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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, which may represent compensatory mechanisms, and potentially, avoidance of the accelerated aging typically associated with schizophrenia.
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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1. Introduction

Schizophrenia is generally associated with psychosocial disability and accelerated biological aging, but there is substantial inter-person variability (Hjorthøj et al., 2017; 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 neuropsychological functioning, 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 the key focus on a single person, IP, the present study is focused on hypothesis generation (i.e. by identifying IP's scores or characteristics relative to NC and the SC comparison subjects). However, we did have some a priori expectations about where IP would resemble NCs and where she would the SC comparison group. Specifically, given her

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history of schizophrenia, including ongoing treatment with antipsychotic medications, we anticipated that IP would resemble the SC group in severity of symptoms, but that she would resemble NCs in neuropsychological ability and brain functioning as these latter two are important for social-occupational functioning (Lepage et al., 2014; Wojtalik et al., 2017), as well as in decisional capacity, which is at least conceptually relevant to independent functioning and is strongly associated with neurocognitive function (Palmer and Savla, 2007). IP also participated in a study of biological aging in schizophrenia from which we had data on blood-based biomarkers relevant to biological aging (specifically, measures of metabolic function, oxidative stress, and inflammation). 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 anticipated that IP's levels of biomarkers of aging would be better than other participants with schizophrenia, group, although perhaps still being worse than those of NC subjects.

2. Methods

2.1. Participants

2.1.1. 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. She also noted that during the first two years of her illness she had inability to work or have friends. 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. 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.

2.1.2. 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. The 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.

2.1.3. 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., 2017; 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.

2.1.4. 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.

2.2. Measures and procedures

2.2.1. 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.

2.2.2. 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).

2.2.3. Neuropsychological 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 SC 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.

2.2.4. 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.

2.2.5. 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:

2.2.5.1. 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).

2.2.5.2. 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.

2.2.6. Biomarkers

Data on blood-based biomarkers or metabolic function, oxidative stress, and inflammation were drawn from our ongoing study of aging

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