeed, we studied the effect of neuroleptics as well as other psychiatric medications routinely given to inpatients with schizophrenia on time estimation.
The assessment of the ability to perceive the passage of time was completed with the use of two computerized tasks, time perception and time production, which demonstrated satisfactory psychometric properties (Keilp, unpublished data, 2001). These tasks were used in all analyses included in the present study.

Time Estimation: Performance in Patients with Schizophrenia and in a Non-Patient Comparison Group

Through the evaluation of time estimation with the time perception and time production tasks, we expected to find significant differences between a group of adult inpatients with a DSM-IV diagnosis of schizophrenia or schizoaffective disorder and a non-patient comparison group. We did, indeed, find a trend for significant differences between the groups when comparing overall percent deviations for the time perception task. Patients exhibited a sense of the passage of time that tended to be faster than the internal time sense among participants in the non-patient group. Consistently, analyses of results obtained for the time production task indicated differences between the two groups were significant, whereby patients demonstrated a sense of the passage of time that was significantly faster.

Overall, results obtained in this study are consistent with prior literature that examined time estimation in patients with schizophrenia (Clausen, 1950; Densen, 1977; Tysk, 1983) by means of verbal estimation and production methods with durations ranging from 5s to 120s. Our findings appear to provide further support to earlier reports that individuals with schizophrenia tend to overestimate the passage of time for relatively short durations.

The effect of gender on time estimation was carefully examined in both tasks. With regard to the time perception task, females in the patient and non-patient comparison groups tended to exhibit a faster internal time sense than males in both groups. Upon analyses of individual intervals, females with schizophrenia were overall faster than the other three groups, particularly for the shortest intervals, 5s and 15s. For

these durations, female patients demonstrated a time sense that was 71% and 59% faster, respectively, than the objective time. An inspection of the scatter plot for individual durations revealed that, while female patients were the fastest group, male non-patients exhibited the slowest internal time sense. When comparing the performance of females with schizophrenia and males in the non-patient group across intervals, results indicate that female patients were 65%, 57%, 34%, 28%, and 23% faster than male non-patients for the 5s, 15s, 35s, 55s, and 85s, respectively. The interest to interpret these results is twofold. First, because the accelerated sense of time among female patients could not be accounted only by gender. Female non-patients, although exhibiting a fast internal sense, were to a great extent slower than females with schizophrenia (refer to Table 12, p.123). Second, the overall pattern of performance across intervals in the latter group was similar to the remaining groups. That is, while female patients demonstrated larger estimations for the shorter intervals, the internal time sense became gradually slower across longer durations and decreased by an overall 55%. This deceleration effect also was observed, to a much lesser extent, among male non-patients whose internal time sense slowed down by an overall 10%; among female non-patients who decreased their estimation by 18%; and male patients whose internal sense of time diminishes by 25% from the shortest to the longest interval. The overall pattern of participants providing gradually smaller estimations for increasingly longer durations for the time perception task will be discussed later in this chapter.

With regard to the time production task, female patients exhibited a significantly faster internal time sense than the other three groups. Examination of the performance of all groups across intervals indicates that females with schizophrenia were significantly

faster than the other groups for the shortest durations (i.e., 10s and 20s), but their sense of time remained fairly constant for all durations. Their estimations were reduced by overall only 7%, a rate that was comparable to the other groups. Again, male non-patients were fairly accurate and demonstrated the slowest internal sense of time, actually overestimating the standard durations by less than 10%. The difference in performance between female patients and male non-patients was less than the one observed in the time perception task. However, females with schizophrenia demonstrated, on average, an internal time sense that was approximately 40% faster than the sense of time of male non-patients. Interestingly, the time estimation of female non-patients and male patients was quite accurate since their estimations were less than 10% faster than the standard durations.

To understand better the dissimilar performance among males and females with schizophrenia on time estimation, we examined the effect of neuroleptic medication on these gender differences. Despite the lack of significant results, females were on higher dosages of antipsychotics than males. Within gender correlations between neuroleptics doses and time estimation, yielded a moderate to strong association within the female group, suggesting that females on higher doses of antipsychotics exhibited a faster internal time sense. This was not the case for males. Although the correlations were quite weak, the direction of the relationship clearly indicates that male patients on higher doses of neuroleptics demonstrated a slower internal time sense both in time perception and time production. Given these findings, we decided to compare male and female patients on both time perception and time production while adjusting for different dosages of neuroleptics. The gender differences on time estimation performance were eliminated,

although females continued to exhibit a faster internal time sense, particularly for time production. This group was still 24% faster than males on this task.

Upon further exploration for an explanation of the faster internal sense among female patients compared to males, we examined the possible synergistic effect of other medications given in addition to neuroleptics during the fixed-dose phase. Interestingly, patients on antispychotics and adjunctive medications (i.e., serotonin agonists, anticholinergics, tranquilizers, anticonvulsants, and beta-blockers) exhibited an overall faster sense of the passage of time than patients exclusively on neuroleptics. Again, there were no gender differences in the time perception task. However, females tended to exhibit a faster internal time sense than males in the time production task. Males exclusively on neuroleptics had a slightly slow, rather accurate, sense of the passage of time whereas those on several medications exhibited a fast internal time sense. Interestingly, in this task, females on adjunctive medications were only 5% faster than those exclusively on neuroleptics, whereas males on adjunctive medications were 17% faster than males on neuroleptics only. This reverse proportion was found for the time perception task. It is likely that the synergistic effect of neuroleptics and adjunctive medications had a greater impact on time estimation than antipsychotics acting alone. The differential performance of both genders on the time perception and production indicates that these tasks are apparently sensitive to different cognitive processes and underlying functioning.

Additional analyses were conducted to identify the role of specific adjunctive medications that, in combination with neuroleptics, contributed to the synergistic effect in the acceleration of the internal time sense. Initially, we found, regardless of the gender

and the type of task, patients on neuroleptics and anticonvulsants exhibited a faster internal time sense than patients off anticonvulsants. When examining the performance of males and females off and on anticonvulsants separately, no differences were observed in the time perception task. However, males on neuroleptics and anticonvulsants exhibited a faster internal time sense than females on this combination and males off anticonvulsants. In fact, males on anticonvulsants were 37% faster in time perception and 41% faster in time production than males on antipsychotics but off anticonvulsants. This important change was not shown among females as they were actually 8% slower on anticonvulsants than females off anticonvulsants. The differential effect of anticonvulsants in the perception of time based on gender was not anticipated in our study. Given the apparent acceleration of the internal time sense among males on this type of medication, a higher proportion of them taking neuroleptics and adjunctive anticonvulsants could have yielded smaller differences between genders in time estimation.

Certainly, the gender differences found in time perception among patients are likely to be the result of uncontrolled factors, mainly the dosage of neuroleptics and the inclusion of other types of medication. With regard to dosage, it is feasible to speculate that if, on average, females were on higher doses of neuroleptics they were probably overmedicated with respect to males. Unfortunately, this is only a conjecture since we did not consider body weight in our analyses.

Gender differences in the non-patient comparison group, particularly for the time perception task, also were not predicted in our hypothesis. In our review of the literature, we were unaware of any significant findings indicating that females exhibited a faster

sense of the passage of time, compared to objective time, than males. Based on our findings, this variable should be carefully controlled in further investigations of time estimation. Moreover, it would be interesting to study the generalizability of these results to time estimation research on patients with neurological disorders such as Parkinson's Disease (PD), cerebellar dysfunctions, and other psychiatric populations.

Time Estimation and Psychotic Symptomatology

Based on the idea that hyperdopaminergia underlies psychotic symptomatology, mainly positive symptoms (Creese, Burt & Snyder, 1976) and the regulation of the perception of the passage of time, we postulated that there would be a positive correlation between estimation of the passage of time and positive symptoms among patients. Also based on a similar reasoning and on reports of pharmacotherapeutic effects on negative symptoms, no direct relationship between estimation of elapsed time and negative symptoms was expected, since dopamine (DA) apparently does not play a significant role in the mediation of this cluster of symptoms (Duncan, Zorn & Lieberman, 1999; Seeman, 2002).

Our findings indicated that there were no significant correlations between the percent deviations for the time perception and time production tasks and either positive or negative symptoms, as measured by total scores on each scale of the PANSS at the time of the assessment.

When examining gender effects, there were no differences in positive symptoms but males had significantly higher scores on negative symptoms than females. Given that the assessment was done during the fixed-dose of medication, these findings suggest that

females appear to be better responders to psychotropic treatment, at least in terms of negative symptomatology. Most interestingly, an examination of the correlations between PANSS scores and time estimation within each gender indicated that female patients with higher scores on the negative symptoms scale exhibited a faster internal time sense than females with lower scores. Moreover, females with higher scores on the positive symptoms scale demonstrated a slower internal sense than those who exhibited lower scores. Inspection of the scatter plots for these correlations indicate that, while there was some degree of variability in the time estimation performance, females with high scores on the PANSS negative symptoms demonstrated a time sense that was between 25% to 65% faster than the objective time in time production. In time perception, females with high scores on this scale were 15% faster or less than the objective time. With regard to the PANSS positive symptoms scale, females with low scores were 15% to 65% faster than the objective time in the time production task, and 5% to 10% in time perception. Although correlations were weak, their direction was similar for the male group. Once more, these results suggest that both time estimation tasks appear to be tapping into somewhat different underlying timing functions.

These findings contradict our hypothesis, at least among female patients. A possibility that might account for these results is the pharmacological treatment used in this sample, which was not reduced exclusively to neuroleptics. As described earlier in this chapter, there were other medications that appeared to have a synergistic effect on time estimation. In this scenario, it seems fair to speculate that positive and negative symptoms and internal time sense, although mediated by DA, exhibited dissimilar responses to medications, particularly when considering the different dosages among

males and females. In fact, it is possible to postulate an interaction between neuroleptics and anticonvulsants. Anticonvulsants may have had a greater impact among females on negative symptomatology, particularly affective symptoms, compared to positive ones. As mentioned previously, this type of drug could well reduce the speed of the internal time sense, particularly for time production. On the other hand, neuroleptics may have been effective on the treatment of positive symptoms, but may have acted to increase the speed of the internal time sense.

Clearly, these speculations demand further research into the differential effects of psychotropic medications on psychotic symptomatology and time estimation.

The Effect of Neuroleptics on Time Estimation

In view of the growing data provided by drug manipulations in animal and clinical samples that suggest timing mechanisms are mediated by DA, we generated our third hypothesis in which we examined the ability of patients with schizophrenia to estimate durations both off and on antipsychotic medication. Thus, we anticipated that patients on a fixed-dose of medication would exhibit smaller estimates on time perception and larger estimates on time production compared to their performance when unmedicated. Basically, we expected that patients' internal time sense would be fast while being off antipsychotic medication during four weeks, and would become slower on a fixed-dose of neuroleptics.

A significant difference was found between the performances on the time perception task off and on antipsychotic medication. However, our analyses yielded a result in the opposite direction to our expectations. After being medicated for four weeks,

patients' sense of the passage of time compared to objective time became faster by 37%. No significant differences were observed for the time production task, although the patients' estimation of time was 43% faster on neuroleptics compared to the off neuroleptics phase.

The significant change in time estimation off and on medication suggests that, at least in our subsample, patients with schizophrenia exhibited a fairly accurate sense of time while unmedicated. Certainly, for the time perception task, patients off neuroleptics were approximately 3% faster than objective time and were actually 17% slower than objective time for the time production task.

The acceleration in time estimation appears to be a medication effect. This represents a very interesting finding that underscores the importance of including the effect of antipsychotic medications on time estimation as one of our study hypotheses. In this sense, our results question earlier reports (Clausen, 1950; Densen, 1977; Tysk, 1983) that suggest that patients with schizophrenia demonstrate a fast internal time sense. In fact, this could be the case when patients are medicated, but not while unmedicated. An interesting approach to this subject would be to compare time estimation performance in normal controls and unmedicated patients and examine whether differences still persist between both groups.

Our findings are inconsistent with animal and clinical data (Gibbon, Malapani, Dale & Gallistel, 1997; Malapani, et al., 1998; Maricq, & Church, 1983; Meck, 1986, 1996) that indicate DA agonists appear to speed the internal sense of time, while DA antagonists have the opposite effect. An explanation that might account for these significant unexpected results is that neuroleptics, both typical and atypical, are likely to

affect the dopaminergic balance between cortical-subcortical systems. Some authors (Weinberger, Berman & Zec, 1986) propose that increased DA activity is behaviorally reflected in the positive/psychotic-like symptoms (i.e., hallucinations and delusions), while DA deficits, affecting mainly the PFC, are likely to underlie the negative/deficit symptoms (i.e., flat affect, anhedonia, asociality, poverty of speech) that are characteristic of this disorder. To date, the conceptualization that a dopaminergic upregulation in limbic and striatal areas paired with a downregulation in the prefrontal cortex (PFC) stands as the most satisfactory neurobiological explanation for this disorder. Thus, antipsychotics have a possible twofold effect. On the one hand, the blockage of DA receptors in the nigrostriatal and mesolimbic areas, particularly the striatum, reduces the dopaminergic level in subcortical areas but, at the same time, increases it in cortical ones, particularly the PFC. It is feasible that this mechanism of action of neuroleptic drugs has an impact on the time estimation of medicated patients with schizophrenia. Indeed, a reduction of DA in subcortical areas should produce a timing performance in patients with schizophrenia that resemble that observed in PD patients (i.e., slowing of the internal time sense) (Malapani et al., 2002; Rakitin, Stern & Malapani, 2002). However, a potentially unidentified mediating factor is generating the opposite effects. Based on Grace's model (1991), PFC dopaminergic inputs are reinforced after medication and are likely to potentiate and stimulate inappropriate cell groups in the NA. This change in the subcortical-cortical DA balance generates an excitatory loop in the NA that the PFC is unable to inhibit. Therefore, it is possible that this recurrent DA hyperactivity in the striatum unbalances the speed of the perception of time and, instead of slowing, changes towards a faster internal sense compared to baseline when patients were unmedicated.

An important limitation of this study was the lack of control of adjunctive medications, particularly anticonvulsants. These may indeed have complex interactions with neuroleptics on the DA system and, perhaps, reduced the availability of these types of drugs within this system. Given the growing trend of adjunctive pharmacotherapy, including antipsychotics and anticonvulsants for the treatment of schizophrenia and particularly schizoaffective disorders, future research should address the issue of their neurochemical interaction.

Relationship between Change in Time Estimation and Psychotic Symptomatology

We anticipated that neuroleptics would affect both positive symptoms and time estimation abilities, such that after medication a reduction in both positive symptomatology and estimation of time intervals, associated to a fast sense of the passage of time, was expected. Furthermore, it was anticipated that the change in positive symptoms would be positively correlated with the change in estimation of time intervals, such that the internal time sense would become slower. No specific relationship was posited between negative symptoms and time estimation after neuroleptic medication.

As predicted, there was a significant improvement in positive symptoms after treatment with neuroleptic medication. Although not significant, a moderate negative correlation was observed between the change in positive symptomatology and the change in time estimation, such that the improvement in positive symptoms was moderately associated with an acceleration of the internal sense of time. Presumably with a larger sample, the correlation between positive symptoms and both time perception and production would have been significant. As it was mentioned previously, the direction of

the change in time estimation was contrary to our prediction. Negative symptoms worsened significantly after medication. As expected, this change was uncorrelated with time estimation. Nevertheless, this deterioration in negative symptoms appears to be consistent with our previous speculation about the possible change in DA balance between cortical-subcortical structures after antipsychotic medication. The change pattern off and on medication resembles that one of time estimation, in terms of clinical characteristics (i.e., deterioration of symptoms, a faster and less accurate sense of time). The potential lack of effectiveness of neuroleptics in upregulating DA in the PFC might account for the increased symptomatology and the inability to counteract the hyperdopaminergic state of the striatum.

Interestingly, the correlations between PANSS positive and negative symptoms scores and both time estimation tasks during the off antipsychotics phase, although not significant, were modest given the small sample. However, during the on medication phase, these variables became uncorrelated. These findings are suggestive that the effect of medications, both neuroleptics alone and neuroleptics with adjunctive drugs, have a differential action on symptoms and time estimation. Therefore, on a purely speculative domain, it is probable that while relying on DA systems, symptoms and time estimation are slightly different in terms of specific physiology.

Time Estimation and Impulsive Behavior

Based on previous literature (Bachorowski & Newman; 1985; Barratt, 1967; Barratt and Patton, 1983; Barratt, Patton, Olsson, & Zucker, 1981; Lennings & Burns, 1998; Standford and Barratt, 1996) and in our conceptualization that impulsive behaviors

are likely to be regulated by an accelerated time sense, we examined the relationship between impulsiveness, as measured by the BIS-11, and overall percent deviations in time perception and time production. We hypothesized that patients' scores on the BIS-11 would be positively correlated with estimates in time perception and negatively correlated with estimates in time production. More specifically, patients with high scores on the BIS-11would exhibit a faster sense of the passage of time compared to patients with low scores on the BIS-11.

Contrary to our expectations, there were no significant correlations between impulsiveness scores, as measured by the BIS-11, and overall percent deviations for both time estimation tasks.

The exploratory analysis of gender differences in the relationship between time estimation and impulsiveness yielded no correlation between these two variables among males. Nevertheless, in the group of female patients, a moderate relationship was found between BIS-11 scores and both time estimation tasks, such that females with lower scores on this scale exhibited a faster internal time sense than those whose scores were higher. In view of the medication differences reported between males and females, we examined the relationship between neuroleptics dosage and scores on the BIS. No strong association was found for males. However, although extremely modest, a negative correlation was found in the female group such that higher levels of antipsychotic medication were associated with lower impulsiveness scores. Again, the mediating effect of neuroleptics and, perhaps, of adjunctive medications cannot be ruled out in the outcome of the relationship between time estimation and impulsiveness in this subsample.

While some authors successfully found a relationship between fast internal time sense and impulsive behavior (Bachorowski & Newman, 1985; Standford and Barratt, 1996), others (Barratt, 1967; Barratt, Patton, Olsson, & Zucker, 1981; Lennings, & Burns, 1998) failed to find significant correlations between BIS scores and time estimation among normal controls for brief durations ranging from 60s to 120s. Our finding that females with low scores on the BIS-11 appeared to exhibit a fast internal time sense, concurs with an early work of Barratt (1967) who reported, contrary to his prediction, that low impulsive individuals were faster in a RT motor task that required them to release a key "as fast as possible." Unfortunately, no gender differences were reported in this study.

With the use of measures of impulsive behavior other than self-reports (i.e., a motor inhibition task), some authors (Bachorowski & Newman, 1985) found a significant correlation between scores on this task and BIS scores, such that high impulsive subjects obtained smaller scores (i.e., less inability to slow down motor behavior) compared to low impulsive subjects. When analyzing the relationship between impulsiveness scores on the BIS and time estimation, these researchers failed to report significant findings. However, the correlation between scores in the motor inhibition task and estimation of intervals ranging from 5s to 25s was significant, indicating that low scores in the motor inhibition task (i.e., greater inability to inhibit motor behavior) correlated with overestimations of elapsed time (i.e., subjects perceived objective time as passing too slowly compared to their internal sense of time).

Our lack of significant findings in the entire patient sample and among males might be explained on the basis that personality measures of behavioral impulsiveness are

not sensitive enough to detect aspects of this type of behavior that might be associated with a fast internal tempo. Two caveats must be addressed in relation to this point. First, it is possible that impulsive subjects are too habituated to the impulsive style that permeates their behaviors. Therefore, there is a chance that they underrate impulsiveness in their everyday actions in self-report scales (i.e., BIS-11) simply because they are oblivious to them. Second, impulsive subjects may not perhaps take enough time to carefully and thoroughly reflect about each item of the self-report scales, thus rushing into finishing them without accurate responses. These cases could be applied particularly to our subsample of female patients. It is possible that they rated themselves low in impulsive behaviors included in the BIS-11. However, a sensitive measure like time estimation (i.e., pressing a key in the computer or verbalizing a number after a predetermined elapsed duration) could be more accurate in describing their cognitive tempo.

In light of these conclusions, future studies should include measures of cognitive impulsiveness (i.e., motor inhibition task) to assess the association between an impulsive cognitive style and time estimation, while examining more exhaustively the effect of gender on this behavior.

The Perception of Time among Suicide Attempters and Non-Attempters

Suicide has been reported to be the primary cause of premature death in schizophrenia (Sartorious et al., 1987). It is estimated that suicide occurs at a rate between 20 to 23 times higher than in the general population (Caldwell & Gottesman, 1990; Verdoux, 1998). Early reports (Brockopp and Lester, 1970; Greaves, 1971;

Neuringer and Harris, 1974; Neuringer and Levenson, 1972) indicate that attempters tend to have a faster internal time sense compared to objective time. Therefore, it appeared crucial to examine the perception of time in a population that displays the overlap of both disorders, as is the case of individuals with schizophrenia who have attempted suicide.

We anticipated that suicide attempters would exhibit a faster sense of the passage of time compared to the objective time. No significant differences were found for time perception between attempters and non-attempters in this patient sample. A trend for significant differences was observed in the time production task such that, contrary to our prediction, attempters tended to exhibit a slower internal sense of the passage of time compared to the non-attempter group.

Given the gender differences observed in time estimation, we examined the performance of male and female patients separately. Female suicide attempters tended to demonstrate a faster internal sense of the passage of time in both time estimation tasks compared to female non-attempters and males in both groups. Upon inspection of the scatter plots, it is clear that female attempters exhibited an internal time sense that was nearly 60% faster than objective time in time perception and 45% faster in time production. The group of male attempters was the slowest, as they exhibited a sense of internal time that was 5% slower overall than objective time for time perception, and 15% slower for time production.

Subsequently, we analyzed the effect of neuroleptic medication on time estimation among these four groups. While attempters were on higher doses than non-attempters, the first group exhibited the reverse pattern than the one found in the entire patient sample and among non-attempters. As such, males were on higher dosages of

antipsychotics than females. After adjusting for differences in neuroleptics doses, there were no differences between attempters and non-attempters. However, females in both groups demonstrated an overall faster internal time sense than males.

Despite the lack of general group differences between attempters and non-attempters, upon further examination of both groups, the subsample of attempters exhibited fairly unique characteristics. Thus, when analyzing the correlations of potential covariates and both time estimation tasks, we obtained interesting results. No correlations were found between age, education, duration of illness and time estimation in the non-attempter group. On the contrary, these characteristics exhibited strong associations among attempters. There were strong positive correlations between age, level of education, and a fast internal time sense. Similar results were obtained for duration of illness, with longer duration strongly correlated with a faster internal sense of the passage of time. Clearly, age, education, and duration of illness are highly interrelated. A close analysis of the differential pattern of correlations between these variables and time estimation among attempters and non-attempters leads us to speculate that the clinical and time estimation profile of the attempter group is significantly different from the other patients. A potential explanation for these associations is that, while attempters were older and had a higher educational level compared to the other two groups, the first group might have been more insightful of the effects of their illness because of their overall longer duration. However, the trend for a slow sense of the passage of time, better captured by the time production task, contradicts our understanding of the widespread conception that suicide attempters have an increased subjective experience of changeless present and unattainable future, frequently associated with feelings of hopelessness (i.e.,

Beck, 1963; Kovacs, Beck & Weissman, 1975). Given that these results challenge prior research done among other psychiatric populations (Neuringer and Levenson, 1972; Neuringer and Harris, 1974), further investigation is needed to replicate these findings among patients with schizophrenia while controlling for confounding variables (i.e., medication).

Interestingly, among this subsample, attempters with no suicidal ideation or with low scores on the SSI during the week of the assessment demonstrated a fast internal sense. On the contrary, attempters with high scores on the SSI exhibited a slow sense of the passage of time. Similar findings were obtained among non-attempters. On a speculative note, these results could be understood within the context of reflection versus impulsiveness. As such, there are attempters who do not act on impulse to kill themselves and, nevertheless, have a quite elaborate ideation and planning about possible future attempts. These appear to be characterized by a more reflective attitude and a slow cognitive tempo that could be captured by time estimation as a slow internal time sense.

The Perception of Time: Relationship to Suicide History

Analyses of the correlations between time estimation and indicators of prior history of suicide suggest that suicidal intent scores on the SIS for the most lethal and the most recent attempts were strongly correlated with a slow internal time sense. On the contrary, the number of prior suicide attempts was associated moderately to strongly with a fast internal sense of the passage of time. Again, it seems fair to explain these findings by applying the conjecture of reflective-impulsive behavior. A high number of attempts may be a sign of impulsive acts and of quick responses for the short-term reward (Barratt

& Patton, 1983), such as death to alleviate suffering. This style could be associated with a fast internal time sense. On the other hand, high intent in prior attempts could indicate more planned, reflective, and premeditated actions to ensure success in the attempt, a result of a type of ideation that ensures a more successful long-term reward (Barratt and Patton, 1983). This style is probably associated to a slow internal time sense. Without doubt, the relationship between intent, lethality and suicidal ideation cannot be explained in such simplistic terms. Indeed, some attempts could be impulsive, with low intent and highly lethal, while more premeditated ones could be accompanied by high intent and would entail methods that have less lethality (Beck, Beck & Kovacs, 1975).

Certainly, the complex aspects of suicide and its relationship with the perception of time among attempters require further research.

Time Estimation and Severity of Illness

An examination of variables related to clinical deterioration, such as age of onset of schizophrenia, age at first mental health contact, and duration of the current psychotic episode were also strongly correlated with a fast internal time sense.

Again, the distortion of the perception of time emerges as a cognitive dysfunction that should be carefully considered. Its better understanding could shed light on the heterogeneous clinical and cognitive characteristics of schizophrenia.

Time Estimation: Importance of its Measurement

In agreement with prior reports (Carlson & Feinberg, 1968), the methods selected for this study, time perception and time production, demonstrated a reciprocal linear

relationship. Our results indicate that the performance of participants in the time perception task is more fluctuating compared to time production, particularly for the shortest interval used (i.e., 5s). This issue has been addressed in the literature by Bindra and Waksberg (1956), who described this process as indirect because it entails the translation of the subject's internal experience of elapsed time, which is by definition free of measurement in arbitrary time units, into verbalized conventional clock units that could be precise (i.e., 8s), but pose the risk of being rounded up (i.e., 10s).

The instruction given to the participants in our study to "count seconds like a clock" constitutes an improvement in the measurement of time estimation that should be considered in the design of future studies. However, several issues should be addressed regarding this strategy to measure the passage of time. First, while counting seems to be an effective strategy for both tasks, it seems more successful for time production. During this task, percent deviations remained fairly constant across intervals, although female patients with schizophrenia appeared to count faster than the remaining groups. Second, during the time perception task, counting seems to slow down with the increase of the interval length for both samples. In relation to this point, the possibility of rounding up estimations, when asked to verbalize the number of seconds that had elapsed, is likely to have a stronger impact on brief durations. However, this explanation does not account for the remarkable slowing down of counting in perception and, to a lesser degree, in time production among patients.

Based on the internal clock models, counting is a conscious activity and a natural strategy that subjects frequently use. It closely resembles the properties of the "pacemaker-accumulator" (Gibbon, Church, & Meck, 1984) posited for the internal clock

model as it accumulates pulses in a linear fashion over time. It could be speculated that the significant overestimation observed in the shorter intervals (i.e, 5s and 10s) is due to a fast counting activity that encompasses small units of time to ensure precision. In analogy to the pacemaker-accumulator, while the counting rate is rapid to ensure an accurate discrimination of small differences in durations, it must also ensure stability to account for the reliability of temporal discriminations (Meck, 1983, 1996). Perhaps, the rate starts rapid to ensure accuracy and while it appears to slow down for participants in the non-patient sample, a successful and complete reduction in the speed of counting fails to occur among our sample of patients with schizophrenia. Interestingly, this process seems to affect time perception but not time production. Thus, the emphasis is on the idea that both processes, although related, encompass at least partially different cognitive processes. As it was demonstrated by Logie and Baddeley (1987), even a simple task like mental counting involves the articulatory loop that is likely to be activated through a subvocal rehearsal process, with a phonologically-based store of working memory. The differential effect of counting on time perception and time production could be explained by the idea that, during the time perception task, subjects are aware of their requirement to verbalize the elapsed time. This condition could accentuate the participants' attention to the subvocal rehearsal. Along this line of thought, an alternative explanation for the overestimation of the shorter intervals might rely on the idea that counting digits under 10 is faster because the subvocal rehearsal process involves the repetition of monosyllabic units (i.e., from one to 10). Contrarily, longer durations involve digits with two or three syllables which are likely to prolong the subvocal process and, consequently, slow the overall count maintained in the articulatory loop. Certainly, the use of counting in time

estimation and the cognitive processes associated with this strategy demands further research. Future studies should address this issue by including the estimation of one and two-syllables durations while comparing groups using counting versus not-counting (i.e., ask participants to perform a filling verbal activity to ensure interference with subvocal rehearsal).

In any case, despite the overlap between time perception and time production, our analyses indicate that the time production task appears as a more reliable method across intervals, within subjects, and between subjects. Indeed, pressing a key instead of verbalizing the elapsed intervals, as is the case of the time perception task, appears to make the time production task a more sensitive and reliable tool to assess time estimation.

Conclusions, Methodological Issues, and Future Directions

Among patients with schizophrenia, particularly females medicated with neuroleptics, a faster sense of the passage of time in relation to the objective time was observed. However, while unmedicated, these patients exhibited a fairly accurate sense of time. This finding poses interesting questions with respect to our clinical practices, given that patients with schizophrenia receiving antipsychotic treatment are frequently considered more stable and with a superior overall functioning compared to when they are unmedicated. The reduction of the most prominent aspects of schizophrenia after medication treatment, namely positive symptoms (i.e., delusions, hallucinations, positive formal thought disorder), suggests clinical improvement. However, the acceleration of their internal sense of time coupled with the worsening of negative symptoms challenge

our customary assumption that patients get better with neuroleptic medication. Time estimation, understood as a cognitive function, worsens significantly in terms of accuracy after drug treatment. In this sense, the significant antipsychotic effect of accelerating the internal time sense should be addressed in future studies including larger samples of patients off and on mediation. Indeed, in light of these findings, it seems accurate to emphasize the central role of DA in the mediation of schizophrenia and in the regulation of the internal time sense. Future research should further explore this area while assessing time estimation off and on medication using drugs with higher affinity to the D^2 receptor (i.e., typical neuroleptics or newer drugs such as abilify) in order to confirm our preliminary results and shed further light into the underlying biological mechanisms of timing abilities and this psychiatric disorder.

Moreover, the unexpected finding of the effect of anticonvulsants on the accurate perception of time definitely encourages further research. The study of the impact on time estimation of pharmacotherapy with neuroleptics and adjunctive anticonvulsants among populations that receive it routinely (i.e., bipolar disorders with psychotic features) remains a challenging proposition. Furthermore, even the study of the isolative effects of anticonvulsants on time perception (i.e., among patients with epilepsy) could be an interesting proposal.

Among patients with schizophrenia, future designs should include the assignment of patients to different neuroleptic groups (i.e., typical, atypical, and combined) in order to examine the specific effect of each type of medication on time estimation. Based on this study, it is inconceivable to propose research on time estimation without controlling for medication effects.

The systematic gender differences observed across analyses should be further investigated in other patient populations, and definitely replicated in schizophrenia.

The lack of significant findings for the attempter and non-attempter comparisons on time estimation may have been, in part, due to the small samples. Given that a trend for a slow internal time sense was shown by attempters, an increased number would greatly improve the robustness of future analyses of this type. Prospective research involving time estimation in suicide attempters with schizophrenia should include age, level of education, and duration of illness into serious consideration when evaluating suicidal behavior and internal time sense.

It is important to highlight that our samples were integrated by participants, non-patients and inpatients, willing to do research. Therefore, the generalizability of our results should be done with caution. We encourage the replication of this study in a sample of outpatients with schizophrenia.

Finally, the results of this study highlight the importance of pursuing the investigation of the perception of time as a crucial cognitive activity, affected by demographic (i.e., gender, age, educational level) and clinical (i.e., medication, duration of illness, suicidal ideation, number of prior suicide attempts) variables.

Future research in schizophrenia should examine core issues of this disorder under the light of timing deficits. As such, cognitive impairment including working memory deficits, difficulties in reaction time and speed tasks, behavioral symptoms such as motor perseveration, blocking, disorganized speech and behavior, as well as patients' everyday performance of activities of their daily living should be reconceptualized in view of a distorted perception of time, particularly while being medicated. Further

exploration of gender differences on cognitive and behavioral deficits in schizophrenia could certainly be reinterpreted based on our results that indicate that females with schizophrenia demonstrate a faster internal sense of time than males with this psychiatric disorder. Without doubt, a replication of these findings is an essential step for further progress in the complex field of neuropsychology of schizophrenia.

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