No potential conflict of interest

THE COMPLEXITY OF GENETIC EFFECTS IN PHARMACOGENETICS: focus on Neuroplasticity, Environmental stress and Response to antidepressants

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ABSTRACT

Aims. To evaluate the role of genetic variation within two genes involved in neuroplastic processes in early response to antidepressants (ADs) and the potential differential effect depending on environmental exposure to stressful life events (SLEs).

Methods. 114 patients affected by Mood or Anxiety disorders under antidepressant treatment were enrolled in the study.

We evaluated the interactive effects of 3 *Brain derived neurotrophic factor* gene (BDNF) single-nucleotide polymorphisms (SNPs), 5 Syaliltransferase 8B (ST8SIA2) SNPs and SLEs at different time points (Childhood SLEs, SLEs occurring before the onset of the disease and SLEs reported over the last year preceding current episode) on a 1 month AD treatment.

Results Some genetic variants in both BDNF and ST8SIA2 were associated with a slower response to antidepressants in individuals non-exposed to SLEs at onset only, whilst subjects exposed to SLEs at onset did not differ for early response to ADs independently from BDNF and ST8SIA2 alleles ($p<.007$). Haplotype analyses confirmed these trends.

Conclusions. According to our data, variants in BDNF and ST8SIA2 may influence differentially the early response to ADs depending on exposure to SLEs at illness onset, confirming a remarkable gene–environment interaction.

INTRODUCTION

During the last few years, the "neuroplastic" hypothesis has received increasing interest, not only as a novel etiologic model for psychiatric disorders, but also as an explicative paradigm of the mechanism of action of pharmacological treatments (Baudry et al. 2011).

Both animal and human studies have provided mixed and conflicting results so far, suggesting that the effect of neuroplastic factors may be moderated by a number of influences other than genetic, and genetic effects may be modulated by other biological, environmental, and individuals' factors.

The aim of the present study was to preliminarily investigate the interactive effect of Stressful Life Events (SLEs) and genes involved in neuroplasticity on the short-term response to antidepressant (AD) treatment.

We investigated the role of genetic variation within two genes involved in neuroplastic processes in early response to ADs: the Brain Derived Neurotrophic Factor (BDNF) coding for a major prosurvival factor in the brain, and Sialyltransefarase 8B (ST8SIA2), which product modulates the adhesive properties of Neural cell adhesion molecule (NCAM). Finally, we investigate the potential differential effect depending on environmental stress exposure.

METHODS

Sample and Evaluations: The sample was composed by 114 patients affected by Mood or Anxiety disorders, enrolled for treatment with ADs, scoring 8 or more at the Hamilton Rating Scale for Depression score (HAMD), and having filled at the time of recruitment a modified version (self-report) of the Brown & Harris Stressful Life Events and Difficulties Interview (SLEDS). This modified version allows to collect stressful life events (SLEs) in young age (less than 15 years old), the year before illness onset, and the month preceding current episode. All the patients were evaluated at baseline and weekly thereafter until the fourth week by the Hamilton Rating Scale for Depression (HRSD).

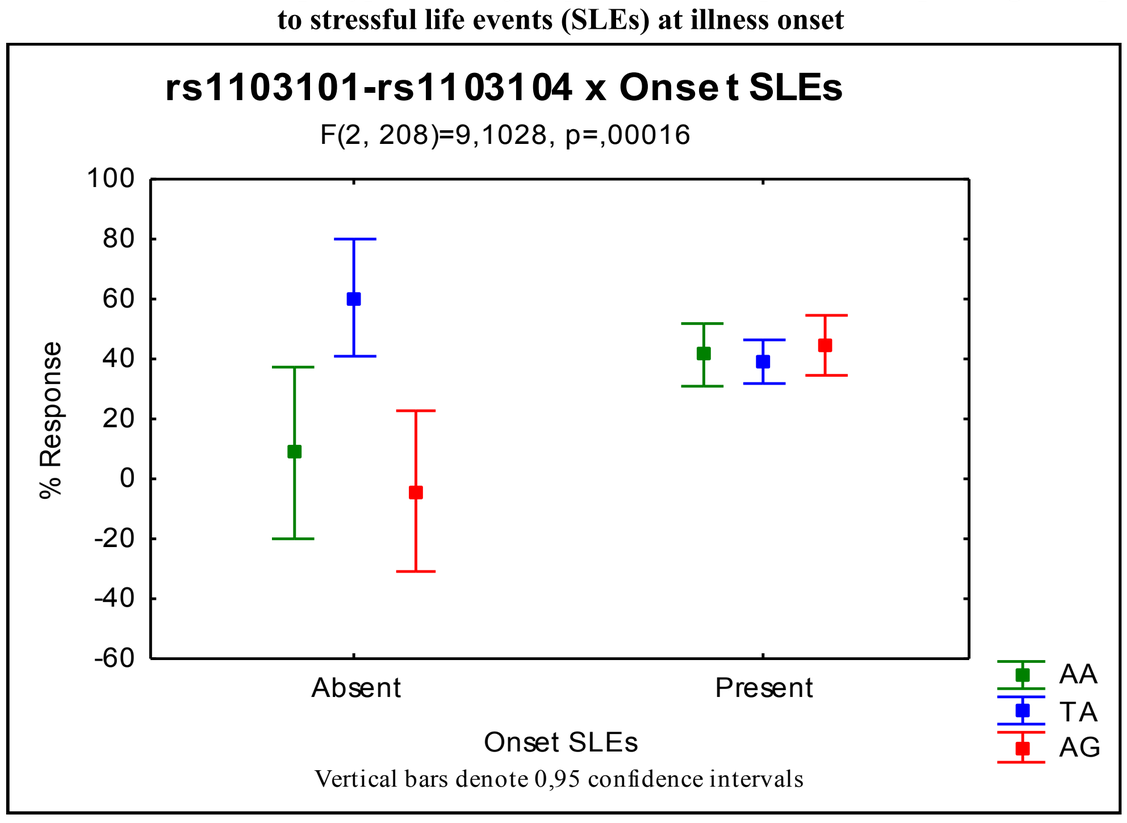
Genetic analysis were performed according to standardized protocols. Subjects were genotyped for 3 single-nucleotide polymorphisms (SNPs) in BDNF (rs6265; rs11030101; rs11030104) and 5 in ST8SIA (rs11632521; rs4777989; rs8035760; rs11853992; rs1752208).

Statistical analysis: Linkage disequilibrium among SNPs was calculated by Haploview software and haplotypes were obtained by the R-software. The GLM model was employed to test the effect of alleles and haplotypes, crossed with exposure to stress, on % response at follow-up.

RESULTS

Short-term response to AD treatment was neither associated to SLEs at different time points (early, at onset, preceding current episode) or genetic variations in BDNF and ST8SIA2. Nevertheless, when crossing SLEs and genetic variants we found **individuals carriers of the BDNF rs11030101 A-allele and rs11030104 G-allele having a slower response to ADs if non-exposed to SLEs at disease onset**, whilst individuals exposed to SLEs at onset had a similar response compared to the carriers of the other genetic variants (allelic analysis, $F= 18.322$ df=1,200 $p<.001$ and $F= 7.69$ df=1,200 $P=.006$ respectively). Haplotype analysis confirmed this effect ($F= 9.10$ df=2,208 $P<.001$) (figure 1).

Figure 1. Effect of BDNF haplotypes on early response to antidepressants depending on exposure to stressful life events (SLEs) at illness onset



Similar results were obtained with ST8SIA2 polymorphisms. The influence of SLEs was remarkable only taking into account the SLEs occurred at illness onset in interaction with rs11853992 and rs17522085. More specifically, **the rs11853992 A-allele carriers and the rs17522085 G-allele carriers showed a worse response to AD treatment if not exposed to SLEs at illness onset** (rs11853992: $F=4.08$ df=1,204 $p=.04$; rs17522085: $F=4.57$ df=1,198 $p=.033$). Haplotype analysis was not significant ($p>.05$), but a trend in a similar direction was observed (data available on request).

DISCUSSION

According to our data, **variants in BDNF and ST8SIA2 may influence differentially the early response to ADs depending on exposure to SLEs at illness onset.** Exposure to stress may impact the transcriptional activity of genes through epigenetic mechanisms, resulting in unexpected phenotypes.

A recent animal study has reported that an over expression of BDNF may have detrimental effects on anxiety-like behavior (Govindarajan et al., 2006). Given that stressors seem to down-regulate BDNF secretion (Pittenger and Duman, 2008), **a genetically-based excess of prosurvival factors may interfere with ADs mechanism of action and/or other intervening biological process in the absence of environmental stress and/or in non-stress induced depressive states.**

The complex gene-environment interplay as well as other biological systems deserves further investigations and innovative models should be implemented to clarify the role of these biological factors in the response to drugs, as well as in stress response and disease risk.

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