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Features of schizophrenia following premorbid eating disorders

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ABSTRACT

Objective: Eating disorders (ED) and schizophrenia are frequently comorbid and schizophrenia shares genetic susceptibility with anorexia. Many factors associated with schizophrenia can disrupt eating, but ED can present years before schizophrenia. If premorbid ED distinguishes a particular subtype of schizophrenia, then phenotypic features may differ between schizophrenia cases with and without premorbid ED.

Method: This secondary analysis used data from an inpatient schizophrenia research study that comprehensively assessed life course psychiatric disorders (DIGS interview), intelligence (WAIS), global assessments of function (GAF) and assessed symptoms during medication-free and fixed dose neuroleptic phases (PANSS).

Results: Premorbid ED was identified in 27 of the 288 schizophrenia cases (9.4%). This group had more females than the group without premorbid ED (74.1% vs. 30%); premorbid ED was 5-fold more common in female than male cases (χ^2 (17.9, $P < .0001$). Only the premorbid ED group had gustatory hallucinations. They also demonstrated significantly more severe psychotic and disorganization symptoms during medication-free and fixed dose treatment phases, despite similar negative symptoms and GAF scores, as other cases. The premorbid ED group had significantly better cognition overall, but relatively lower nonverbal than verbal intelligence.

Discussion: Premorbid ED may define a specific subtype of schizophrenia that is common in females. Their more severe psychotic symptoms and better IQ, despite similarly impaired function and negative symptoms as other cases, suggests a distinct pathophysiology. Premorbid ED should be considered in evaluating risk states for schizophrenia, and as a relevant phenotype for treatment resistant schizophrenia.

1. Introduction

Schizophrenia is a complex syndrome defined by psychotic symptoms, including hallucinations, delusions and disorganized thoughts, and by social and emotional deficits, respectively denoted as positive and negative symptoms. Functional decline is required for the schizophrenia diagnosis and cognitive impairments are typical (DSM-5 APA, 2013). Eating disorders (ED) are marked by systematic changes in eating-related behavior that result in diminished or excessive consumption of food along with impaired psychosocial function or physical health. Bulimia Nervosa (BN) entails recurrent episodes of binge eating over which one feels no control and for which one may try to compensate (Wade, 2019). It is often comorbid with Anorexia Nervosa (AN), which is characterized by weight loss, or by lack of appropriate weight gain in growing children, and difficulties in maintaining an appropriate body weight for one's height, age, and stature (Frank et al., 2019). Persons with ED commonly demonstrate poor insight and misperceptions of their body weight or shape that unrealistically influence their behavior.

The proportion of schizophrenia cases with ED is ~5 fold higher than the general population, with 1–4% of cases meeting criteria for AN and 5–20% having binge eating episodes (Kouidrat et al., 2014). This comorbidity was described by Eugen Bleuler over a century ago (Hoff, 2012). More recently, Genome Wide Association Studies (GWAS) revealed shared genetic susceptibility for anorexia and schizophrenia (Brandys et al., 2015). It thus seems plausible that a particular developmental pathology might underlie an earlier presenting susceptibility for ED and a later emergence of schizophrenia, with the age-dependent penetrance differing for the conditions.

When altered eating behavior presents contemporaneously or after

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the onset of schizophrenia, then psychotic symptoms, medications, or other illness factors may confound the assessment of ED. A more conservative approach is to compare the phenotypes of schizophrenia cases with and without premorbid ED. One such study found significantly more disordered eating among 50 antipsychotic-naïve schizophrenia cases than for age and sex matched controls (30% vs. 12%, $p = .027$) (Fawzi and Fawzi, 2012). The schizophrenia cases with disordered eating had significantly more severe psychotic symptoms, disorganized thoughts, hostility/excitation, and symptoms of anxiety and depression than the other schizophrenia cases. By contrast, the schizophrenia subgroups with and without disturbed eating had similarly severe social and emotional deficits, assessed as negative symptoms.

These results suggest that prodromal eating disturbances may be specific to a particular subtype of schizophrenia. The greater severity of psychotic symptoms in the above study suggest a shared pathology that could include the dopaminergic system, which is the target for the antipsychotic medications (Seeman, 2014) and is also implicated in ED (Barbato et al., 2006). Antipsychotic medications have reduced anorexia symptoms in some ED patients without psychosis (Bosanac et al., 2005; Brambilla et al., 2007), and the antipsychotic olanzapine improved cognitive distortions and reduced the delusional intensity of beliefs in some ED cases (Delsedime et al., 2013; Mondraty et al., 2005; Powers et al., 2010).

Despite the many associations between ED and schizophrenia, the comorbidity remains understudied. The current post hoc analysis compared the phenotypes of groups of schizophrenia cases with and without premorbid ED from a rich database of comprehensively assessed subjects who had participated in an inpatient research study. The protocol included best-estimate life course diagnoses and employed reliable assessment procedures. In addition to the measures examined in the Egyptian study, described above, this analysis included intelligence testing and the assessment of symptom severity in both medication-free and fixed dose neuroleptic treatment phases.

2. Method

2.1. Participants

The subjects for this study were 288 sequential cases with schizophrenia from an inpatient schizophrenia research study conducted between 1994 and 2008. Participants were comprehensively evaluated in an “umbrella protocol” using a common set of measures. The Institutional Review Board approved the study and all subjects signed informed consent.

2.2. Antipsychotic-free and antipsychotic treatment phases

Symptom ratings were obtained while the cases were medication free (typically at admission) and after 4 weeks of treatment on a stable dose of a typical antipsychotic medication (haloperidol or its equivalent titrated up to 15 mg/day; benztropine, as needed, 1–2 mg twice a day; lorazepam, 1–2 mg/day oral or intramuscular, as needed for severe agitation, anxiety, or insomnia). Treatment phases were typically separated by 8 weeks.

2.3. Diagnoses

The Diagnostic Interview for Genetic Studies (DIGS) (Nurnberger et al., 1994) was used to ascertain life course psychiatric diagnoses meeting DSM-IV-TR criteria, which included an eating disorders assessment, as well as demographic information. All subjects in the series received diagnoses of schizophrenia or schizoaffective disorder, herein referred to as schizophrenia (Association, 2000). ED diagnoses considered in the criteria included AN, BN, both, and ED not otherwise specified [ED-NOS]).

2.4. Demographics

Other information obtained from the DIGS interview included sex, educational attainment, ages at onset of disordered eating and psychotic symptoms, and Global Assessment of Function (GAF) scores for the current-episode and for the past-month.

2.5. Symptoms

Assessments were conducted during both treatment phases using the 30-item PANSS, interpreted by using 25 of the items in the pentagonal model to yield 5 separate factors (White et al., 1997): (1) positive symptoms (hallucinations, delusions, grandiosity), (2) negative symptoms (avolition, blunted affect, social withdrawal), (3) dysthymic symptoms (depressed mood, anxiety, guilt), (4) activation (excitement, hostility, agitation, poor impulse control), and (5) disorganization (stereotyped thinking, conceptual disorganization, lack of judgment, and insight). Specific psychotic symptoms in the DIGS that are not represented in the PANSS were also compared across the groups, including somatic delusions and somatic, tactile, gustatory, and olfactory hallucinations.

2.6. Cognition

Neuropsychological testing was conducted during the neuroleptic treatment phase to optimize performance on the WAIS-III (Wechsler, 1981) to yield the Full-Scale Intelligence Quotient (FSIQ), Verbal IQ (VIQ), and Performance IQ (PIQ).

2.7. Reliability of measures

The clinical raters were master's-level or above psychologists or the equivalent, trained to an inter-rater reliability of $\kappa > 0.80$ for individual symptoms and 95% for diagnoses. Best estimate research diagnoses were established in consensus team conferences led by expert diagnosticians.

2.8. Statistical analyses

Data were evaluated for normality using histograms and P–P plots, and assessed for kurtosis and skewness. Levene's test for the equality of variances evaluated the homogeneity of these data across the cases with and without premorbid ED. Frequencies and histograms were used to check for outliers and boxplots were used to identify outlier cases. Ethnicity was evaluated as Caucasian or other. Differences in demographic information between the groups of cases with and without an ED were assessed using the Pearson chi-square statistic for categorical data (sex and race) and analysis of variance (ANOVA) for continuous data (current age, age at onset of psychotic symptoms, educational attainment, illness duration, current episode GAF, and past-month GAF). Differences between the groups of cases with and without ED in PANSS factor scores (positive, negative, dysthymic, activation, and disorganization) for the medication free and fixed dose of typical antipsychotic treatment phases were examined using multivariate analysis of variance (MANOVA). ANOVA was used to further explore group differences on individual indices and items on the PANSS chosen for their potential to identify group differences relevant to the comorbidity, including somatic concern (item G1), unusual thought content, (item G9), lack of judgment and insight (item G12); impulse control (item G14), and avolition (item G13). The chi-square statistic was used to evaluate individual items of interest from the DIGS not included in the PANSS (somatic delusions; somatic, tactile, gustatory, and olfactory hallucinations) at admission. Split-plot (mixed design) ANOVA was used to determine whether groups of cases with and without ED differed in PANSS score changes medication free to treatment phases. Finally, differences in WAIS-III scores were evaluated using MANOVA

Table 1
Demographics of schizophrenia subgroups categorized by premorbid eating disorders.

	Schizophrenia only		Schizophrenia + ED		ANOVA			
	Men (n = 175)	Women (n = 86)	Men (n = 7)	Women (n = 20)	ED Diagnosis		Sex	
	M (SD)	*M (SD)*	*M (SD)*	*M (SD)*	*F*	*p*	*F*	*p*
Current Age	31.7 (11.0)	34.2 (9.6)	29.6 (7.7)	35.4 (9.0)	0.35	.557	4.25	.040*
Age at Psychosis Onset	20.3 (6.2)	23.6 (7.7)	19.0 (4.0)	21.9 (7.2)	0.04	.836	13.87	.000**
Onset Age of Eating Disorder	–	–	11.0 (4.7)	17.7 (5.5)	–	–	7.12	.014*
Duration of Psychotic Illness	12.4 (10.3)	11.1 (9.4)	2.7 (3.7)	10.7 (6.9)	1.20	.274	0.69	.406
Education (grade level)	12.8 (2.6)	13.7 (3.1)	13.1 (1.4)	14.3 (2.2)	2.27	.133	12.26	.001**
GAF Current Episode	31.9 (8.6)	32.3 (7.1)	38.0 (18.2)	31.7 (11.1)	0.60	.441	0.01	.922
GAF Past Month	38.2 (9.2)	39.5 (9.8)	45.4 (18.3)	38.7 (11.7)	0.85	.358	0.46	.491

There were no significant interactions between the ED diagnosis and sex factors. GAS: global assessment scale.
*$p < .05$. **$p < .01$. *** $p < .001$.

for PIQ and VIQ and ANOVA for FSIQ.

3. Results

3.1. Proportion with premorbid ED

Twenty-seven of 288 schizophrenia cases met diagnostic criteria for an ED (9.4%) that presented before their onset age of psychosis; including anorexia, $n = 8$; bulimia, $n = 9$; both anorexia and bulimia, $n = 6$; ED, not otherwise specified, $n = 4$. Cases with premorbid ED were more likely to be Caucasian than from an ethnic minority group (χ^2 (288) = 21.17, $p < .001$).

3.2. Sex differences

Compared to cases without ED, the premorbid ED group had significantly more females (20/27 vs. 86/261: χ^2 (288) = 17.79, $p < .001$). ED was 5 fold more prevalent among females (20/106 =18.9%) than males (7/182 =3.8%): (χ^2 (17.9, $p < .0001$). As shown in Table 1, females, with and without ED, were more educated and older than males. The durations of psychotic illness preceeding the premorbid ED assessments were similar for males and females, however, as ED began at younger ages for males than females. No other interactions between diagnostic group and sex were found in other analyses, as below, at either time point.

3.3. Global assessments of function and negative symptoms

Cases with and without premorbid ED had similar functional impairments based on GAF scores for their entire current episode and for the past month. They also had a similar severity of negative symptoms during both treatment phases: medication free and fixed dose of neuroleptics.

3.4. Psychotic and disorganization symptoms

By contrast, the cases with premorbid ED demonstrated significantly more severe psychotic and disorganized symptoms at both assessment phases (Table 2).

3.5. Depression and anxiety symptoms

The ED group only demonstrated higher depression and anxiety scores on antipsychotic treatment, based on their dysthymic factor scores. Their affective symptoms did not improve with antipsychotic treatment, whereas improvement is evident for the subgroup of cases without premorbid ED. No interactions between diagnostic group and sex were found in these analyses at either time point.

3.6. Individual PANNS items

Post hoc examination of individual items, using a Bonferonni corrected significance of <0.005, only showed substantially more unusual thought content for the group of cases with premorbid ED during the fixed dose treatment phase (4.3 +/−1.5; 2.5+/−1.6 vs. 2.1 +/−1.4; 1.9+/−1.4: F[1, 198] = 9.92, $p = .002$]. A similar group difference of more unusual thoughts in those with premorbid ED was also shown in the medication free phase (2.3+/−1.6; 2.7+/−1.6 vs. 3.6 +/−1.7; 3.2+/−1.7: F[1, 198] = 4.60, $p = .034$).

3.7. Individual DIGS psychotic symptom items

Cases with and without ED showed similar somatic delusions and as well as somatic, tactile and olfactory hallucinations. Cases with premorbid ED had significantly greater gustatory hallucinations over their lifetimes (χ^2 [210] = 12.516, $p < .001$) and for the current-episode (χ^2 [210] = 3.962, $p = .047$).

3.8. Cognition

Schizophrenia cases with ED group had significantly higher IQ scores than the other cases (ANOVA: F [1, 166] = 11.32, $p = .001$), with somewhat higher scores for the males than females (F [1, 166] = 3.93, $p = .049$) (see Table 3). Multivariate analyses showed that both PIQ and VIQ scores were significantly higher for the ED group than the other cases (overall Wilks' $\lambda = 6.41$, $p = .002$; for PIQ (F [1, 166] = 5.87, $p = .016$); especially VIQ (F [1, 166] = 12.89, $p < .001$). There were no other interactions between diagnostic group and sex in these analyses. The mean spread between verbal and performance in ED cases was >10 IQ points, consistent with a nonverbal deficit.

4. Discussion

Almost a tenth (9.4%) of 288 comprehensively assessed participants with schizophrenia from in an inpatient research study also fulfilled DSM-IV criteria for a premorbid eating disorder. Anorexia, with or without bulimia, was identified in 5.2% of the cases and the others had diagnoses of BN or ED not otherwise specified. The study results suggest that premorbid ED could identify a specific and homogeneous subgroup of cases in the schizophrenia syndrome.

This proportion is somewhat higher than rates of premorbid ED reported in other schizophrenia studies (Kouidrat et al., 2014). As this group had significantly more severe psychotic and disorganization symptoms, they could be over-represented among persons entering an inpatient research study compared to clinical samples. Our proportion is very likely accurate, as these subjects underwent structured life course interviews and the diagnoses were determined through best estimate research procedures, involving family informants and prior records. Such rigor is not applied in usual clinical assessments and is

Table 2
Positive and negative syndrome scale (PANSS) factor scores for medication free and treatment phases.

	Schizophrenia only		Schizophrenia + ED		MANOVA			
	Men	Women	Men	Women	ED Diagnosis		Sex	
	M (SD)	*M (SD)*	*M (SD)*	*M (SD)*	*F*	*p*	*F*	*P*
Medication Free Phase								
Multivariate Wilks' lambda					1.27	.278	0.61	.691
Positive Factor	12.2 (5.3)	13.7 (4.7)	17.8 (3.4)	13.9 (3.9)	4.63	.033*	0.70	.405
Negative Factor	19.1 (7.4)	15.5 (5.9)	20.6 (9.2)	19.5 (6.5)	2.13	.146	1.55	.214
Activation Factor	9.6 (3.9)	9.4 (4.5)	11.0 (3.0)	10.6 (4.3)	1.15	.235	0.07	.80
Dysthymia Factor	10.7 (5.0)	11.2 (3.6)	13.4 (7.4)	11.1 (3.7)	1.21	.273	0.50	.481
Autism Factor	12.7 (4.6)	12.5 (4.2)	15.4 (6.8)	14.7 (4.7)	3.94	.048*	0.16	.686
	$n = 120$	$n = 62$	$n = 5$	$n = 15$				
Treatment Phase								
Multivariate Wilks' lambda					2.51	.031*	0.58	.718
Positive Factor	10.3 (4.7)	10.7 (4.7)	13.7 (4.5)	13.6 (5.8)	4.07	.045*	0.011	.917
Negative Factor	17.5 (6.5)	16.4 (6.6)	20.3 (2.9)	20.4 (8.5)	2.48	.117	0.057	.811
Activation Factor	8.4 (3.2)	9.2 (4.5)	9.0 (3.6)	10.7 (4.4)	.82	.37	1.07	.302
Dysthymia Factor	8.7 (3.8)	9.5 (4.4)	13.7 (5.5)	12.4 (4.8)	8.51	.004**	0.049	.826
Autism Factor	11.2 (4.3)	11.1 (4.4)	15.0 (1.7)	14.4 (6.5)	5.85	.017*	0.079	.779
	$n = 122$	$n = 62$	$n = 3$	$n = 14$				

Note. There were no significant interactions between the ED diagnosis and sex factors.
*$p < .05$. **$p < .01$. *** $p < .001$.

even uncommon for research studies.

Sex differences mirrored those reported for ED in the population, as a significantly higher proportion of females than males (74.1% vs. 30%) comprised the group of schizophrenia cases with premorbid ED (Hudson et al., 2007). Female cases, with or without ED, had later onsets of psychosis and more education than males, as is well described in the schizophrenia literature (Andia et al., 1995; Galderisi et al., 2012). The females also had later onsets for ED. The onset of schizophrenia followed the ED diagnosis by 4 years for females and by 8 years for males. ED could thus represent a prodromal manifestation of a particular vulnerability pathway for schizophrenia. The lesser proportion of ethnic minorities in the group with premorbid ED is of interest, but must be replicated. If stress exposure plays a greater role in the etiology of schizophrenia for minorities, then the subtype of schizophrenia with premorbid ED may be less environmentally determined with a greater influence from genetic factors.

The cases with premorbid ED had similarly severe negative symptoms and functional impairments (GAF scores) as other cases, which were considered to be the "core" disturbance in schizophrenia by early theorists (Hoff, 2012). These deficits may have emerged before the diagnosis of schizophrenia in the ED cases, as impaired social function and poor perception of nonverbal gestures and vocal prosody is reported in AN, wherein social deficits are not related to anxiety, depression, body mass or other state measures (Bentz et al., 2017). Body dysmorphic preoccupations in a community sample, although not considered to be delusions, are nonetheless related to an increased psychosis proneness (Keating et al., 2016).

Together, these finding illuminate the keen overlap of the features of ED with schizophrenia related phenomenology. If ED is a prodromal illness feature for some schizophrenia cases, then worsening psychotic and disorganization symptoms, declining function and negative symptoms may herald the onset of schizophrenia. Supporting the notion that schizophrenia cases with premorbid ED have a distinct pathophysiology, this group demonstrated significantly more severe psychotic and disorganization symptoms during both the medication free and treatment phases, and higher depression scores in the treatment phase, in addition to their distinct cognitive profiles. By convention, the interoceptive misperceptions and false fixed beliefs concerning eating behaviors and body image in ED are not regarded as hallucinations and delusions, but this might deserve greater consideration in some portion of cases.

These features strikingly replicate the previously reported phenotype of medication-naïve schizophrenia cases in the Egyptian study (Fawzi and Fawzi, 2012). The cross-cultural similarity in phenotypes heightens the likelihood that a distinct biology underlies this subtype of schizophrenia, which may account for some heterogeneity in the illness. While the Egyptian study did not inquire about specific psychotic symptoms pertaining to food or weight, we had such items available from the DIGS interview, which directly inquires about somatic, olfactory, and gustatory psychotic symptoms. These items showed that lifetime and current gustatory hallucinations robustly distinguished schizophrenia cases with premorbid ED form other cases, which is consistent with several case reports (Miotto et al., 2010; Rojo-Moreno et al., 2011; Wenokur and Luby, 1997).

An additional strength of the current study in advancing our understanding of the overlap of ED and schizophrenia is our examination of symptoms across treatment phases, which demonstrate that the group differences are not a consequence of differential antipsychotic

Table 3
WAIS-III scores by ED diagnosis and sex.

	Schizophrenia Only		Schizophrenia + ED		ANOVA			
	Men ($n = 101$)	Women ($n = 53$)	Men ($n = 2$)	Women ($n = 14$)	ED Diagnosis		Sex	
	M (SD)	*M (SD)*	*M (SD)*	*M (SD)*	*F*	*P*	*F*	*P*
FSIQ	87.2 (13.4)	86.2 (13.7)	114.0 (7.1)	94.4 (13.2)	11.32	.001**	3.93	.049*
					MANOVA			
Multivariate Wilks' lambda					6.41	.002**	2.30	.104
PIQ	83.4 (15.5)	81.6 (13.8)	103.0 (8.5)	89.6 (13.1)	5.87	.016*	1.73	.185
VIQ	90.9 (13.7)	89.3 (15.3)	121.0 (4.2)	98.9 (14.7)	12.89	.000***	4.58	.034

Note. There were no significant interactions between the ED diagnosis and sex factors. WAIS-III: wechsler adult intelligence scale, third edition; FSIQ: full scale IQ; PIQ: performance IQ; VIQ: verbal IQ.
*$p < .05$. **$p < .01$. ***$p < .001$.

treatment.

Our cognitive data provide another novel finding, as cases with premorbid ED showed significantly higher intelligence overall, and demonstrated a higher VIQ and PIQ. Although there were scant males with ED who had IQ testing, these had a very high verbal intelligence. Nonetheless, the ED group showed relative deficits in PIQ compared to VIQ, consistent with a nonverbal learning issue. This nonverbal deficit, demonstrated through WAIS testing, aligns with the slower reaction times and impaired visuospatial processing reported for persons with anorexia on a battery that was developed for schizophrenia research (MATRICS) (Phillipou et al., 2015), and on the CANTAB cognitive assessment (Fowler et al., 2006). These prior reports and our cognitive findings do not conflict with the results from a meta-analysis of 30 studies showing higher average intelligence in AN than in the normative population, as this meta-analysis emphasized verbal tests (Lopez et al., 2010). Our findings may challenge the concept that cognitive deficits and negative symptoms tap a specific common defect in schizophrenia, as groups with and without premorbid ED showed similar negative symptoms and functional impairments, but those with premorbid ED showed significantly better IQ scores.

The double dissociation between worse/better psychotic symptoms and cognition argues that groups of schizophrenia cases defined by premorbid ED are not just more or less severe forms of a common pathology. The phenotypic differences in comorbidities, psychosis and disorganization symptoms, particularly unusual thoughts, intelligence profiles, and gustatory hallucinations may implicate distinct circuitries.

Bleuler proposed the name “schizophrenia” for the syndrome to reflect his hypothesis that its phenomenology arose from a split between emotion and thought, or cognition (Hoff, 2012). Such a disconnection could occur at different points in the neural circuitry. The posterior orbital (OPFC) and ventromedial Anterior Cingulate Cortex (ACC) have distinct and reciprocal interconnections through limbic regions to play complementary roles in sensory processing (Barbas, 2007). The prominent gustatory hallucinations for cases with premorbid ED may implicate the OFC, which is specialized for eating and receives interoceptive signals from the limbic system (Barbas, 1993). Schizophrenia cases without premorbid ED may have a greater pathology in the ACC, which is associated with attention (Botvinick et al., 1999; Johnston et al., 2007), which could explain their worse overall cognition. Nonetheless, the degree to which the OFC participates in many cognitive and emotional interactions is controversial (Stalnaker et al., 2015).

The overlap between schizophrenia and ED could implicate greater or different dopamine dysfunction, given its key role in appetitive motivation and behavior and with respect to psychotic symptoms (Salamone and Correa, 2002). ED and schizophrenia are also both conceptualized as disturbances of reward mechanisms (Avena and Bocarsly, 2012; Davis and Woodside, 2002) with some researchers arguing that dopamine-mediated reward sensitivity is required to sustain ED behaviors (Deckelman et al., 1997).

The genetic architecture of anorexia includes common gene variants also associated with the risk for schizophrenia (Bulik-Sullivan et al., 2015; Duncan et al., 2017). Another shared risk factor is advancing paternal age, which accounts for most of the *de novo* mutations introduced into the human gene pool (Racine et al., 2014; Javaras et al., 2017; Malaspina et al., 2001). The association of paternal age and schizophrenia is independent of parental risk scores supporting the de novo genetic origin of this risk (Wang et al., 2019). Phenotypic features of paternal age related schizophrenia, defined for cases with a paternal age greater than 34 years and no family history of psychosis, notably align with the phenotypic findings found for cases with premorbid ED based on ra hypothesis-independent K-means analysis, which identified one cluster of cases with significantly better verbal than performance IQ and another cluster that was 93% females in association with older fathers (Horwood et al., 2008). A hypothesis independent machine learning algorithm furthermore found later paternal age was the most influential variable for classifying schizophrenia cases, comparable to low function (Lee et al., 2011).

The differences in sex composition, psychotic and disorganization symptoms and cognitive function for schizophrenia cases with premorbid ED compared to other cases support schizophrenia with premorbid ED as a distinct subtype of schizophrenia. If so, the nature of sex differences in schizophrenia could be reconsidered. The larger proportion of the ED variant among females with schizophrenia could contribute to the observation of worse cognition in males and more affective disturbances in females (Han et al., 2012; Sota and Heinrichs, 2003). Alternatively, ED may be an inconsistently penetrant “forme fruste” of schizophrenia, given the breadth of overlapping phenomenology between the disorders; including unusual thought processes consistent with disorganization; fixed false beliefs which are delusions; anhedonia, social and functional deficits, and relative nonverbal intelligence deficits (Boehm et al., 2018; Rojo-Moreno et al., 2011; Steinglass et al., 2007; Striegel-Moore et al., 1999).

These data, although relatively small compared to genetic studies, is the most rigorous methodology that has been applied to understanding the association of premorbid ED with phenotypic features of schizophrenia, while replicating and extending previous observations. The analysis is post hoc, so assessments were unbiased by ED information. Along with the previous data, this work provides some support for the hypothesis that a particular pathophysiology underlies the schizophrenia that follow premorbid ED. It could involve the posterior OPC, and may improve with approaches for treatment refractory psychosis. The absence of anthropometric, metabolic data is regrettable, as schizophrenia cases frequently exhibit a myriad of metabolic disorders (metabolic syndrome, obesity, diabetes, etc.), which could be related to the premorbid ED (Ilyas et al., 2018).

In conclusion, this study demonstrated that premorbid ED is not uncommon in schizophrenia, and that such cases have different phenotypic features from other schizophrenia cases. We propose that it could represent a homogeneous subgroup of cases in the schizophrenia syndrome. Disordered eating should be further evaluated as an influential feature for psychosis risk in prodromal persons and as an indication for treatment approaches aimed at more refractory psychotic symptoms.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2019.06.035.

References

Andia, A.M., Zisook, S., Heaton, R.K., Hesselink, J., Jernigan, T., Kuck, J., Morganville, J., Braff, D.L., 1995. Gender differences in schizophrenia. J. Nerv. Ment. Dis. 183, 522–528.

Association, A.P., 2013. No Title, in: Diagnostic and Statistical Manual of Mental Disorders. Arlington.

Association, A.P., 2000. Diagnostic and Statistical Manual of Mental Disorders. 4th ed. Washington, D.C.

Avena, N.M., Bocarsly, M.E., 2012. Dysregulation of brain reward systems in eating disorders: neurochemical information from animal models of binge eating, bulimia nervosa, and anorexia nervosa. Neuropharmacology 63, 87–96. https://doi.org/10.1016/j.neuropharm.2011.11.010.

Barbas, H., 2007. Flow of information for emotions through temporal and orbitofrontal pathways. J. Anat. 211, 237–249. https://doi.org/10.1111/j.1469-7580.2007.00777.x.

Barbas, H., 1993. Organization of cortical afferent input to orbitofrontal areas in the rhesus monkey. Neuroscience 56, 841–864 https://doi.org/https://doi.org/10.1016/0306-4522(93)90132-Y.

Barbato, G., Fichele, M., Senatore, I., Casiello, M., Muscettola, G., 2006. Increased dopaminergic activity in restricting-type anorexia nervosa. Psychiatry Res. 142, 253–255. https://doi.org/10.1016/j.psychres.2005.07.031.

Bentz, M., Jepsen, J.R.M., Kjaersdam Telléus, G., Moslet, U., Pedersen, T., Bulik, C.M., Plessen, K.J., 2017. Neurocognitive functions and social functioning in young females with recent-onset anorexia nervosa and recovered individuals. J. Eat. Disord. 5, 5. https://doi.org/10.1186/s40337-017-0137-3.

Boehm, I., Flohr, L., Steding, J., Holzapfel, L., Seitz, J., Roessner, V., Ehrlich, S., 2018. The

trajectory of anhedonic and depressive symptoms in anorexia nervosa: a longitudinal and cross-sectional approach. Eur. Eat. Disord. Rev. 26, 69–74. https://doi.org/10.1002/erv.2565.
Bosanac, P., Norman, T., Burrows, G., Beumont, P., 2005. Serotonergic and dopaminergic systems in anorexia nervosa: a role for atypical antipsychotics? Aust. N. Z. J. Psychiatry 39, 146–153. https://doi.org/10.1080/j.1440-1614.2005.01536.x.
Botvinick, M., Nystrom, L.E., Fissell, K., Carter, C.S., Cohen, J.D., 1999. Conflict monitoring versus selection-for-action in anterior cingulate cortex. Nature 402, 179.
Brambilla, F., Garcia, C.S., Fassino, S., Daga, G.A., Favaro, A., Santonastaso, P., Ramaciotti, C., Bondi, E., Mellado, C., Borriello, R., Monteleone, P., 2007. Olanzapine therapy in anorexia nervosa: psychobiological effects. Int. Clin. Psychopharmacol. 22, 197–204. https://doi.org/10.1097/YIC.0b013e328080ca31.
Brandys, M.K., de Kovel, C.G.F., Kas, M.J., van Elburg, A.A., Adan, R.A.H., 2015. Overview of genetic research in anorexia nervosa: the past, the present and the future. Int. J. Eat. Disord. 48, 814–825. https://doi.org/10.1002/eat.22400.
Bulik-Sullivan, B., Finucane, H.K., Anttila, V., Gusev, A., Day, F.R., Loh, P.-R., Duncan, L., Perry, J.R.B., Patterson, N., Robinson, E.B., Daly, M.J., Price, A.L., Neale, B.M., 2015. An atlas of genetic correlations across human diseases and traits. Nat. Genet. 47, 1236–1241. https://doi.org/10.1038/ng.3406.
Davis, C., Woodside, D.B., 2002. Sensitivity to the rewarding effects of food and exercise in the eating disorders. Compr. Psychiatry 43, 189–194.
Deckelman, M.C., Dixon, L.B., Conley, R.R., 1997. Comorbid bulimia nervosa and schizophrenia. Int. J. Eat. Disord. 22, 101–105.
Delsedime, N., Nicotra, B., Giovannone, M.C., Marech, L., Barosio, M., Marzola, E., Abbate-Daga, G., Fassino, S., 2013. Psychotic symptoms in a woman with severe anorexia nervosa : psychotic symptoms in anorexia nervosa. Eat. Weight Disord. 18, 95–98. https://doi.org/10.1007/s40519-013-0009-z.
Duncan, L., Yilmaz, Z., Gaspar, H., Walters, R., Goldstein, J., Anttila, V., Bulik-Sullivan, B., Ripke, S., Thornton, L., Hinney, A., Daly, M., Sullivan, P.F., Zeggini, E., Breen, G., Bulik, C.M., 2017. Significant locus and metabolic genetic correlations revealed in genome-wide association study of anorexia nervosa. Am. J. Psychiatry 174, 850–858. https://doi.org/10.1176/appi.ajp.2017.16121402.
Fawzi, M.H., Fawzi, M.M., 2012. Disordered eating attitudes in Egyptian antipsychotic naive patients with schizophrenia. Compr. Psychiatry 53, 259–268. https://doi.org/10.1016/j.comppsych.2011.04.064.
Fowler, L., Blackwell, A., Jaffa, A., Palmer, R., Robbins, T.W., Sahakian, B.J., Dowson, J.H., 2006. Profile of neurocognitive impairments associated with female in-patients with anorexia nervosa. Psychol. Med. 36, 517–527. https://doi.org/10.1017/S0033291705006379.
Frank, G.K.W., Shott, M.E., DeGuzman, M.C., 2019. Recent Advances in Understanding Anorexia Nervosa. F1000 Research 8. https://doi.org/10.12688/f1000research.17789.1.
Galderisi, S., Bucci, P., Ucok, A., Peuskens, J., 2012. No gender differences in social outcome in patients suffering from schizophrenia. Eur. Psychiatry 27, 406–408. https://doi.org/10.1016/j.eurpsy.2011.01.011.
Han, M., Huang, X.-F., Chen, D.C., Xiu, M.H., Hui, L., Liu, H., Kosten, T.R., Zhang, X.Y., 2012. Gender differences in cognitive function of patients with chronic schizophrenia. Prog. Neuropsychopharmacol. Biol. Psychiatry 39, 358–363. https://doi.org/10.1016/j.pnpbp.2012.07.010.
Hoff, P., 2012. Eugen bleuler's concept of schizophrenia and its relevance to present-day psychiatry. Neuropsychobiology 66, 6–13. https://doi.org/10.1159/000337174.
Horwood, J., Salvi, G., Thomas, K., Duffy, L., Gunnell, D., Hollis, C., Lewis, G., Menezes, P., Thompson, A., Wolke, D., Zammit, S., Harrison, G., 2008. IQ and non-clinical psychotic symptoms in 12-year-olds: results from the ALSPAC birth cohort. Br. J. Psychiatry 193, 185–191. https://doi.org/10.1192/bjp.bp.108.051904.
Hudson, J.I., Hiripi, E., Pope, H.G.J., Kessler, R.C., 2007. The prevalence and correlates of eating disorders in the national comorbidity survey replication. Biol. Psychiatry 61, 348–358. https://doi.org/10.1016/j.biopsych.2006.03.040.
Ilyas, A., Hubel, C., Stahl, D., Stadler, M., Ismail, K., Breen, G., Treasure, J., Kan, C., 2018. The metabolic underpinning of eating disorders: a systematic review and meta-analysis of insulin sensitivity. Mol. Cell. Endocrinol. https://doi.org/10.1016/j.mce.2018.10.005.
Javaras, K.N., Rickert, M.E., Thornton, L.M., Peat, C.M., Baker, J.H., Birgegard, A., Norring, C., Landen, M., Almqvist, C., Larsson, H., Lichtenstein, P., Bulik, C.M., D'Onofrio, B.M., 2017. Paternal age at childbirth and eating disorders in offspring. Psychol. Med. 47, 576–584. https://doi.org/10.1017/S0033291716002610.
Johnston, K., Levin, H.M., Koval, M.J., Everling, S., 2007. Top-down control-signal dynamics in anterior cingulate and prefrontal cortex neurons following task switching. Neuron 53, 453–462. https://doi.org/10.1016/j.neuron.2006.12.023.
Keating, C., Thomas, N., Stephens, J., Castle, D.J., Rossell, S.L., 2016. Dysmorphic concern is related to delusional proneness and negative affect in a community sample. Psychiatry Res. 240, 76–79. https://doi.org/10.1016/j.psychres.2016.03.052.
Kouidrat, Y., Amad, A., Lalau, J.-D., Loas, G., 2014. Eating disorders in schizophrenia: implications for research and management. https://doi.org/10.1155.
Lee, H., Malaspina, D., Ahn, H., Perrin, M., Opler, M.G., Kleinhaus, K., Harlap, S., Goetz, R., Antonius, D., 2011. Paternal age related schizophrenia (PARS): latent subgroups detected by k-means clustering analysis. Schizophr. Res. 128, 143–149. https://doi.org/10.1016/j.schres.2011.02.006.
Lopez, C., Stahl, D., Tchanturia, K., 2010. Estimated intelligence quotient in anorexia nervosa: a systematic review and meta-analysis of the literature. Ann. Gen. Psychiatry 9, 40. https://doi.org/10.1186/1744-859X-9-40.
Malaspina, D., Harlap, S., Fennig, S., Heiman, D., Nahon, D., Feldman, D., Susser, E.S., 2001. Advancing paternal age and the risk of schizophrenia. Arch. Gen. Psychiatry 58, 361–367.
Miotto, P., Pollini, B., Restaneo, A., Favaretto, G., Sisti, D., Rocchi, M.B.L., Preti, A., 2010. Symptoms of psychosis in anorexia and bulimia nervosa. Psychiatry Res 175, 237–243. https://doi.org/10.1016/j.psychres.2009.03.011.
Mondraty, N., Birmingham, C.L., Touyz, S., Sundakov, V., Chapman, L., Beumont, P., 2005. Randomized controlled trial of olanzapine in the treatment of cognitions in anorexia nervosa. Australas. Psychiatry 13, 72–75. https://doi.org/10.1080/j.1440-1665.2004.02154.x.
Nurnberger, J.I.J., Blehar, M.C., Kaufmann, C.A., York-Cooler, C., Simpson, S.G., Harkavy-Friedman, J., Severe, J.B., Malaspina, D., Reich, T., 1994. Diagnostic interview for genetic studies. Rationale, unique features, and training. NIMH genetics initiative. Arch. Gen. Psychiatry 51, 844–849.
Phillipou, A., Abel, L.A., Castle, D.J., Hughes, M.E., Gurvich, C., Nibbs, R.G., Rossell, S.L., 2015. Self perception and facial emotion perception of others in anorexia nervosa. Front. Psychol. 6, 1181. https://doi.org/10.3389/fpsyg.2015.01181.
Powers, M.B., Halpern, J.M., Ferenschak, M.P., Gillihan, S.J., Foa, E.B., 2010. A meta-analytic review of prolonged exposure for posttraumatic stress disorder. Clin. Psychol. Rev. 30, 635–641. https://doi.org/10.1016/j.cpr.2010.04.007.
Racine, S.E., Culbert, K.M., Burt, S.A., Klump, K.L., 2014. Advanced paternal age at birth: phenotypic and etiologic associations with eating pathology in offspring. Psychol. Med. 44 (5), 1029–1041. https://doi.org/10.1017/S0033291713001426.
Rojo-Moreno, L., Plumed, J.J., Fons, M.B., Gonzalez-Piqueras, J.C., Rojo-Bofill, L., Livianos, L., 2011. Auditory hallucinations in anorexia nervosa. Eur. Eat. Disord. Rev. 19, 494–500. https://doi.org/10.1002/erv.1084.
Salamone, J.D., Correa, M., 2002. Motivational views of reinforcement: implications for understanding the behavioral functions of nucleus accumbens dopamine. Behav. Brain Res. 137, 3–25.
Seeman, M.V, 2014. Eating disorders and psychosis: seven hypotheses. World J. Psychiatry 4, 112–119. https://doi.org/10.5498/wjp.v4.i4.112.
Sota, T.L., Heinrichs, R.W., 2003. Sex differences in verbal memory in schizophrenia patients treated with "typical" neuroleptics. Schizophr. Res. 62, 175–182.
Stalnaker, T.A., Cooch, N.K., Schoenbaum, G., 2015. What the orbitofrontal cortex does not do. Nat. Neurosci. 18, 620.
Steinglass, J.E., Eisen, J.L., Attia, E., Mayer, L., Walsh, B.T., 2007. Is anorexia nervosa a delusional disorder? An assessment of eating beliefs in anorexia nervosa. J. Psychiatr. Pract. 13, 65–71. https://doi.org/10.1097/01.pra.0000265762.79753.88.
Striegel-Moore, R.H., Garvin, V., Dohm, F.A., Rosenheck, R.A., 1999. Psychiatric comorbidity of eating disorders in men: a national study of hospitalized veterans. Int. J. Eat. Disord. 25, 399–404.
Wade, T.D., 2019. Recent research on bulimia nervosa. Psychiatr. Clin. North Am. 42, 21–32. https://doi.org/10.1016/j.psc.2018.10.002.
Wang, S.H., Hsiao, P.C., Yeh, L.L., Liu, C.M., Liu, C.C., Hwang, T.J., Hsieh, M.H., Chien, Y.L., Lin, Y.T., Huang, Y.T., Chen, C.Y., Chandler, S.D., Faraone, S.V., Neale, B., Glatt, S.J., Tsuang, M.T., Hwu, H.G., Chen, W.J., 2019. Advanced paternal age and early onset of schizophrenia in sporadic cases: not confounded by parental polygenic risk for schizophrenia. Biol. Psychiatry [Epub ahead of print] pii: S0006-3223(19)30069-1.
Wechsler, D., 1981. Manual for the wechsler adult intelligence scale-revised (WAIS-R). Psychol. Corp.
Wenokur, B., Luby, E.D., 1997. Anorexia nervosa presenting as a somatic delusional disorder responsive to pharmacotherapy. J. Am. Osteopath. Assoc. 97, 231–232.
White, L., Harvey, P.D., Opler, L., Lindenmayer, J.P., 1997. Empirical assessment of the factorial structure of clinical symptoms in schizophrenia. A multisite, multimodel evaluation of the factorial structure of the positive and negative syndrome scale. The PANSS study group. Psychopathology 30, 263–274. https://doi.org/10.1159/000285058.