Synopsis no.: 6.2

Preliminary title:
Emotion recognition, separation from parents and genetics in schizophrenia

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BACKGROUND

Patients with schizophrenia have emotion recognition problems; they also have lower social abilities and significant proportion of behavioral problems. These outcomes are traits present in siblings of subjects with schizophrenia in a lesser degree (1). Poor performance in tests assessing emotion recognition has been associated with disorganized and, to a lesser extent, with negative and positive psychotic symptoms, although results are inconclusive (2). Lower emotion recognition ability has been associated with higher psychosis risk (3). Analyses per emotion category indicate that the overall effect was mainly driven by differences in the recognition of angry and fearful emotion. These findings have been replicated in different studies (4–8).

The heritability of the endophenotype characterized by loss of ability in emotion recognition is estimated to be between 16-32% (9,10). This supports the role of environmental factors in the emergence of these alterations. The evidence about the relationship of stressful life events in childhood and the development of psychosis is growing in recent years (11–15). The negative effect of neglect and parental separations in the development of emotion recognition has also been reported in different studies (16–20). The theory of mind as a whole develops almost completely in the first 6 years of life, although less important changes occur later. Therefore we consider early childhood as the critic period in which stressful experiences could affect the normal development of emotion recognition (21).

Faces of mothers elicited more activity in core and extended brain regions associated with face processing including emotion recognition ability, compared to fathers, celebrity or stranger faces. These differential brain responses elicited by faces of mothers and fathers are consistent with

psychological research on attachment that has been found strong evidence about influence of mother child relationship in emotion recognition development while there is lacking evidence in father child interactions (22–27).

The chromosomal area 1p36 has been implicated in schizophrenia (28) as in difficulties in emotion recognition in schizophrenia patients and their families (9). The same region has been replicated in disorders other than schizophrenia concerning emotion recognition disability as conduct disorder and antisocial personality disorder (29). Several particular alterations in single genes have been associated with this disturbed endophenotype, being the most replicated the serotonin receptor and transporter genes (HTR6 and 5-HTT) (9,30,31).

AIM

The main objective of this study is to go beyond the actual knowledge about interactions between genetics and early stressful experiences in the development of schizophrenia. We will focus our attention in early childhood to study the relationship between separation from parents and genetic markers described above as risk factors in the alteration of emotion recognition ability as a mediator to develop the disorder.

HYPOTHESES

1. Early separation from parents (before 6 years old) is a risk factor in developing schizophrenia.
2. The probability to develop the disease increases in patients who have both risk factors: early separation from parents and the genetic markers associated.
3. Early separation from parents is a risk factor associated to poor performance in emotions recognition tasks.
4. Emotion recognition test is poorer in patients having both risk factors.
5. Functioning (measured by GAF) in patients with early separations from parents is poorer than those without early separations.
6. The functioning in patients having both risk factors is poorer than those with only one.
7. The risk for schizophrenia, poorer performance in emotion recognition task and poorer functioning is larger in cases of separations from the mother than separations from the father.
8. The risk for schizophrenia, poorer performance in emotion recognition task and poorer functioning are directly correlated with the duration of the separation and inversely correlated with the age of the event.

Data needed for the study:

- Combined Social Assessments.
- The Community Assessment of Psychotic Experiences (CAPE).

- Opcrit.
- FIGS: Family Interview for Genetic Studies.
- PAS: Premorbid Adjustment Scale (shortened version).
- Cannabis Questionnaire (+ alcohol and drugs).
- GAF: Global Assessment of Function.
- Medication list/ medication list past.
- IQ
- Degraded facial affect recognition.
- SIS-R
- CTQ

Genetic data needed.

We need those genetic markers (SNPs) included in the genotyping panel (GWAS study) that map the 1p36 region with special relevance of those located nearby or at the *HTR6* gene. If the genotyping panel allows custom SNPs, we can add some HTR6-TagSNPs.

We are also interested in the SNPs included in Table 1 (or in linkage disequilibrium with them) due to fact of their location in candidate genes previously associated with emotional recognition in schizophrenia (30–32).

Table 1. Results referring to candidate genes in emotional recognition (Caucasian population)

GENE symbol	Name	Cr position	SNP	MAF	Ref
GRM4	Glutamate RC metabotropic 4	6p21.31	rs2229901 rs2451383 rs9469690	0.18 0.23 0.16	Greeenwood et al., 2011
GRM1	Glutamate RC metabotropic 1	6q24.3	rs61914 rs362854	0.44 0.38	
RELN	Reelin	7q22.1	rs10487160 rs123712	0.05 0.32	
NRG1	Neuregulin 1	8p12	rs10110401	0.01	
GRID1	Glutamate RC ionotropic delta 1	10p23.2	Rs4393254	0.05	
YWHAE	Tyrosine 3 monooxygenase/tryptophan 5-monooxygenase act…	17p13.3	rs9912147	0.5	
DLG4	Discs, large homolog 4	17p13.1	rs507506	0.47	
GABRA3	GABA A receptor alpha 3	Xq28	rs389292	0.37	
SLC6A4 (SERT o 5-HTT)	Serotonin transporter	17q12	5-HTTLPR	0.4	Beeves et al., 2009

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Plan for statistical analysis (overall strategy):

Depending on results of the assumptions of the General Lineal Model check (Kolmogorov–Smirnov and Shapiro–Wilk tests), parametric or no parametric analyses will be selected. All analyses will be two tailed and with a 95% confidence interval. Effect sizes or statistical power measures will be reported.

According to each Hypothesis:

1- Early separation (yes/no) and developing schizophrenia (yes/no) will be assessed by chi-square test.

2- The influence of early separation (yes/no) and genetic markers (yes/no) separately and linked (interaction) in develop the disease (yes/no) will be assessed by logistic binary regression.

3- The influence of early separation (yes/no) in emotion recognition task will be assessed by simple linear regression model.

4- The number of risk factors (0, 1 or 2) in emotion recognition task will be tested by analyses of variance (ANOVA).

5- Differences in functioning (GAF) between early separation (yes/no) will be assessed by unpaired T-Test.

6 - Differences in functioning (GAF) between patients (one or two risk factors) will be assessed by unpaired T-Test.

7 – We will separate the sample in two parts, separation from the mother and from the father, and repeat all the previous analyses considering these groups.

8 - Correlations between: schizophrenia risks, emotion task performance and functioning, with duration of the separation and age of event will be assessed by a Pearson product-moment correlation coefficient.

Other analyses/methods: In order to study the influence of confounding variables, descriptive analyses between groups will be performed. Depending on statistically significance of confounding variables, univariate analyses (T-Test, ANOVA test and simple regression) will be repeated using multivariate analyses (ANCOVA, MANCOVA and multiple linear regression model) considering the confounding variables effect. Results would suggest a combination of statistically significance variables and their interactions in a multivariate analyses of covariance.
Involvement of external Parties (non EU-GEI):
IPR check:
Timeframe:
Additional comments: