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Avoidance of Accelerated Aging in Schizophrenia?: Clinical and Biological Characterization of an Exceptionally High Functioning Individual

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Abstract

Objective: To determine the clinical and biological characteristics of an exceptionally high functioning index person (IP) with schizophrenia in her mid-50s, that may represent compensatory mechanisms, and potentially, avoidance of the accelerated aging typically associated with schizophrenia, that could inform development of novel interventions.

Method: IP, 11 other women with schizophrenia, and 11 non-psychiatric comparison (NC) women were assessed with standard ratings of psychopathology, neurocognitive function, decisional capacity, and functional brain imaging. IP was also compared to a sample of demographically similar NCs (N=45) and persons with schizophrenia (N=42) on a set of blood-based biomarkers of aging related to metabolic function, oxidative stress, and inflammation.

Results: IP's scores on working memory, and levels of brain activation during an affective face matching task in the left fusiform, right lingual, and left precentral gyri, exceeded NCs. IP was similar to NCs in severity of negative symptoms, most neurocognitive functions, decisional capacity, and brain activation in the left inferior occipital gyrus during a selective stopping task. IP's levels on 11 of 14 metabolic and inflammatory biomarkers of aging were better than NCs and the schizophrenia group.

Conclusion: Although speculative, results suggest a possible model in which superior working memory permits a person to be aware of the potentially psychotic nature of a thought or perception, and adjust response accordingly. Compensatory overactivity of brain regions during affective processing may also reflect heightened meta-awareness in emotional situations. Biomarker levels raise the possibility that IP partially avoided the accelerated biological aging associated with schizophrenia.

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INTRODUCTION

Schizophrenia is generally associated with psychosocial disability and accelerated biological aging, but there is substantial inter-person variability (Hjorthøj et al.; Kirkpatrick and Kennedy, 2017; Palmer et al., 2002). A subset of people, albeit of unknown proportion, is able to achieve normal or higher levels of functioning and to maintain those levels into mid- and-later life over the course of the life-span. It is conceivable that such individuals avoid the accelerated biological aging that is typically associated with schizophrenia. Identifying factors underlying the ability of some people with schizophrenia to achieve and maintain high levels of functioning may elucidate characteristics and strategies that can inform prevention and rehabilitation efforts for others with schizophrenia. Relevant domains include severity of psychopathology, neurocognition, brain function, capacity to consent (a key aspect of independent functioning), and biomarkers of aging. Yet, other than a recent qualitative study of high functioning people with schizophrenia (Cohen et al., 2017), there has been a dearth of empirical research concerning such persons.

This report focuses on a very high functioning middle-aged woman with schizophrenia (Index Person [IP]) whom we comprehensively evaluated and compared to non-psychiatric comparison (NC) women and women with schizophrenia (SC) with standard levels of psychosocial functioning. Given her history of schizophrenia, includes prior episodes requiring hospitalization, we hypothesized that IP would resemble the SC group in severity of symptoms, but that she would resemble NCs in neuropsychological ability and brain functioning which are known to be important to social-occupational functioning (Lepage et al., 2014; Wojtalik et al., 2017, as well as decisional capacity, which is at least conceptually relevant to independent functioning and associated with better neurocognitive function {Palmer, 2007 #3345). as well as decisional capacity, which is at least conceptually relevant to independent functioning and associated with better neurocognitive function (Palmer and Savla, 2007)IP simultaneously participated in an ongoing study of biological aging in schizophrenia, from which we obtained data on blood-based biomarkers relevant to biological aging. We compared IP's values on 14 biomarkers relative to a sample of women with (SC_B) and without (NC_B) schizophrenia in that study. Guided by the premise that the accelerated biological aging typically associated with schizophrenia may have deleterious impact on everyday functioning (Harvey and Rosenthal, 2017), we also speculated that IP's levels of biomarkers of aging would be intermediate between those of NC_B and SC_B groups.

METHODS

Participants

Index Person (IP): IP was in her mid-50s and had been living with chronic schizophrenia since her early 20s. Diagnosis was confirmed with a Structured Clinical Interview for DSM-IV-TR (SCID; First et al., 2002). She has had three psychiatric hospitalizations during her

lifetime, but experienced numerous additional episodes of acute psychotic exacerbation. She reported that during such exacerbations her symptoms have been severe. IP also reported having previously had several serious physical illnesses, including a subarachnoid hemorrhage, and three different primary cancers, but has survived and even overcome these medical problems. While living with schizophrenia, IP completed several post-graduate programs from prestigious institutions and continues to maintain a highly successful academic career. She maintains strong interpersonal relationships, including an ongoing successful marriage, several close friendships, and cordial professional relationships with colleagues and students. At the same time, she still has some psychopathologic symptoms and is taking antipsychotic medications.

Comparison Groups: Primary comparison groups included 11 SC women and 11 NC women. Inclusion criteria were: (1) female, (2) age 45–59 years, (3) right-handed, and (4) English fluency. SC group inclusion criteria also included currently: (1) being non-institutionalized/non-hospitalized at the time of enrollment, (2) meeting DSM-IV-TR criteria for schizophrenia, episodic with inter-episode residual symptoms, and (3) receiving antipsychotic medication. Exclusion criteria for both groups included physical/medical problems interfering with ability to complete the study. The NCs were recruited to be comparable to the SC group in ethnic background. This project was approved by the UC San Diego Human Research Protections Program; all participants provided written informed consent.

Comparison Samples for Blood-based Biomarker Analyses: We compared IP's results on 14 blood-based biomarkers of aging to those of 45 NC women and 42 SC women participating in a separate ongoing study of aging in schizophrenia. Sampling and methods for this study, and rationale for the selected biomarkers, have been described elsewhere (Hong et al., 2016; Joseph et al., 2015; Lee et al., 2016; Lee et al., 2017). To keep the samples gender- and age-comparable, the present subsample was restricted to women participants ages 46–65 years.

Diagnostic Confirmation: Diagnoses for IP and other participants were determined with the SCID, administered by a trained research associate and confirmed by a licensed psychiatrist or psychologist.

Measures and procedures

Sociodemographic and clinical information: Age, education, living situation (Board-and-Care residency), and current antipsychotic dose (expressed in terms of Defined Daily Dose; World Health Organization, 2009) were determined via interview and/or record review.

Psychopathology: Severity of symptoms for the primary sample was measured with the Positive and Negative Syndrome Scale for Schizophrenia (PANSS; Kay et al., 1987) and Hamilton Depression Rating Scale (HAM-D; Hamilton, 1967), and with the Scales for Assessment of Positive and Negative Symptoms (SAPS and SANS; Andreasen, 1982, 1984) and the Calgary Depression Scale for Schizophrenia (CDSS; Addington et al., 1992) for the

biomarker sample. Also for biomarker sample, smoking status was determined via interview and/or record review, and medical comorbidity was determined from the total and severity scores from the Cumulative Illness Rating Scale (CIRS; Parmelee et al., 1995).

Neurocognitive Functioning: Participants completed a comprehensive neuropsychological battery (see Online Supplement Table 1). To place each neuropsychological test score on a common metric, raw scores were converted to z-scores based on the entire sample (IP, and the 22 participants in the schizophrenia and NC groups), coded so higher scores represented better performance, using the normalized rank function of SPSS 24.0. A composite mean z-score for the entire battery, as well as for each cognitive domain, was calculated.

Decisional Capacity: Participants completed the MacArthur Competence Assessment Tool for Clinical Research (Appelbaum and Grisso, 2001) and the Thinking Rationally About Treatment (TRAT) scale (Grisso et al., 1995). The MacCAT-CR content assessed capacity to consent to a hypothetical clinical trial of a cognitive enhancing medication. Given that reasoning may be important for maintenance of high psychosocial functioning, the TRAT was included for a more in-depth assessment of the reasoning component of decision-making capacity than available in the MacCAT-CR.

Functional Magnetic Resonance Imaging (fMRI): Details of Blood Oxygen Level-Dependent (BOLD) fMRI data acquisition and analyses, conducted using standard methods, are provided in the Online Supplement. Subjects completed the following two tasks during fMRI:

Affective Face Matching (Hariri et al., 2000): Participants were presented with two faces depicting happy, angry, or fearful expressions and were asked to indicate which depicted an emotion matching a third (target) face. Emotion identification has been found impaired among some people with schizophrenia but may be critical for effective psychosocial functioning (Green, 2016).

Selective Stopping (Aron and Poldrack, 2006): Participants were presented with a series of trials with an arrow pointing left or right and were instructed to rapidly push one of two buttons to indicate the direction of the arrow (go signal). On 25% of trials, a tone (stop signal) immediately followed the presentation of the arrow, and the participant's task was then to refrain from button pushing. The ability to stop an action once it has begun may be important for everyday functioning in that it may aid in overcoming impulsive tendencies.

Biomarkers: Data on blood-based biomarkers or metabolic function, oxidative stress, and inflammation were drawn from our ongoing study of aging in schizophrenia. (Specific biomarkers are described in Table 2.)

Statistical analyses

For non-categorical sociodemographic characteristics, psychopathology ratings, neurocognitive functioning, and decisional capacity scores, we calculated the 95% confidence interval (CI) around the means for each variable, in the NC and SC groups,

respectively, using SPSS version 24.0 (cite SPSS). Significant differences between the SC and NC groups were defined as non-overlapping CIs. We then evaluated IP's performance relative to these CIs for each variable.

Standard fMRI data analysis methods were employed. (Details presented in the Online Supplement).

RESULTS

Results below are first presented for IP relative to the 11 NC and 11 SC group participants in terms of sociodemographics, psychopathology, neuropsychological functioning, and fMRI results; then the results of comparison of IP to 45 NC_B women and 42 SC_B groups are presented for biomarkers.

Sociodemographics:

There were no significant group differences in age, but IP completed significantly more years of education than either comparison group (Table 1). IP's ethnic/racial background was non-Latina Caucasian; the NC group included six non-Latina Caucasian, three African American, two Latina, and one Asian-American persons; the SC group included six non-Latina Caucasian, three African American, two Latina, and one multiethnic/multiracial persons.

Psychopathology:

The NC group had significantly less psychopathologic symptoms than the SC group (Table 1). IP's depressive symptoms were worse than the NCs and commensurate with those in the SC group, her positive and general symptoms were between those for the NC and SC groups, and her negative symptoms were commensurate with NCs

Neuropsychological Functioning:

Mean Composite z-score for NCs was significantly better than SCs'; IP's overall and specific domain z-scores were consistently above the CIs for the SC group. IP's composite z-score was within the CI for NCs and above that for the SC group (Table 1). IP's working memory was above the CIs for the means of NC and SC groups, whereas her verbal, attention/vigilance, processing speed, executive functioning, and motor speed and dexterity were within the 95% CIs around the means for NCs and her episodic memory and visual-spatial reasoning were between the CIs for NC and SC groups (Table 1).

Decisional capacity:

There were no significant group differences in Expression of a Choice. IP's scores were commensurate with the NCs and above the CIs for the means for the SC group on all other decisional capacity scores (Table 1).

Neuroimaging:

Behavioral Performance During Emotional and Cognitive Tasks: There were no significant group differences in behavioral performance on the emotional identification task.

IP performed better than the SC group on all behavioral domains of the selective stopping task, had equal reaction time and discrimination errors as NCs and had less omission errors than the NCs (Online Supplement Table 2).

Task-Related Activation and Comparisons Between Groups: When examining whole brain group maps, no clusters of significant difference in response between the NC and SC groups were found (data not shown).

Functional Brain Response During Affective Face Matching: There were 14 regions of significant response to emotional faces in the NC group during the Affective Face Matching task, including: bilateral fusiform gyrus, thalamus, middle frontal gyrus and precentral gyrus, right lingual and middle temporal gyrus, left inferior parietal lobule; midline precuneus, and superior frontal gyrus. The response of the five SC participants (fMRI results on this task were not available for six SC participants), was significantly lower in six of these regions: left fusiform, right lingual, left middle frontal, left inferior frontal, right middle temporal, and left precentral gyri.

IP had greater activation than NC and SC groups in the left fusiform, right lingual, and left precentral gyri (example depicted in Figure 1 for right lingual gyrus). In the right middle frontal and right middle temporal regions IP's brain response was significantly *lower* than the NCs', and was similar to that of the SCs. We also examined response in the amygdala, a region important for emotional reactions and which has previously been related to clinical symptoms in people with schizophrenia (Fakra et al., 2008), but found no significant group differences.

Functional brain response during Selective Stopping: NCs showed brain response during successful stopping in right middle frontal and left inferior occipital gyrus, and in left precentral gyrus when failing to stop. The SC group showed diminished response in all three regions. IP's brain response was significantly greater than the mean response in the SC group and similar to that of the NC group in the left inferior occipital gyrus region (Figure 1). Similar to the SC group, IP had a diminished response in the left precentral gyrus compared to the NCs (Figure 1). IP was not significantly different from either group in the right middle frontal gyrus (data not shown). (fMRI results were not available for one NC and three SCs on this task.)

Biomarker analyses:

IP's values on 11 of the 14 biomarkers of aging relevant to metabolic function, oxidative stress, and inflammatory processes were outside the CI for the means of NCs and those for SC subjects in the direction of better metabolic function, lower pro-inflammatory, and higher anti-inflammatory (IL-10) levels; IP's values were equivalent to NC subjects' on F2-Isoprostanes, a marker of oxidative stress (Table 2). IP's scores were above (worse than) the CI around the means for NCs and SC subjects on only two pro-inflammatory markers (TARC and Fractalkine). Of note, IP's current antipsychotic dose (World Health Organization (WHO) defined daily dose; WHO, 2009) was within the 95% CI of the mean

for the schizophrenia group. IP's medical comorbidity was above the CIs for the NC group and below or equal to the SC group.

DISCUSSION

This study was focused on a woman (IP) in her mid-50s with schizophrenia who had nonetheless achieved and maintained exceptionally high occupational and psychosocial functioning throughout her adult life. Here we summarize the overall pattern of findings across domain, in terms of where IP exceeded both groups, was similar to the NC group, worse than the NC group and/or similar to the SC group, prior discussing the results in terms of the specific hypotheses and relevant prior literature.

IP performed above (better than) the 95% CI around the mean for NCs on working memory, brain response to emotional faces in the left fusiform gyrus, right lingual, and left precentral gyri, and for 11 of the 14 biomarkers of aging related to metabolic function and inflammation. IP was similar to NCs in terms of severity of negative symptoms, most neurocognitive domains, decisional capacity and reasoning, brain activation level in the left inferior occipital gyrus during a selective stopping task, and a biomarker of oxidative stress. This pattern is generally consistent with our a priori expectations that IP would more closely resemble the NC than SC group on neurocognitive and brain functioning, as well as decisional capacity.

Although IP's symptoms at the time of assessment were generally mild, she has had past acute exacerbations at which time her symptoms have been severe, and her current symptoms are managed with continued daily antipsychotic medication. She also showed worse episodic memory, visual-spatial reasoning, and levels of two biomarkers of inflammation compared to the NC groups. Thus, IP does not merely have a minimal or mild form of schizophrenia. IP is a highly accomplished person, yet is neither fully symptom-free nor without any neurocognitive or biological alterations. The logical question is thus what factors have enabled her to achieve and maintain such high functioning, despite the challenges of these symptoms and deficits in episodic memory and visual-spatial reasoning?

IP's exceptional working memory and activation in brain regions relevant to facial recognition and the processing of visual information may help explain her ability to achieve and maintain exceptional occupational and psychosocial functioning, despite living for decades with chronic schizophrenia. Working memory is generally conceptualized as a limited capacity short-term conscious temporary storage for holding and manipulating/using information (Baddeley, 2007). This concept has potential relevance to "meta-consciousness," defined as explicit awareness of the contents of one's own consciousness (Schooler, 2002). Although at this time we must describe this as reasoned speculation, a plausible model suggested by these findings is that a strong working memory may permit a person to experience a delusion or other psychotic thought or perception, while simultaneously being at least partially aware of/entertain the possibility of, the psychotic nature of that thought or perception, and to choose not to act on it and/or take it as a sign that treatment may need adjustment (Davies et al., 2016; Nicolo et al., 2012). Another way conceptualize such ability is in terms of a robust "observing ego."

The above, even if speculative, model is also related to the concept of “belief flexibility,” defined as “the metacognitive skill of reflecting on one’s own beliefs, reviewing their likelihood, considering the evidence for them and that of alternative hypotheses” (Colbert et al., 2010, p. 45), which has in turn been suggested as a target for psychotherapies focused on delusions (Garety et al., 2015). The neurobiological underpinning of “belief flexibility” have not yet been established, and there may be an important distinction to be made between the neurobiology of psychotic thoughts or beliefs and that underlying the capacity for meta-mental reflection on those thoughts, beliefs, and perceptions. The findings from Cohen et al. (2017) are relevant in that high functioning people with schizophrenia self-reported engaging in such reflection/meta-mental processing as one of their key coping strategies. We also retrospectively contacted IP after completion of the present study and asked her about her self-perceived coping strategies. She mentioned several, described below, but among them was enacting cognitive strategies, such as stepping back and trying to assess her thoughts. Her self-description suggested an ability, at least at times, to stand back, and hold different ideas in her mind, which she is then able to review. [Other coping strategies mentioned by IP included

IP showed greater than normal activation in several brain regions on an affective face matching task, which may also represent a compensatory skill. Notably, identification of the emotional state of others, a form of social cognition related to “theory of mind,” has been shown to be frequently impaired in schizophrenia and a proximal cause of impaired psychosocial functioning (Bora et al., 2009). IP continues to maintain excellent social relationships. Increased activation of brain regions relevant to identification of the emotional states of others may, in part, help her compensate for other deficits that might otherwise be presented by schizophrenia.

Additionally, IP’s negative symptoms were similar in level to both NC groups, which is also of potential relevance to understanding her exceptional occupational and psychosocial functioning. The schizophrenia literature has a long history of studies of the deleterious impact of negative symptoms (Buchanan et al., 1990; Crow, 1985). Negative symptoms are more strongly correlated with functional status than positive symptoms (Green, 1996), yet beneficial effects of currently available pharmacologic agents are still primarily limited to management of positive symptoms (Miyamoto et al., 2012).

IP showed evidence of activation patterns similar to NCs in several brain regions important for sensory and motor processing. In frontal and temporal regions, however, her brain response was more similar to other individuals with schizophrenia. Interestingly, IP’s responses were similar to other individuals with schizophrenia in the precentral gyrus during the Selective Stopping task, but higher than normal during the Affective Face Matching task. This suggests the possibility that her brain’s compensatory ability in this region may be task dependent, perhaps due to complex interplays with other brain regions. Future research should examine the possibility of compensatory responses by testing whether there are additional regions, not responsive in NCs, that are active in either high functioning or typically functioning people with schizophrenia, and whether the functions subserved by those regions or systems have a logical (or empirically documented) relevance to better social-occupational functioning.

In addition to findings of brain and neurocognitive strengths, at least some of which may be involved in compensatory process, the findings from IP's biomarkers suggest that she may have avoided much of the usual pro-inflammatory dysregulation seen in many other people with schizophrenia. Specifically, IP's values on most of the biomarkers of aging were generally in the less metabolically dysregulated, less pro-inflammatory and more anti-inflammatory direction compared to the NC and SC participants, while SC_B group in this study generally showed more unhealthy marker levels compared to the NC_B group. Given the potential relationship of immune and brain function, it is possible there could be a biological link underlying cognitive/brain and biomarker function (Misiak et al., 2017; Muller, 2016). On the other hand, relatively strong cognitive and brain reserve may indirectly lead to better biomarker values through environmental factors. This finding is, admittedly tentative, and the pattern of better than NC_B and SC_B groups' biomarker function in IP was not uniform across all the biomarkers. Nonetheless, given the biological toll of schizophrenia on overall health and mortality, prospective research on people with schizophrenia who may avoid the accelerated aging typically associated with schizophrenia is clearly warranted.

Rather than traditional null hypothesis testing, the primary focus of the present report was on comprehensively characterizing a very high functioning person, IP, relative to NC and SC groups. Nonetheless, it may be noted that we chose to compare the group means in terms of CIs rather than with t-tests or similar statistical methods. One disadvantage of using CIs for comparing NC versus SC group means is that false-negative errors are more likely, i.e. although non-overlapping 95% CIs will also be significantly different with a corresponding t-test at $p < .05$, it is possible to have a significant difference on a t-test even when the CIs overlap (Schenker and Gentleman, 2001). However, there is already a large body of empirical research documenting differences between NC groups and people with schizophrenia on brain activation patterns, neurocognitive function, and decisional capacity, as well as aging related biomarkers. T-tests or similar variance-dependent methods would not be appropriate for comparing scores from a single individual to the mean values from other groups. But CIs are ideal for this purpose as are a well-established method of estimating and clearly communicating the range within which the true group mean scores are likely to be. If on a particular measure IP's score is outside the range for the true mean for similarly aged people with schizophrenia, but within the range of NC subjects, it provides some evidence that she more closely functions like the non-psychiatric population in that particular area.

Contrary to our expectations, at the time of assessment IP had less severe psychopathologic symptoms than the SC and SC_B groups, although, as expected, IP did have worse symptoms than the NC groups. These differences, as well as IP's substantially higher education, represent a potential limitation in interpreting those neurocognitive domains where IP performed better than the SC group. Unfortunately, matching the comparison groups for education level would be problematic as education is directly tied to the very phenomenon under investigation (Meehl, 1970; Resnick, 1992). Use analysis of covariance to "control" or adjust for such differences is also problematic (Miller and Chapman, 2001). However, a large body of prior research has shown that positive and depressive symptoms have minimal association with severity of neurocognitive deficits in schizophrenia, and even the

correlations with negative symptoms tend to be modest in size (de Gracia Dominguez et al., 2009). Also, even within the SC and SC_B groups, the mean scores for each of the psychopathology measures were in the mild-range. Thus, it appears unlikely that the neuropsychological differences were primarily driven by differences in current psychopathologic symptoms

A related limitation of the study is the absence of other high functioning persons with schizophrenia, and small sample sizes in the NC and SC groups. In light of this limitation, there is a need for caution in drawing definitive conclusions, i.e. until larger scale confirmatory studies can be conducted. However, the present results serve as a solid basis for *a priori* hypotheses to inform and guide larger scale research. Although IP is one person there are other people, albeit of unknown prevalence, who have high social-occupational functioning while living with schizophrenia (Cohen et al., 2017). Further research is needed to determine the prevalence of such persons, and the degree to which the pattern of results demonstrated by IP generalizes to other high functioning persons with schizophrenia.

Our findings call for two forms of follow-up research. Foremost, there has been a dearth of quantitative research on high functioning individuals with schizophrenia. It would be important to determine whether superior working memory abilities and brain response in sensory and motor regions, along with biomarker levels suggesting an avoidance of the accelerated aging typically seen in schizophrenia, may be common (or at least frequent) among high functioning people with schizophrenia. The likelihood of divergent rates of aging in different body systems and functions in schizophrenia should also be evaluated (Jeste et al., 2011). Further qualitative investigation is also called for, i.e., to ask such persons about their perspective on meta-conscious strategies for identifying and coping with psychotic thoughts and perceptions. If the answer is affirmative, then efforts to develop working memory/meta-consciousness-based interventions are warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Upper left: Plot of mean cognitive composite z-score for Index Person (IP), normal comparison (NC), and schizophrenia comparison (SC) subjects.

Upper right: Plot of brain response (mean fit coefficient) in right lingual gyrus cluster of significant response in IP, NC, and SC comparison groups during the Affective Matching Task.

Lower left: Plot of brain response (mean fit coefficient) in left precentral gyrus cluster of significant stop fail > success response in IP, NC, and SC comparison groups during the Selective Stopping Task.

Lower right: Plot of brain response (mean fit coefficient) in left inferior occipital gyrus cluster of significant stop success > fail response in IP, NC, and SC comparison groups during the Selective Stopping Task.

Table 1.

Comparison of Index Person (IP) with Normal and Schizophrenia Comparison Groups (NC and SC, respectively) on Sociodemographics, Psychopathology, Neurocognitive Functioning, and Decisional Capacity

	Index Person (N=1)	Normal Comparison (N=11)	Schizophrenia Comparison (N=11)	
	Observed Value	Mean (95% CI)	Mean (95% CI)	Pairwise Differences
<u>Socio-demographics</u>				
Age (years)	54.3	52.2 (50.0 – 54.3)	54.7 (52.4 – 56.9)	None
Education (years)	20.0	14.7 (13.4 – 16.0)	12.6 (10.8 – 14.3)	IP > NC = SC
Board-and-Care Residents	0.0%	0.0%	45.5%	
<u>Psychopathology</u>				
Positive symptoms (PANSS Positive)	10.0	8.8 (8.0 – 9.6)	16.4 (11.6 – 21.3)	SC > IP > NC
Negative Symptoms (PANSS Negative)	9.0	8.6 (7.7 – 9.6)	15.3 (12.1 – 18.4)	SC > IP = NC
General Psychopathology (PANSS General)	26.0	20.2 (18.4 – 21.9)	35.4 (31.0 – 40.0)	SC > IP > NC
Depressive symptoms (HAM-D total)	7.0	2.5 (1.2 – 3.7)	9.4 (6.4 – 12.3)	SC = IP > NC
<u>Antipsychotic Medication</u>				
Antipsychotic daily dosage (total WHO DDD)	2.0	n/a	1.3 (0.8 – 1.8)	SC < IP
<u>Neuropsychological Functioning</u>				
Verbal	+0.45	+0.36 (–0.09 – +0.82)	–0.48 (–0.94 – –0.03)	IP = NC > SC
Attention/Vigilance	+0.60	+0.74 (+0.28 – +1.20)	–0.71 (–1.01 – –0.41)	IP = NC > SC
Working Memory	+1.10	+0.54 (+0.19 – +0.90)	–0.68 (–1.07 – –0.30)	IP > NC > SC
Processing Speed	+0.63	+0.69 (+0.30 – +1.09)	–0.75 (–1.13 – –0.36)	IP = NC > SC
Episodic Memory	+0.01	+0.62 (+0.26 – +0.97)	–0.62 (–1.05 – –0.18)	NC > IP > SC
Visual-Spatial Reasoning	+0.07	+0.35 (+0.13 – +0.58)	–0.35 (–0.76 – +0.06)	NC > IP > SC
Executive Functioning	+0.24	+0.12 (–0.07 – +0.30)	–0.16 (–0.40 – +0.08)	IP = NC, IP > SC
Motor Speed and Dexterity	+0.37	–0.18 (–0.50 – +0.14)	+0.09 (–0.21 – 0.41)	IP = NC > SC
Cognitive Composite	+0.37	+0.37 (+0.15 – +0.60)	–0.42 (–0.67 – –0.17)	IP = NC > SC
<u>Decisional Capacity</u>				
MacCAT-CR				
Understanding	26.0	25.0 (23.9 – 26.0)	22.4 (19.8 – 25.0)	IP = NC, IP > SC
Appreciation	4.0	3.4 (2.6 – 4.0)	1.8 (1.0 – 2.6)	IP = NC, IP > SC
Reasoning	8.0	7.4 (6.5 – 8.0)	6.8 (6.0 – 7.6)	IP = NC, IP > SC
Expression of a Choice	2.0	1.9 (1.7 – 2.0)	2.0 (2.0 – 2.0)	None
TRAT scale total	18.0	17.1 (16.1 – 18.0)	12.9 (11.7 – 14.2)	IP = NC, IP > SC

Note: CI = Confidence Interval; PANSS = Positive and Negative Syndrome Scale for Schizophrenia; SC = Schizophrenia Comparison group; IP = Index Person; NC = Normal Comparison group; HAM-D = Hamilton Depression Rating Scale; MacCAT-CR = MacArthur Competence Assessment Tool for Clinical Research; TRAT = Thinking Rationally About Treatment scale. Significant differences between the normal comparison and schizophrenia comparison groups are those with non-overlapping 95% CIs.

Table 2.

Comparison of Index Person (IP), Biomarker Study Normal and Schizophrenia Comparison Groups (NC_B and SC_B, respectively) on Blood-based Biomarkers of Aging.

	Index Person (N=1) Observed Value	Biomarker Study Normal Comparison Mean (95% CI)	Biomarker Study Schizophrenia Comparison Mean (95% CI)	Pairwise Differences
<u>Sociodemographic and other characteristics</u>				
Age (years)	57.2 ^a	55.5(54.0 – 57.1) (n=45)	54.7 (53.0 – 56.5) (n=42)	IP > NC _B = SC _B
Education (years)	20.0	14.7 (14.1 – 15.2) (n=45)	12.7 (12.1 – 13.3) (n=42)	IP > NC _B > SC _B
Board-and-Care Residents	0.0%	0.0%	47.66% res%	
SAPS total	2.0	0.5 (0.2 – 0.8) (n=45)	6.7 (5.5 – 8.0) (n=42)	SC _B > IP > NC _B
SANS total	2.0	1.7 (1.0 – 2.4)	7.9 (6.6 – 9.3)	SC _B > IP = NC _B
CDSS	2.0	(0.5 – 1.5) (n=45)	3.9 (2.4 – 5.3) (n=42)	SC _B > IP > NC _B
Current smoking status (% current smokers)	0.0%	6.7%	42.9%	SC _B > NC _B
Antipsychotic daily dosage (total WHO DDD)	2.0	n/a	1.6 (1.1 – 2.1) (n=42)	SC _B = IP
CIRS-total score	6.00	3.51 (2.57 – 4.45) (n=45)	8.40 (6.68 – 10.13) (n=42)	SC _B > IP > NC _B
CIRS – severity index	1.50	1.12 (0.95 – 1.31) (n=45)	1.47 (1.32 – 1.62) (n=42)	SC _B = IP > NC _B
<u>Metabolic</u>				
HOMA-IR	0.63	2.10 (1.37 – 2.83) (n=38)	3.39 (2.08 – 4.72) (n=37)	SC _B = NC _B > IP
<u>Oxidative Stress</u>				
F2 Isoprostanes	0.0320	0.0345 (0.0296 – 0.393) (n=43)	0.0485 (0.0408 – 0.0562) (n=40)	SC _B > NC _B , = IP
<u>Inflammation</u>				
hs-CRP	0.28	2.24 (1.14 – 3.33) (n=43)	5.38 (3.87 – 6.89) (n=40)	SC _B > NC _B > IP
IP-10	262.4	486.3 (288.0 – 684.6) (n=37)	566.6 (412.9 – 720.3) (n=38)	SC _B = NC _B > IP
MCP-1	59.3	101.7 (76.8 – 126.6) (n=37)	108.5 (92.9 – 124.2) (n=38)	SC _B = NC _B > IP
MCP-4	65.3	82.4 (60.5 – 104.4) (n=29)	83.7 (63.6 – 103.8) (n=26)	None
MDC	513.7	779.5 (697.5 – 861.5) (n=37)	1108.3 (931.0 – 1285.6) (n=38)	SC _B > NC _B > IP
MIP-1α	11.4	13.1 (11.4 – 14.7) ^b (n=28)	16.2 (13.7 – 18.8) (n=26)	SC _B = NC _B > IP
MIP-1β	30.4	63.2 (54.5 – 71.8) (n=37)	80.0 (67.4 – 92.5) (n=38)	SC _B = NC _B > IP

	Index Person (N=1) Observed Value	Biomarker Study Normal Comparison Mean (95% CI)	Biomarker Study Schizophrenia Comparison Mean (95% CI)	Pairwise Differences
TARC	103.0	65.6 (49.9 – 81.3) (n=29)	60.4 (44.1 – 76.7) (n=26)	IP > NC _B = SC _B
IL-6	0.55	0.76 (0.62 – 0.90) (n=37)	1.34 (0.91 – 1.77) (n=37)	SC _B > NC _B > IP
IL-8	2.63	3.91 (3.23 – 4.59) (n=37)	4.45 (3.60 – 5.30) (n=37)	SC _B = NC _B > IP
IL-10	0.93	0.37 (0.20 – 0.53) (n=37)	0.52 (0.38 – 0.66) (n=37)	IP > NC _B = SC _B
Fractalkine	10415.2	5890.3 (5365.0 – 6595.6) (n=37)	6880.5 (5939.7 – 7821.4) (n=38)	IP > NC _B = SC _B

^aIP's age is older than in Table 2 than in Table 1 because the data for Table 2 were completed as part of a later study.

^bOne extreme statistical outlier (MIP-1α = 378.0) was deleted from this calculation.

Note: CI = Confidence Interval IP = Index Person; NC_B = Biomarker study normal comparison group; SC_B = Biomarker study schizophrenia comparison group; SAPS and SANS = Scales for the Assessment of Positive and Negative Symptoms; CDSS = Calgary Depression Scale for Schizophrenia; WHO DDD = World Health Organization defined daily dose; CIRS = Cumulative Illness Rating Scale; HOMA-IR = Homeostatic Model Assessment of Insulin Resistance; hs-CRP = high sensitivity C-reactive protein; IP = interferon gamma-induced protein; MCP = monocyte chemotactic protein; MDC = macrophage-derived chemokine; MIP = macrophage inflammatory protein; TARC = thymus and activation regulated chemokine; IL = interleukin

Significant differences between the normal comparison and schizophrenia comparison groups are those with non-overlapping 95% CIs