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Impulsivity in unaffected adolescent biological relatives of schizophrenia patients

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ABSTRACT

Objective: Although schizophrenia is not a prototypic impulse-control disorder, patients report more impulsive behaviors, have higher rates of substance use, and show dysfunction in brain circuits that underlie impulsivity. We investigate impulsivity in unaffected biological relatives of schizophrenia patients to further understand the relationships between schizophrenia risk and impulse control during adolescence.

Method: Group differences in impulsivity (UPPS-P Impulsive Behavior Scale and delay discounting) were tested in 210 adolescents contrasting 39 first- and 53 second-degree biological relatives of schizophrenia patients, and 118 subjects with no schizophrenia family history (NSFH).

Results: Compared to NSFH adolescents and to second-degree relatives, first-degree relatives of schizophrenia patients had increased impulsivity-related behaviors (higher UPPS-P Perseverance, Positive Urgency and Premeditation subscale scores) and greater preference for immediate rewards (smaller AUC and larger discounting constant). Second-degree relatives did not differ significantly from NSFH adolescents on self-report impulsive behaviors or on measures of impulsive decision-making. These group differences remained even after careful consideration of potential confounding factors.

Conclusion: Impulsivity is associated with schizophrenia risk, and its severity increases with greater familial relatedness to the schizophrenia proband. Additional studies are needed to understand the role impulsivity may play in mediating schizophrenia susceptibility during adolescence.

1. Introduction

Impulsivity is a multi-dimensional construct with its core feature being impairment in the inhibition of impulses (Hofmann et al., 2009). There is no consensus on a single gold standard for the assessment of impulsivity. Various self-report questionnaires and neurocognitive-behavioral tasks are frequently used to measure impulsivity and related constructs of poor decision-making, risk taking and response inhibition. Self-report impulsivity is often weakly correlated with behavior-based measures (Caswell et al., 2015). This is consistent with the multi-dimensional nature of impulsivity, and suggests that individual dimensions may have differing yet overlapping neural substrates.

Whiteside and Lynam proposed that four distinct personality traits form discrete psychological processes that lead to impulsive behaviors (Whiteside and Lynam, 2001): 1) Urgency (or tendency to act impulsively as a result of intense emotions), 2) (lack of) Premeditation (or tendency to act without reflecting on the consequences of the act), 3) (lack of) Perseverance (inability to remain focused on a task that may be boring or difficult), and 4) Sensation Seeking (tendency to seek out new and exciting experiences). This conceptual framework, derived from personality theories and factor analysis of 8 impulsivity questionnaires, forms the basis of the UPPS Impulsive Behavior Scale, a comprehensive and widely used self-report rating scale for assessing impulsivity.

From among the different neurocognitive-behavioral tasks that have been used to measure impulsivity, the delay discounting task (de Wit et al., 2007; Mitchell, 1999) (DDT) emphasizes aspects of impulsivity that relate to the failure to consider future consequences during decision making (Ainslie, 1975). In the DDT, test subjects are presented with a series of hypothetical scenarios from which they choose between a smaller immediate reward or a larger delayed reward (e.g. Would you rather have $2 now or $10 in 1 year?). Delay discounting is the phenomenon where the current value of a future reward decreases with increased time delay to receiving the reward. More impulsive individuals tend to have a steeper rate of delay discounting, and are more likely to prefer immediate gratification over a larger delayed reward.

Impulsivity manifests in a wide range of complex behavioral phenotypes, including substance use, personality disorders, bulimia,

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suicidality and aggressive behaviors (Evenden, 1999). Schizophrenia (SZP) is not conventionally considered an impulse-control disorder. However, there is an accumulating literature indicating that SZP patients are more impulsive than healthy volunteers as assessed by self-report questionnaires or through experimental behavioral paradigms (Gut-Fayand et al., 2001; Hoptman et al., 2002; Ouzir, 2013). On the Barratt Impulsivity Scale (BIS), SZP patients have significantly higher ratings of impulsivity than healthy controls (Ahn et al., 2011; Amr et al., 2016; Enticott et al., 2008; Kaladjian et al., 2011; Krakowski and Czobor; Nanda et al., 2016; Reddy et al., 2014; Zhornitsky et al., 2012). Between patients with SZP, most studies (Dervaux et al., 2001, 2010; Gut-Fayand et al., 2001; Ouzir, 2013) but not all (Dervaux et al., 2004) have found that patients with concomitant drug use, or history of violence or suicidality scored higher on impulsivity than SZP patients without these behaviors. Dysfunctions in cognitive control neural circuitry postulated to mediate impulsivity have been frequently implicated in SZP patients (Aron et al., 2007; Hoptman et al., 2014).

Unaffected biological relatives of SZP patients have similar albeit less severe neurocognitive, neuroanatomic, electrophysiological and behavioral abnormalities seen in SZP patients (Boos et al., 2007; Ho, 2007; Ho and Magnotta, 2010; Keshavan et al., 2002; Lawrie et al., 1999; Thermenos et al., 2013). Such intermediate phenotypes likely result from the genetic and environmental risk factors that biological relatives shared with SZP probands (Cannon, 2005; Gottesman and Gould, 2003; Moldin, 1994). Studies using quantitative traits or endophenotypes have aided in identifying SZP susceptibility genetic loci (Freedman et al., 1997; Liu et al., 2002), and may further serve as biomarkers of SZP susceptibility useful for the early identification of SZP. To our knowledge, there has only been one family study examining impulsivity in twins of SZP patients (Fortgang et al., 2016). Impulsivity was found to be moderately heritable with 38–60% of its variance accounted by genetic factors. Twins of SZP probands were also more impulsive than healthy controls on some impulsivity measures (BIS Attentional and Nonplanning subscales) but not others (BIS Motor Impulsivity, Zuckerman Sensation-Seeking Scale (SSS) ratings or Stop Signal Task (SST) performance). Given the limited knowledge regarding impulsivity in biological relatives of SZP probands, we sought to expand on the work of Fortgang and colleagues. Therefore, we assessed both self-report impulsive behaviors as well as DDT in unaffected biological relatives of SZP patients so as to comprehensively assess facets of impulsivity that have not been previously studied. Additionally, we contrasted first- and second-degree biological relatives to further explore how familial relatedness to the SZP proband may influence differences in impulsivity.

2. Materials and methods

2.1. Sample

In this study, we evaluated 210 adolescents comprising of 92 biological relatives (39 first- and 53 second-degree relatives) of SZP patients and 118 comparison subjects with no SZP family history (NSFH). Participants and their parents/legal guardians gave written informed consent approved by the University of Iowa Human Subjects Institutional Review Board.

Study participants (aged 12–17 years) were recruited from the community via advertisements through mass emails, social media, and posting flyers at local mental healthcare providers and mental health advocacy groups. Following initial telephone screening to rule out serious medical/neurological disorders, study participants were assessed in-person to further exclude adolescents with intellectual disability (WRAT3 Reading Score (Wilikinson, 1993) < 30). All subjects and their parent/legal guardian were also administered the CAPA (Child and Adolescent Psychiatric Assessment, Child Interview (Angold et al., 2008)), a semi-structured interview instrument, so as to determine lifetime history of psychiatric or substance use disorders in the adolescent study participant. Presence (or absence) of SZP family history was verified using Family History-Research Diagnostic Criteria (FH-RDC) interview administered to the study participant's parent or legal guardian. The FH-RDC has well-established reliability and validity for the assessment of SZP family history (Andreasen et al., 1977).

Table 1
Sociodemographic characteristics of sample: first-degree relatives of schizophrenia patients (1°), second-degree relatives of schizophrenia patients (2°) and adolescent controls with no schizophrenia family history (NSFH).

	1°	2°	NSFH	Statistic[a] (p)
N	39	53	118	
Sex (Males, N (%))	23 (58.97)	30 (56.60)	55 (46.61)	2.55 (0.28)
Mean age (years (SD))	14.8 (1.49)	14.5 (1.71)	14.9 (2.11)	0.97 (0.38)
Ethnicity (White, N (%))	34 (87.18)	48 (90.57)	108 (91.53)	(0.10)
Handedness[b] (L/M/R (% R))	1/8/30 (76.92)	6/5/42 (79.25)	5/11/102 (86.44)	(0.12)
Any psychiatric disorders (N (%))	12 (30.77)	9 (16.98)	19 (16.10)	4.28 (0.12)
MDD (N (%))	9 (23.08)	5 (9.43)	11 (9.32)	5.70 (0.06)
ADHD (N (%))	5 (12.82)	6 (11.32)	10 (8.47)	0.75 (0.69)
ODD (N (%))	2 (5.13)	0 (0)	0 (0)	(0.03)
Current/Past drug use (N (%))	6 (15.38)	11 (20.75)	17 (14.41)	1.11 (0.57)
Tobacco use (N (%))	2 (5.13)	3 (5.66)	4 (3.39)	(0.72)
Alcohol use (N (%))	4 (10.26)	10 (18.87)	17 (14.41)	1.35 (0.51)

MDD: Major Depressive Disorder; ADHD: Attention Deficit Hyperactivity Disorder; ODD: Oppositional Defiant Disorder.
[a] Sex and psychiatric diagnoses (χ^2); age (F); ethnicity and handedness (Fisher's Exact).
[b] Annett Scale of Hand Preference (L: left; M: mixed; R: right).

Sociodemographic characteristics of the sample are summarized in Table 1. The sample comprised predominantly of right-handed (82.9%) Caucasian (90.5%) adolescents (Mean age = 14.8 years (SD = 1.91)) with approximately equal gender distribution (51.4% males). First-degree relatives had higher rates of Major Depressive Disorder (MDD) ($p = 0.06$) and Oppositional Defiant Disorder (ODD) ($p = 0.03$). Otherwise, gender, mean age, ethnicity, handedness and prevalence of psychiatric disorders and drug/alcohol use did not differ significantly between first-degree relatives, second-degree relatives and NSFH (Table 1; $p \geq 0.10$). None of the study participants met DSM criteria for schizophrenia-spectrum disorders, or alcohol or drug use disorders. Thirty-four subjects (16.2%) reported current or past tobacco and/or alcohol use. There were no current or past use of other substances. Tobacco use and alcohol use did not differ significantly across the 3 comparison groups ($p \geq 0.51$).

2.2. UPPS-P Impulsive Behavior Scale

We used a revised version of the UPPS that assesses the 4 original personality pathways to impulsive behaviors (Negative Urgency, Premeditation, Perseverance, and Sensation Seeking) (Whiteside and Lynam, 2001) as well as a fifth Positive Urgency subscale (Cyders et al., 2007; Lynam et al., 2006) (UPPS-P). The UPPS-P consisted of 59 statements. Subjects were instructed to indicate how much he/she agreed with each statement on a scale of 1–4 (agree strongly, agree some, disagree some or disagree strongly respectively). Since agreement with some statements while disagreement with others suggested greater impulsivity and vice versa, all responses were re-scored such that higher ratings indicated more impulsive behaviors. Each subject's subscale score is the sum of ratings of its component statements: Negative Urgency (12 statements), Premeditation (11 statements), Perseverance (10 statements), Sensation Seeking (12 statements), and Positive Urgency (14 statements). There were no missing responses from any of the subjects.