Title: Altered Functioning of Reward Circuitry in Youth Offspring of Parents with Bipolar Disorder

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Abstract

IMPORTANCE

Offspring of parents with BD (BO) are at higher risk of bipolar disorder (BD) than offspring of parents with non-BD psychopathology (NBO), although both groups are at higher risk than offspring of psychiatrically healthy parents (HC) for other affective and psychiatric disorders. Abnormal functioning in reward circuitry has been demonstrated previously in individuals with BD.

OBJECTIVE

To determine whether activation and functional connectivity in reward circuitry circuitry during decision-making differentiated BO, NBO and HC.

DESIGN, SETTING, AND PARTICIPANTS

This study was conducted at the University of Pittsburgh Medical Center. BO (n=29;mean age=13.8 years;14 female), NBO (n=28;mean age=13.9 years;12 female) and HC (n=23;mean age=13.7 years;11 female) were scanned while performing a number guessing reward task. 11 BO and 12 NBO had current non-BD psychopathology; 5 BO and 4 NBO were taking psychotropic medications.

MAIN OUTCOMES AND MEASURES

Region-of-interest analyses examined neural activation within prefrontal-ventral striatal reward circuitry and functional connectivity between bilateral ventral striatum (VS) and right ventrolateral prefrontal cortex during a reward paradigm (win, loss, and control conditions).

RESULTS

A 3(Group) x 2(Conditions:Win-Control/Loss-Control) ANOVA revealed a main effect of Group on right frontal pole activation: BO showed significantly greater activation than HC. There was a significant main effect of Group on functional connectivity between bilateral ventral striatum (VS) and right ventrolateral prefrontal cortex (voxel $p<0.001$, cluster $p<0.05$): BO showed significantly greater

inverse functional connectivity than other participants. These between-group differences remained after removing youth with psychiatric disorders and psychotropic medications from analyses.

CONCLUSIONS AND RELEVANCE

This is the first study to demonstrate that reward circuitry functioning distinguishes BO from NBO and HC. The fact that the pattern of findings remained when comparing healthy BO vs. healthy NBO vs. HC suggests that these neuroimaging measures may represent neurobiological markers conferring either risk for, or protection against, BD in youth.

Introduction

It is well established that offspring of parents with bipolar disorder (BD) are at increased risk of developing anxiety disorders and BD.[1-3] Furthermore, offspring of parents with BD (BO) are at higher risk of BD than offspring of parents with non-BD psychopathology (NBO), although both groups are at higher risk than offspring of psychiatrically healthy parents (HC) for other affective disorders.[2] Little is known regarding the neurophysiological processes that predispose to, or protect from, risk for BD versus risk for other affective and psychiatric disorders in these offspring, however, given that no study has directly compared neurophysiological processes in BO, NBO and HC. Critically, studies examining these processes have potential to help identify biomarkers denoting which at-risk offspring are most likely to develop which specific psychiatric disorders in the future, and ultimately provide biological targets to guide early interventions for these individuals. Neuroimaging studies are appropriate as a way forward in this research field, as they can determine the extent to which BO and NBO show abnormal functioning in neural circuitries supporting information processing domains known to be aberrant in individuals with established BD. One such information processing domain is reward processing, as an increasing number of studies reported abnormally heightened reward sensitivity in individuals with BD.[4-6]

Reward circuitry comprises a complex, highly-interconnected network of fronto-subcortical regions.[7,8] The ventral striatum (VS) supports reward anticipation and prediction error,[9-13] the pallidum encodes expected reward value,[14] the amygdala, stimulus-value associations,[15] and the putamen, action-specific value signals[16] and effort costs.[17] Different prefrontal cortical (PFC) regions contribute differently to reward processing and decision-making.[18] The ventromedial prefrontal (vmPFC) and the orbitofrontal (OFC) cortices encode reward values and compare values of different options.[19] The ventrolateral PFC (vlPFC) encodes the value of choice/decision-making options and is important for credit assignment.[20] The frontal polar (FP) region encodes the value of a non-chosen option during decision-making,[19] responds in situations of uncertainty,[21] and maintains possible behavioral choices[22]

and intentions[23] in memory for future use. The anterior cingulate cortex (ACC) is involved in cost-benefit decision-making[24,25] and action-reward associations.[18] Neuroimaging studies report abnormal functioning in reward circuitry in individuals with BD during reward and loss expectation and processing, in particular, elevated activity in vmPFC, OFC, vlPFC, FP and striatum,[26-32] and reduced inverse VS-vlPFC functional connectivity.[33]

Many components of reward neural circuitry undergo developmental changes during adolescence[34,35] and have different maturation curves.[36,37] For example, the later maturation of the prefrontal cortex[37] may underlie the difficulty in regulating behaviors in potentially rewarding contexts, and the high prevalence of risky behaviors, in adolescence.[38-40] In parallel, studies report that youth with BD, relative to healthy youth, show impaired reward learning[41,41] and greater reward-related arousal.[43,44] Genetic risk for BD (and other affective disorders) may thus influence the course of reward circuitry maturation, leading to heightened reward sensitivity, that ultimately predispose to development of BD.

No study to date compared reward circuitry functioning in BO and NBO who have not as yet developed BD, and HC, although one recent study showed elevated vlPFC activity and altered vlPFC-ACC functional connectivity during reward processing in healthy BO vs. HC.[45] In the present study, we thus aimed to identify the effect of familial genetic risk for BD (BO>NBO>HC) on activation and functional connectivity in reward circuitry by comparing these neural measures in BO vs. NBO vs. HC during a decision-making task.[46] Choice of regions in reward circuitry was determined from previous neuroimaging findings.[7-25] Given that NBO, like BO, are at significantly higher risk for affective and other psychiatric disorders than HC,[2] inclusion of NBO allowed us to control for risk for non-BD disorders in BO. BO and NBO included youth with and without current non-BD psychopathology, some of whom were treated with psychotropic medications. This allowed us to determine the effect of genetic risk for BD on reward circuitry functioning in participants without current psychopathology and psychotropic medication.

Based on the above neuroimaging findings in adults and youth with BD, we hypothesized the following:

1. Given previous findings showing abnormally elevated fronto-striatal activity in individuals with BD,[26-32] we hypothesized that BO (who are at highest risk for BD) would show abnormally elevated activity in this circuitry during reward processing, relative to NBO and HC.
2. Given a key role of the VS in reward processing,[9-13] and previous findings showing altered functional connectivity between VS and anterioventral prefrontal cortex in individuals with BD versus HC,[33] we hypothesized that BO, but not NBO, would show significantly altered functional connectivity between these regions during reward processing compared with HC.
3. This differential pattern of reward circuitry functioning between BO and other participants would be present in participants without current psychiatric diagnoses and unmedicated participants.

Methods and Materials

The Bipolar Offspring Study (BIOS) is an ongoing longitudinal study examining psychiatric symptomatology in youth offspring of parents with BD[2] and functioning in neural circuitries underlying information processing domains implicated in the pathogenesis of BD, including reward circuitry. The study was approved by the Institutional Review Board of the University of Pittsburgh. Prior to study participation, parents/guardians provided written informed consent, and children provided written informed assent. Participants received monetary compensation for their participation.

Participants

Three groups of participants aged 7-17 years who were not affected with BD took part in this study: youth offspring of parent(s) with BD (BO;n=35), youth offspring of parent(s) with non-BD psychopathology (NBO;n=37) and psychiatrically healthy youth offspring of psychiatrically healthy

parents (HC;n=25) without family history of any psychiatric disorders (including first-degree relatives). Twenty-four HC were recruited from the healthy comparison youth group of the Longitudinal Assessment of Manic Symptoms (LAMS) study[47,48] at the University of Pittsburgh Medical Center/Western Psychiatric Institute and Clinic, a parallel study examining neural circuitry functioning in youth with behavioral and emotional dysregulation. One HC was recruited from BIOS. Most BO and NBO were recruited from BIOS,[1] with the exception of 2 BO and 5 NBO, who were recruited from LAMS.[47,48]

Exclusion criteria for all participants were: systemic medical illness, neurological disorders, head trauma, alcohol or illicit substance use, standard exclusion criteria for MRI research (metal in the head or body, claustrophobia, etc), IQ<70 (using the Weschler Abbreviated Scale of Intelligence[49]), unable to read and write in standard English, and corrected far visual acuity worse than 20/40 on the Snellen visual acuity test. Six BO, 9 NBO, and 2 HC were excluded from data analysis due to inability to complete the scanning session or due to excessive motion in the scanner (translation≥4mm in any direction). The total numbers of participants with usable fMRI data were:29 BO, 28 NBO, and 23 HC. Eleven BO and 12 NBO had current non-BD psychopathology. Five BO and 4 NBO were taking one class of psychotropic medications (Table 1). Given ethical concerns with stopping medication for research participation, participants were permitted to use prescribed medication(s) before, and on the day of, scanning.

Assessment procedures

Parental psychopathology was ascertained by a trained clinician using the Structural Clinical Interview for DSM-IV (SCID-I)[50] for BIOS youth, and using detailed clinical assessment for LAMS youth. Another trained clinician, blind to the parent's condition, interviewed the parents about their children, and also interviewed their children, using the Kiddie Schedule for Affective Disorders and Schizophrenia-Present and Lifetime version (KSADS-PL).[51] All cases were supervised by a "blind"

child psychiatrist who was responsible for the ultimate parental and children diagnoses. Inter-rater reliability for all psychiatric diagnoses ascertained through the KSADS>.8.

On the day of scan, parents/guardians of youth participants completed the PGBI-10M (Parent Version, General Behavior Inventory,[52] to assess the severity of behavioral and emotional dysregulation in their offspring during the last 6 months; only parents of BO and NBO completed this questionnaire); the SCARED-P (Self-Report for Childhood Anxiety Related Emotional Disorders, parent version, to assess offspring anxiety over last 2 weeks);[53] the CALS-P (The Children's Affective Lability scale, parent version);[54] the MFQ-P (Mood and Feelings Questionnaire, parent version, to assess the severity of depression during the last 2 weeks);[55] and a questionnaire to assess sociodemographic status represented by parental education.[56] Youth participants completed child report versions of affective symptomatology scales: the CALS-C, SCARED-C, MFQ-C. All participants completed medication forms that documented psychotropic medications used that day, during the last 24 hours, and those used on regular basis; drug/alcohol/pregnancy screens; the Edinburgh Handedness Inventory (EHI;[57] and the Snellen visual acuity test. Table 1 reports demographic and clinical variables. Table S1 reports demographic and clinical variables for youth without psychopathology and youth untreated with psychotropic medications. Table 2 reports lifetime psychiatric diagnoses in parents.

Reward task

Participants were scanned while performing a number guessing reward task[46] (*Supplemental Methods*, Figure 1) that activates fronto-striatal reward circuitry, and has been used previously in neuroimaging studies of adults and youth with mood disorders.[46,58]

fMRI data acquisition and analysis

fMRI data were acquired using a Siemens MAGNETOM TrioTim 3T MR system. Acquisition parameters, preprocessing and co-registration procedures are described in *Supplemental Methods*. fMRI data were analyzed using FSL5.0.2(www.fmrib.ox.ac.uk/fsl). Preprocessed data were submitted to a

first-level GLM analysis implemented using FEAT (FMRI Expert Analysis Tool,v6.0). The model included four regressors (Win, Loss, and Control trials, and Instructions). The magnitude of activation was examined for each of these conditions and to the Win-Control, Loss-Control, and Win-Loss contrasts. All group-level analyses were conducted using FLAME1 (FMRIB's Local Analysis of Mixed Effects). Significant clusters of activation were determined by thresholding Z-statistic images in the reward circuitry mask using voxel-wise $p<0.001$ ($z>3.09$) and a corrected cluster significance threshold of $p<0.05$.[59]

Hypothesis 1 testing

Activity in the reward circuitry ROI:

Brain activation in the reward circuitry ROI was analyzed using a 3(Group: BO/NBO/HC)x2(Condition:Win-Control/Loss-Control) ANOVA. The reward circuitry ROI mask was the anatomical mask used in a previous study[58] that examined reward circuitry function in emotionally dysregulated youth, using the same reward task. The mask included key neural regions implicated in reward processing: bilateral dorsal ACC(BA24/32), medial and lateral FP(BA10), OFC(BA11), vlPFC(BA47), and ventral striatum (VS; spherical ROIs with radius of 8mm centered [±9,9,−8]).

Hypothesis 2 testing

Functional connectivity between bilateral VS and the reward circuitry mask:

Functional connectivity was examined using psychophysiological interaction (PPI) analysis,[60] in FEAT. The bilateral VS served as a seed region and the reward circuitry mask served as a target region. The PPI first-level analysis model included four psychological regressors (Win, Loss, and Control trials, and Instructions), one physiological regressor—a mean time course extracted from the seed region, and three interaction terms between the physiological and Win, Loss and Control regressors. To parallel the activation analysis, the group-level connectivity analysis was conducted using a 3(Group)x2(Condition) ANOVA.

Post-hoc tests

To determine the direction of the between- or within-group effects, post-hoc t-tests of activation and connectivity values (parameter estimates extracted from the significant activation and connectivity clusters) were conducted in R (http://www.r-project.org/) and Bonferroni corrected to control for multiple t-tests.

Hypothesis 3 testing

Here, we examined the effect of diagnosis and medications on activation and connectivity in the brain regions identified in the previous analyses. For this purpose, we first extracted activation and connectivity values from the significant clusters. Then, we conducted two 3x2 ANOVAs, using SPSS, on 1) participants without diagnoses; 2) unmedicated participants.

Results

Behavioral data

There were no between-group differences in decision-making reaction time across all trials or across Reward and Loss trials separately.

Neuroimaging

Hypothesis 1

Activation

A 3(Group:BO/NBO/HC)x2(Condition:Win-Control/Loss-Control) ANOVA revealed main effects of Group (Figure 2A) and Condition (Table S2), but no Group x Condition interaction, on brain activation. A main effect of Group was found in the right frontal pole (RFP; nvox=66, z-max=4.0, [24,64,6]). Follow up t-tests conducted on RFP activation values revealed that activation was significantly greater in BO than HC ($t(50)=3.7$, $p<0.001$), and just missed significance in BO vs. NBO ($t(55)=2.3$, $p=0.02$), using a Bonferroni-corrected statistical threshold of $p=0.05/3$ for between group

tests p=0.017.

Hypothesis 2

Connectivity

The PPI analyses conducted with the bilateral VS as a seed region and the reward circuitry mask as a target region revealed a main effect of Group (Figure 2B), but no main effect of Condition or Group x Condition interaction, on functional connectivity. A main effect of Group was found in the right vlPFC(nvox=96, z-max=4.7, [40,46,-10]). Follow up t-tests revealed that functional connectivity between bilateral VS and right vlPFC was significantly more negative in BO than NBO (t(55)=-3.3, p=0.002) and in BO than HC (t(50)=-6.2, p<0.001), using a Bonferroni-corrected threshold of p=0.017, as above.

Hypothesis 3

Activation and connectivity

The results of RFP activation and bilateral VS-right vlPFC connectivity analyses in unmedicated participants and those without psychopathology were consistent with the results of the full-sample analyses testing Hypotheses 1-2. There was a significant effect of Group on RFP activation (participants without psychopathology: F(2,54)=11.1, p<0.001; unmedicated participants: F(2,68)=7.3, p=0.001; Figure S1), and on bilateral VS-right vlPFC functional connectivity (participants without psychopathology: F(2,54)=14.4, p<0.001; unmedicated participants: F(2,68)=16.1, p<0.001; Figure S2). The results of the post-hoc comparisons have paralleled main findings from *Hypotheses 1-2*, and are in *Supplemental Results*.

Exploratory analyses

Across all participants, RFP activation positively correlated with CALS-P (r=0.34, p=0.002) and MFQ-P (r=0.23, p=0.047). In BO, RFP activation positively correlated with CALS-P (r=0.37,

$p<0.05$).

Discussion

The goal of the present study was to determine the extent to which alterations in reward circuitry function characterized at-risk youth offspring of parents with BD (BO) relative to offspring of non-bipolar parents (NBO) and healthy youth offspring of psychiatrically healthy parents (HC). Main findings supported all three hypotheses, that activation and functional connectivity in the reward circuitry are associated with genetic risk for BD. RFP activation for decision (Win and Loss) trials, relative to non-decision (Control) trials, was significantly greater in BO than in HC. In contrast, bilateral VS-right vlPFC functional connectivity was significantly more inverse in BO than in NBO and HC. These patterns of activation and functional connectivity remained for umedicated participants and those without psychopathology, supporting our third hypothesis.

The FP is involved in decision-making and prospective memory by supporting the maintenance of delayed intentions and representations[22,23] and integrating outcomes of previous trials[61] for potential use in future trials. The magnitude of FP activation positively correlated with amount of uncertainty remaining between multiple choices,[21] and tracked unchosen options.[19] Abnormally elevated RFP activation during decision-making trials in BO suggests that they may have experienced abnormal levels of uncertainty during these trials, and maintained non-chosen option-outcome contingencies in memory to predict (i.e., make more certain) response-outcome mapping for future trials. Furthermore, similar patterns of significantly elevated RFP activation during decision-making trials were present in unmedicated BO and NBO vs. HC, and in BO and NBO without psychopathology vs. HC. A recent study demonstrated a similar pattern of significantly greater activation in the right frontal cortex [x=11,y=55, z=14] during reward anticipation in adolescents with BD vs. HC.[31] Taken together, these findings suggest that abnormally elevated RFP activation may represent a vulnerability marker for future development of affective disorders.

The VS supports reward anticipation, reward evaluation and prediction error.[9-13] The vlPFC is

implicated in learning the value of different options and formation of associations between visual stimuli and reward values.[18] Functional interaction between prefrontal cortex and VS influences guided behavior and may be modulated by the environment.[62] In HC, an increase in bilateral VS activation was associated with increase in right vlPFC activation during decision-making vs. non-decision-making trials, highlighting a positive relationship between encoding stimulus-outcome associations and reward evaluation. In BO, an inverse relationship between these regions suggests that learning stimulus-outcome associations may impede reward evaluation, and vice versa.

Given that BO not only differed from HC, but also differed from NBO on the direction of VS-vlPFC functional connectivity, and that this pattern remained significant even for unmedicated participants and those without psychopathology, inverse bilateral VS-right vlPFC functional connectivity during decision-making trials may reflect a vulnerability marker for BD, rather than for affective disorders in general. Because the between-group differences in functional connectivity were independent of the fact that BO, NBO and HC did not differ significantly in magnitude of activation in these regions, our findings may provide further support for dysfunctional coupling between the vlPFC and subcortical regions during emotionally-salient processing as a pathophysiological process underlying vulnerability to BD.[63,64]

Exploratory analyses showed that greater RFP activation was associated with higher mood dysregulation scores (CALS-P) and higher MFQ across all participants, and with higher CALS-P in BO. Higher RFP activation during decision-making trials may thus be a precursor for development of mood dysregulation and depression. Future studies need to examine these exploratory findings.

The fact that findings remained significant even after approximately 40% of participants were removed for comparisons of healthy BO vs. healthy NBO vs. HC suggests that the pattern of findings was robust, at least with regard to the general BO and NBO populations. Given that only a small number of youth were taking medications, there was insufficient statistical power to directly compare unmedicated BO vs. medicated BO vs. unmedicated NBO vs. medicated NBO. Further studies should

compare larger samples of medicated and unmedicated BO and NBO, and BO and NBO with and without current diagnoses. Additionally, future studies can also directly compare youth with established BD, and genetically and symptomatically at-risk youth, to determine the degree of similarity between neural measures of risk status and neural measures of BD.

In summary, our findings demonstrate, for the first time, that youth offspring, as yet unaffected with BD, of parents with BD exhibit altered patterns of frontal activation and vlPFC-striatal functional connectivity, that distinguish these youth from youth offspring of parents unaffected with BD. These activation and connectivity differences remained significant for participants without current psychopathology and medication history and may represent neurobiological markers conferring either risk for, or protection against, BD in youth. Future, longitudinal follow-up studies in youth at-risk for BD should aim to distinguish between these two possibilities, by determining the extent to which abnormal patterns of reward circuitry functioning predict, or protect against, development of BD, and development/worsening of affective pathology in general.

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Author Contributions: Drs. Manelis had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Figure Captions

Figure 1. An example of a Win trial in the reward task. A green arrow shows that a subject correctly guessed that the number was greater than 5.

Figure 2. A main effect of Group on activation in the right frontal pole (RFP [24 64 6]; shown in red) and functional connectivity between the bilateral VS (centered 8 mm around [±9 9 -8]; shown in green) and the right vlPFC ([40 46 -10]; shown in blue) for decision-making trials (i.e., Win and Loss trials) vs. non-decision-making trials (i.e., Control trials). The reward circuitry ROI mask is shown in yellow. "au" stands for arbitrary units. '*' indicates significant t-test results. BO – offspring of parents with bipolar disorder, NBO – offspring of parents with psychiatric disorders other than bipolar disorder, HC – healthy offspring of psychiatrically healthy parents.

Tables

Table 1

Demographic and clinical variables

	BO n=29	NBO n=28	HC n=23	Statistics	p-value
Number of youth without psychiatric diagnoses	18 (62%)	16 (57%)	23 (100%)	BO vs. NBO $\chi2(2)<1$	ns
Number of youth untreated with psychotropic medications	24(83%)	24(86%)	23(100%)	BO vs. NBO $\chi2(2)<1$	ns
Age at scan	13.81(2.45)	13.93(2.38)	13.74(1.80)	$F(2,77)<1$	ns
Gender (female)	14	12	11	$\chi2(2)<1$	ns
Handedness (right hand)	26	26	21	Yates' $\chi2(2)<1$	ns
IQ (WASI)	103.21(14.51)	102.86(14.33)	105.78(13.79)	$F(2,77)<1$	ns
SES based on parental education	5.48(0.95)	5.54(0.96)	5.30(1.02)	$F(2,77)<1$	ns
		Medications			
antidepressants	na	sertraline HCI: n=1	na		
antipsychotics	Risperidone: n=1 Quetiapine Fumarate: n=1	na	na		
mood stabilizers	na	na	na		
stimulants	amphetamine, dextroamphetamine mixed salts: n=1	methylphenidate: n=1 amphetamine, dextroamphetamine mixed salts: n=2	na		
non-stimulants	Atomoxetine HCl: n=2	na	na		
benzodiazepines	na	na	na		
		Youth offspring current psychiatric diagnoses			
Number of youth with more than 1 diagnosis	6	7	na		
MDD/DDNOS	3	2	na		
Attention deficit	6	5	na		

hyperactivity disorder			
Anxiety disorders	2	2	na
Oppositional Defiant Disorder	1	2	na
Phobias	2	2	na
Tourette's Disorder	1	0	na
Obsessive compulsive disorder	0	2	na
Eating disorder	2	0	na

Symptom Assessment Scale Scores administered on the day of scan

SCARED Parent Total	9.45(6.86)	10.85(11.70)	4.17(4.32)	F(2,76)=4.35	**0.02**
SCARED Child Total	11.66(8.61)	10.79(13.80)	9.33(11.42)	F(2,77)<1	ns
MFQ Parent	5.90(8.97)	5.42(9.09)	1.57(2.09)	F(2,75)=2.4	ns
MFQ Child	8.86(10.73)	10.18(10.97)	5.09(10.57)	F(2,77)=1.5	ns
CALS Parent Total	7.97(10.26)	5.07(7.65)	1.78(2.59)	F(2,76)=4.04	**0.02**
CALS Child Total	10.52(12.22)	8.79(11.28)	5.96(13.39)	F(2,77)<1	ns

Note: Standard deviations (SD) are reported in parentheses.

Table 2

Lifetime psychiatric diagnoses in parents

	BO n=29	NBO n=28	Statistics	p-value
BD-I	23	0	$\chi2(1)=37.2$	$p<0.001$
BD-II	6	0	$\chi2(1)=6.5$	$p=0.01$
BD-NOS	0	0		
Major depressive disorder/Depressive disorder NOS	1	20	$\chi2(1)=28.3$	$p<0.001$
Generalized Anxiety Disorder/Anxiety disorders NOS	16	8	$\chi2(1)=4.1$	$p=0.04$
Phobias	21	14	$\chi2(1)<3.0$	ns

	BO n=29	NBO n=28	Statistics	p-value
Alcohol/Drug abuse/dependence	23	13	$\chi 2(1)=6.6$	p=0.01
Post-traumatic stress disorder	12	4	$\chi 2(1)=5.2$	p=0.02
Panic disorder	16	6	$\chi 2(1)=6.8$	p<0.01
Eating disorder	4	1	$\chi 2(1)=1.8$	ns
Obsessive-compulsive disorder	10	0	$\chi 2(1)=11.7$	p<0.001
Attention deficit hyperactivity disorder	4	2	$\chi 2(1)<1$	ns