Bipolar Affective Disorders: Activity of the Limbic Hypothalamo Pituitary Adrenal Axis in an Acoustic Startle Paradigm

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ABSTRACT

The aim of our study is to determine if patients with bipolar affective disorder have an increased stress response than normal control participants. We have measured startle responses in a bipolar disorders group compared with normal volunteers. We have measured physiological responses to 106 db pulse, pre pulse inhibitions (80 and 90 db pulse going 60 ms before 106 db pulse) and startle responses to a fear-potentiated visual stimulus. In addition, we have correlated blood cortisol at entry study (8:00AM) with stressors responses and several psychiatric scales (HAMD-21, MADRS, YMRS) . Ours results demonstrate that bipolar patients have a higher blood cortisol baseline than control participants and that the blood cortisol concentration is positively correlated with intensity response to stressors and with HAMD and MADRS scores. Bipolar patients have significantly higher responses than control participants in several conditions including pre pulse inhibition and fear-potentiated startle responses. These results are interpreted in relation with the LHPA hyperactivity observed in some animals model of depression.

INTRODUCTION

Anxiety and excessive fear is a common comorbid disorder in the affective bipolar illness population. Sudden intense stimuli, like loud sounds, activate an archaic acoustic reflex which implicates few neurons located in the brainstem. One of the results of this startle reflex is a short latency contraction of facial muscles and, in particular, an eye blink. It is possible to observe a decrease of the physiological response, as measured by the electromyography, with a weaker pre-pulse (Pre Pulse Inhibition effect). Moreover, it is well established that the amplitude of this reflex is modulated by several factors, such as emotional context, and could be notably increased by fear (Fear Potentiated effect). On the contrary to the basic circuitry located in the brainstem, the startle modulation implicates higher brain structure in the forebrain such as the amygdala.

OBJECTIVES

The purpose of this study is to determine whether patients with a bipolar affective disorder have a different acoustic startle response than normal control volunteers. We also have correlated the startle response with emotional states as measured with several psychiatric scales (HAMD-21, MADRS, YMRS) and the activity of the LHPA axis at the study entry (8:00AM) as measured with the baseline plasma cortisol level.

PROCEDURE

20 SCID diagnosed bipolar patients and 24 control participants have been tested in this protocol. All participants have been screened for street drugs. One day before the experiment a plasmatic sample of cortisol was drawn and several psychiatric scales were administrated (MADRS, HAMD-21 and YMRS). On the day of testing, the eye blinking component of the auditory startle reflex was measured using electromyography of the orbicularis oculi muscle.

This experiment contains three blocs:

- In the first bloc, a sequence of thirty six 106db pulse occurred randomly, each pulse could go with a pre pulse starting 60 ms before the 106db pulse. The first six trails are rejected.
- In the second bloc, a sequence of seventy six 106 db pulse occurred. Each of these pulse goes with a light, blue for the No Fear condition, red for the Fear condition. The participants are informed before the experiment that an electrical shock could occurred when the light is red. Of course, no electrical shock is given but this particular directive allow us to study the impact of the stress on the startle response.
- The third bloc is a repetition of the first bloc in order to assess habituation.

DEMOGRAPHY

	Age no stat. diff: F(1,42)=1.59 p=.21	Sex	BP type
Patients (n=20)	49.35 +/- 11.54	F: 11 (55%) M: 9 (45%)	BPI: 13 BPII: 7
Controls (n=24)	45.25 +/- 10.04	F: 12 (50%) M: 12 (50%)	

PRE PULSE INHIBITION AND HABITUATION (BLOC 1 & 3)

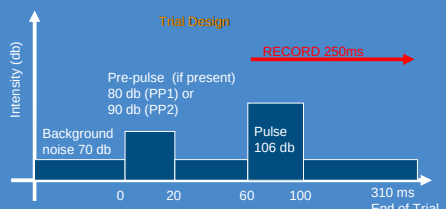

FIGURE 1: Trial Design in Bloc 1 and 3

Statistical Design
General Linear Model – Repeated Measure (SPSS 11.5)
Within Factors: BLOC (2) and PULSE (3)
Between Factor: GROUP (2)

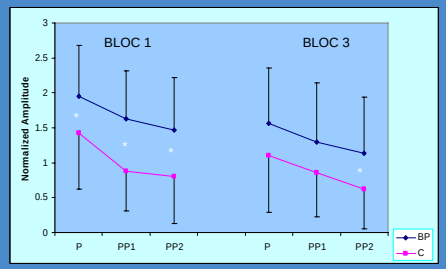

FIGURE 2: Normalized Mean Amplitude Startle Responses (+/- SD) for Bloc 1 and 3 .

Within subjects effects: (Sphericity Assumed)
BLOC (F=34.34), **p<.01**
PULSE (F=45.8), **p<.01**
BLOC*PULSE (F=3.82), **p<.05**

BLOC*GROUP (NS), p=.06
PULSE*GROUP(NS), p=.55
BLOC*PULSE*GROUP (NS), p=.12

These results demonstrate the habituation effect between Bloc 1 and 3 and the pre pulse inhibition effect. We failed to show a statistical difference between group responses even if there is a tendency for the complete design result and the bloc by group analysis. Despite these results we have decided to do the ANOVA analysis to examine the difference between the groups for each pulse type and bloc session but these results must be interpreted cautiously. The post-hoc analysis (Figure 3) shows a higher mean response for almost all the conditions for the bipolar group than the control group.

	BLOC 1	BLOC 3
P	F(1,42)=4.85 **p<.05**	F(1,42)=3.75 p=.06
PP1	F(1,42)=15.97 **p<.01**	F(1,42)=3.8 p=.06
PP2	F(1,42)=9.87 **p<.01**	F(1,42)=6.15 **p<.05**

FIGURE 3: ANOVA Results

FEAR POTENTIATED EFFECT (BLOC 2)

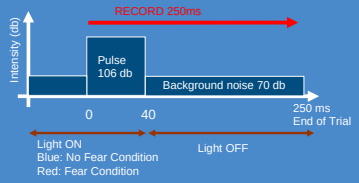

Figure 4: Trial design for the Bloc 2

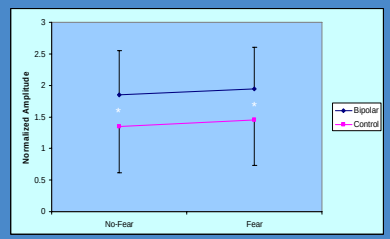

FIGURE 5: Normalized Mean Amplitude (+/- SD) for the BLOC 2.

Bipolar patients have a significantly higher response than Control participants for the No-Fear condition (F(1,42)=5.56, p<.05) and the FEAR condition (F(1,42)=5.16, p<.05). The Bipolar Patients have a significant increase response (Paired Samples T-Test) in the Fear condition (t=3.26, p<.01) as the Control Participants (t=2.8, p<.01). But we failed to demonstrate a significantly higher effect of the Fear Potentiated effect in the Bipolar Group than control (F(1,42)=0.01, p=.98)

PLASMA CORTISOL AT STUDY ENTRY

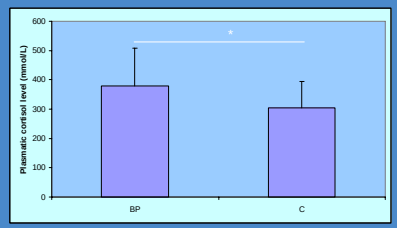

FIGURE 6: Plasmatic cortisol at the entry study (8:00AM).

The Bipolar Patients have a significant higher cortisol level than the Control subjects (F(1,42)=5.08, p<.05)

PLASMA CORTISOL AND BASELINE STARTLE

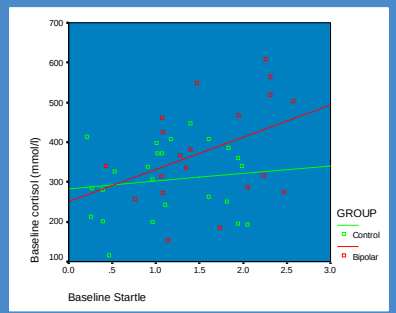

FIGURE 7: Baseline plasmatic cortisol level at the study entry by the baseline startle response.

There is a significant correlation for all the participants (Pearson correlation r=0.36, p<.05) but we fail to demonstrate a correlation for separate groups (Bipolar Patient group p=.08, Control p=.54)

PLASMA CORTISOL AND PSYCHIATRIC SCALES

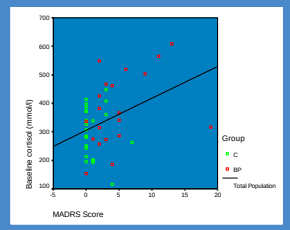

FIGURE 8: Baseline cortisol level and the MADRS score.

There is a significant correlation for all participants (Spearman's Rho = 0.32, p<.05, n=43)

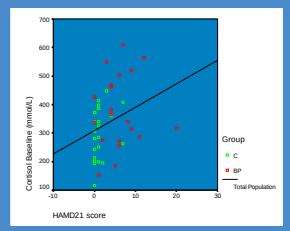

FIGURE 9: Baseline cortisol level and the HAMD-21 score.

There is a significant correlation for all participants (Spearman's Rho = 0.31, p<.05, n=43)

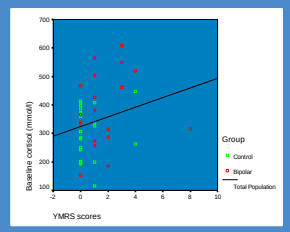

FIGURE 10: Baseline cortisol level and the YMRS score.

There is no significant correlation for all participants (Spearman's Rho = 0.22, p=.15, n=42)

CONCLUSIONS

These results demonstrate that Bipolar Patients have a constantly higher startle reflex than Control participants. Interestingly we failed to observe a different pattern of response to fear potentiated startle between bipolar and control participants for this particular reflex response in each of ours conditions. Cortisol seems to play a crucial role in the hyperactivity of the startle reflex and especially for the Bipolar patients who have a higher activation of the LHPA axis. Further analysis tends to show a link between a depressive state and hyper activity of the LHPA axis but this remains to be explored in more details.

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