



***The Influence of the rs1358278A/G FOXP2 Polymorphism
on Gating, Cognition, Language/Thought and Affect in
Healthy Males***

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**November 2
2012**

Introduction

- Forkhead box P2 (*FOXP2*) encodes a transcription factor involved in
 - speech and language
 - control of the corticobasal ganglia circuits (Takahashi et al 2010)
- *FOXP2* locus involved in
 - schizophrenia (Sanjuan et al 2006)
 - autism (Takahashi et al 2010)
 - ADHD (Ribases et al 2012)
- Language impairment, inattention, impulsivity and abnormalities of corticobasal ganglia circuitry are central features of these disorders.
- **Question:** What is the impact of *FOXP2* risk polymorphisms on relevant intermediate phenotypes?

AIM

- Here we examined the effects of rs1358278A/G *FOXP2* non-coding polymorphism (which has been associated with schizophrenia), in intermediate phenotypes in young healthy males.
- The effects of schizophrenia risk genes on intermediate phenotypes is a promising research as it may point to the mechanisms by which genes increase the risk for the disease
- The study of functional mechanisms of risk genes in healthy people is devoid of confounds which strongly impact the study and interpretation of findings in patient populations, such as:
 - age and gender
 - medication
 - presence of symptoms
 - brain effects of psychiatric illness episodes

Subjects

- **Subjects**

- 829 unrelated Greek/Caucasian healthy males
- Age: 18–35 years (mean±SD, 26.0±4.2)

- **Assessment:**

- IQ testing (Raven's progressive matrices)
- Psychiatric assessment (M.I.N.I.)
- Physical assessment

- **Exclusion criteria:**

- Left-handedness
- Personal history of head trauma
- Medical and neurological conditions
- Use of prescribed and recreational drugs
- Personal or family history of DSM-IV axis I disorders.

Genotype

rs1358278A/G *FOXP2* genotypes

- AA n= 437
- AG n= 322
- GG n=70

HWE $\chi^2=1.4$, df: 3; $p = 0.52$

- No population stratification effects-southeast European ancestry confirmed by STRUCTURE analysis using 58 ancestry informative unlinked markers

Phenotype

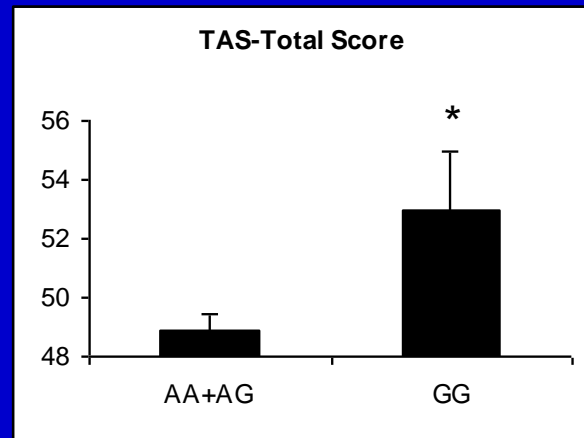
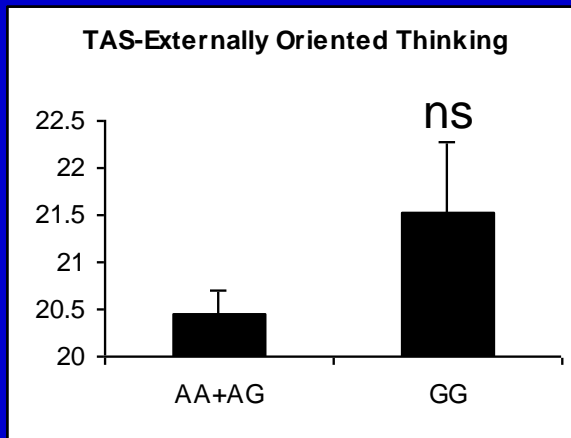
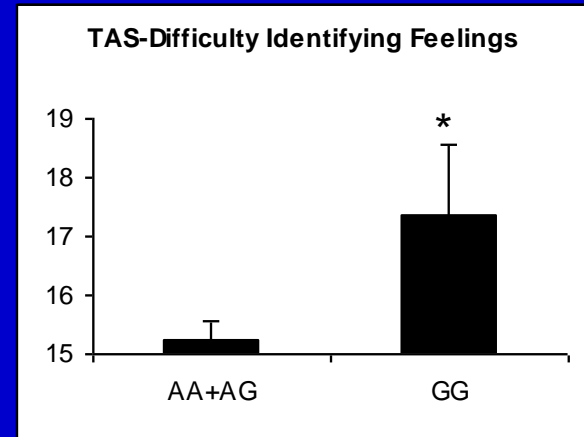
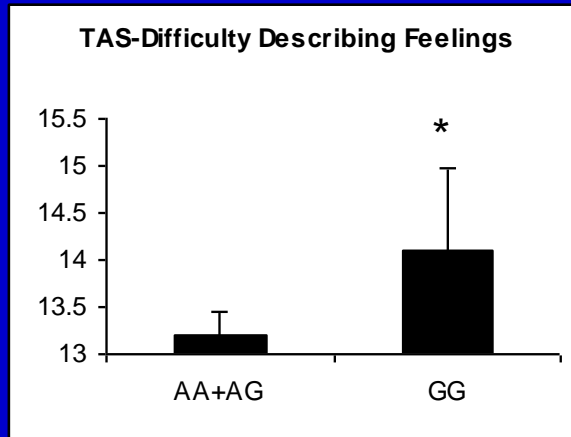
- Gating
 - Prepulse Inhibition
- Cognition
 - CANTAB (Attention, Working Memory, Verbal Memory, Planning and Executive Function)
- Affective Processing
 - Affective Startle Modulation
- Non-affective Personality traits
 - Schizotypy (STQ)
- Affective Personality Traits
 - Alexithymia (TAS-20)
 - Neuroticism (EPQ-R)
 - Extraversion (EPQ-R)
 - Novelty Seeking (TCI)
 - Harm Avoidance (TCI)
 - Social Reward Dependence (TCI)
 - Sensitivity to Reward (BIS/BAS)

Demographics

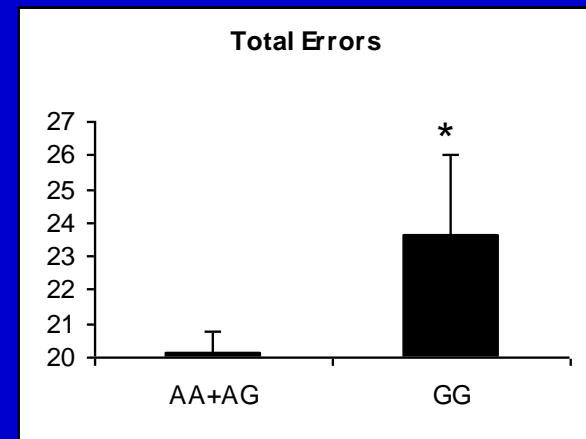
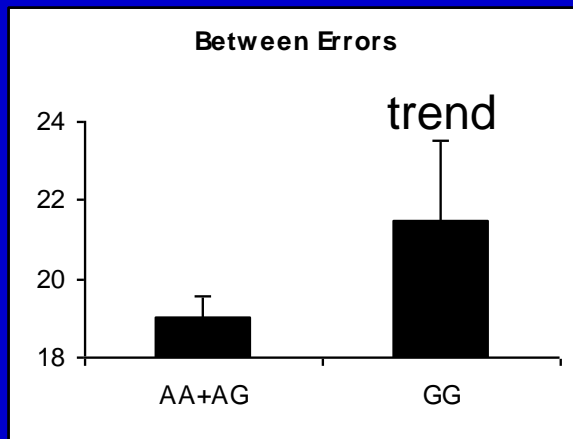
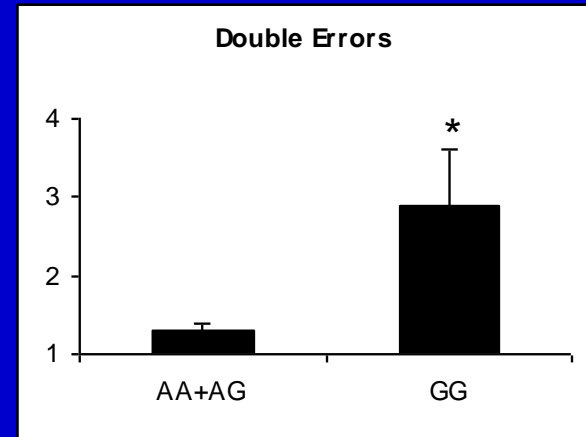
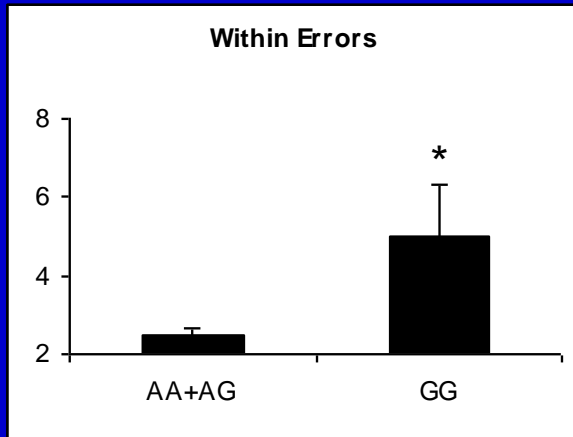
	AA	AG	GG	<i>P</i>
Age (years) ¹	22.5±3.9	22.3±3.7	23.1±3.8	>0.25
Estimated IQ ¹	113.7±10.2	114.2±11.0	112.9±12.2	>0.26
Education (years) ¹	14.7±2.6	14.7±2.5	15.1±2.6	>0.3
Smokers/Non-smokers ²	183/254	137/185	40/30	=0.06
Smokers:cigarettes/day ¹	16.5±8.4	15.3±8.2	17.1±8.5	>0.29

1 Kruskal-Wallis, 2 chi square

Personality: Alexithymia

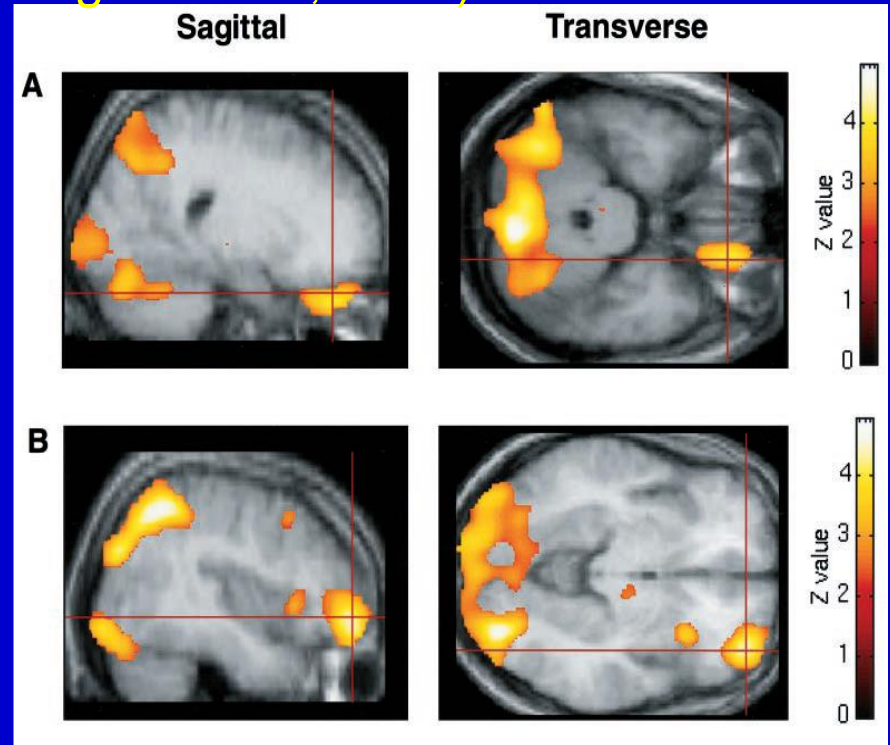
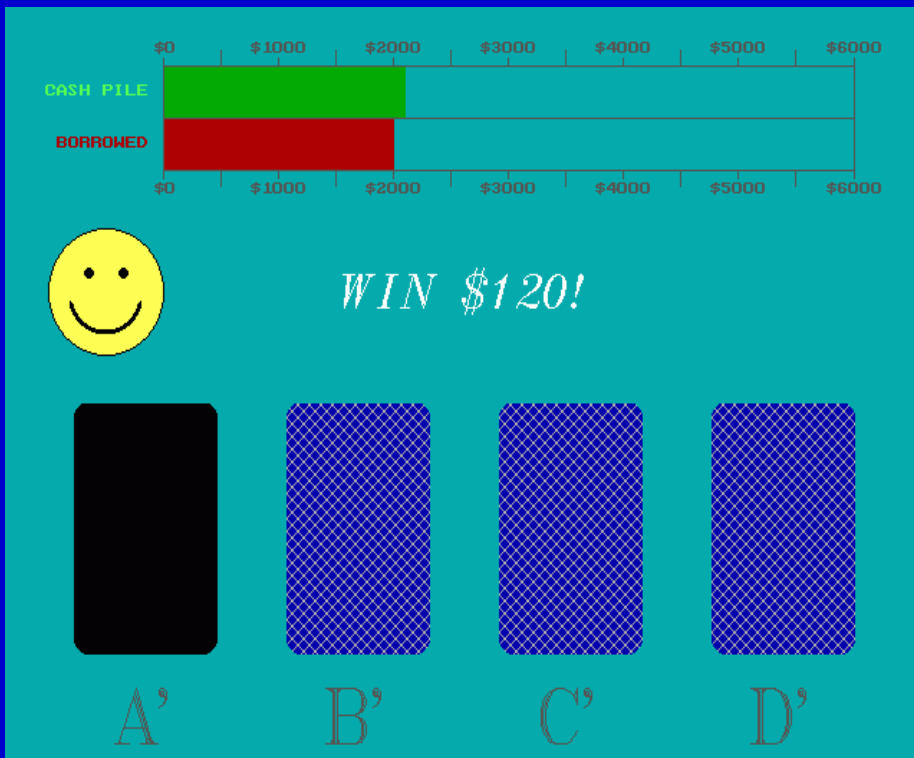


Spatial Working Memory: Errors

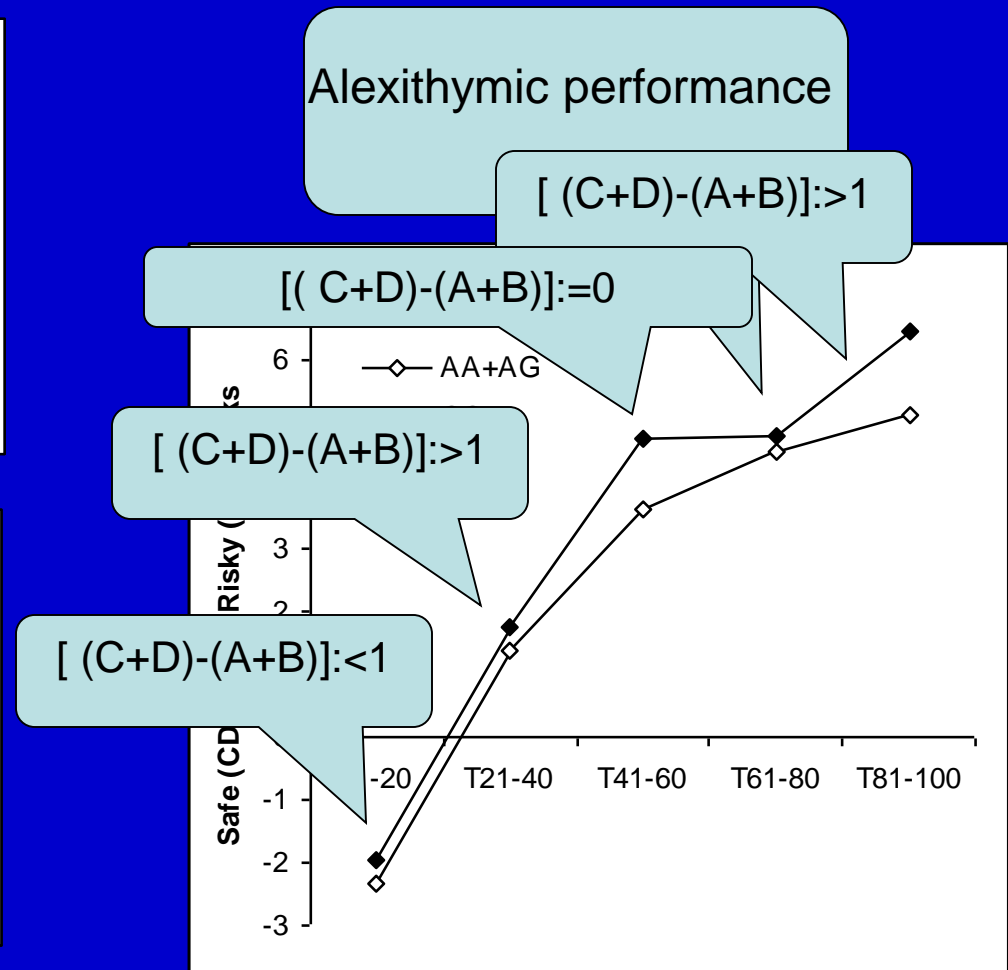
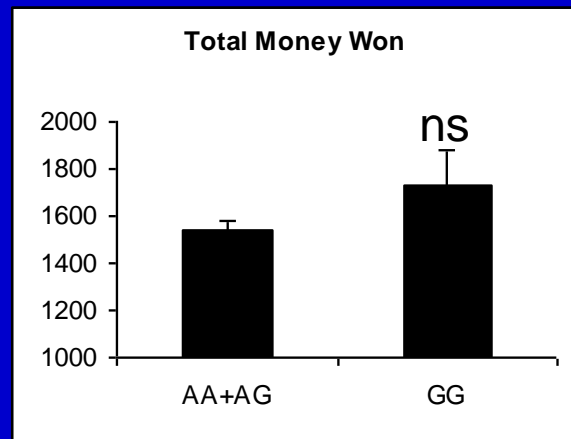
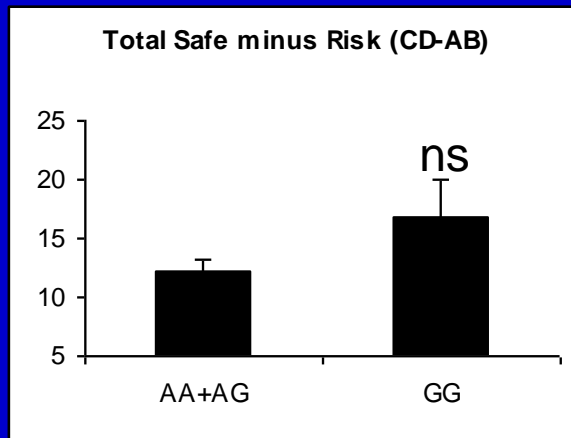


Emotional Decision Making

Activation in the orbito-medial and orbito-lateral PFC during planning under uncertainty (adapted from Rogers et al., 1999).

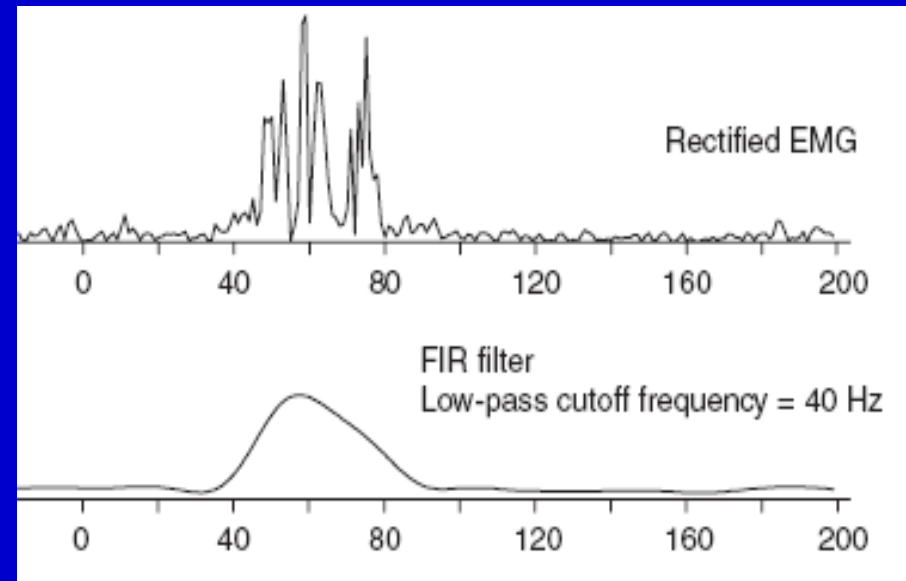


Emotional Decision Making Iowa Gambling Task



Testing of Emotional Processing

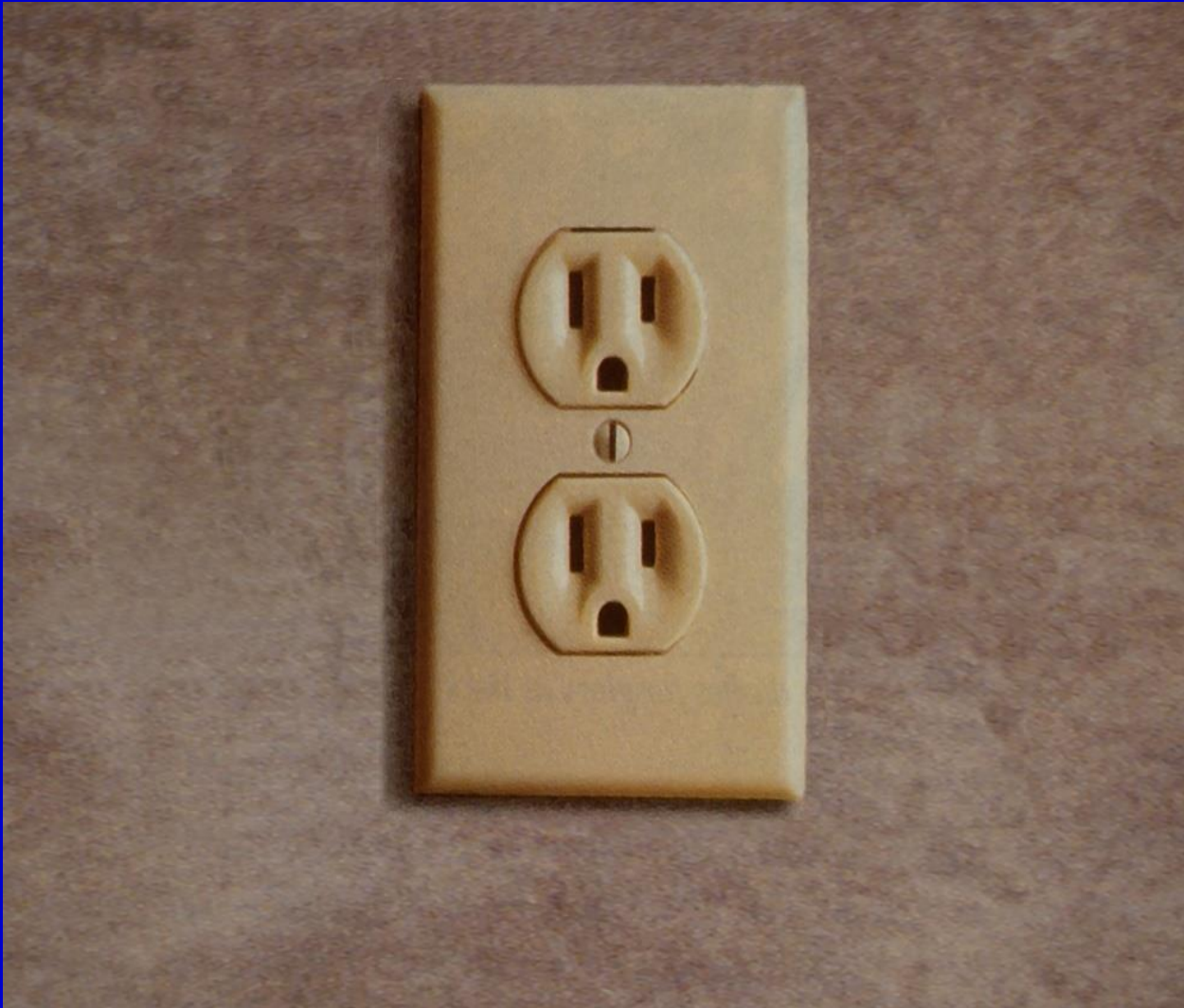
- ACOUSTIC STARTLE REFLEX



Affective Startle Modulation

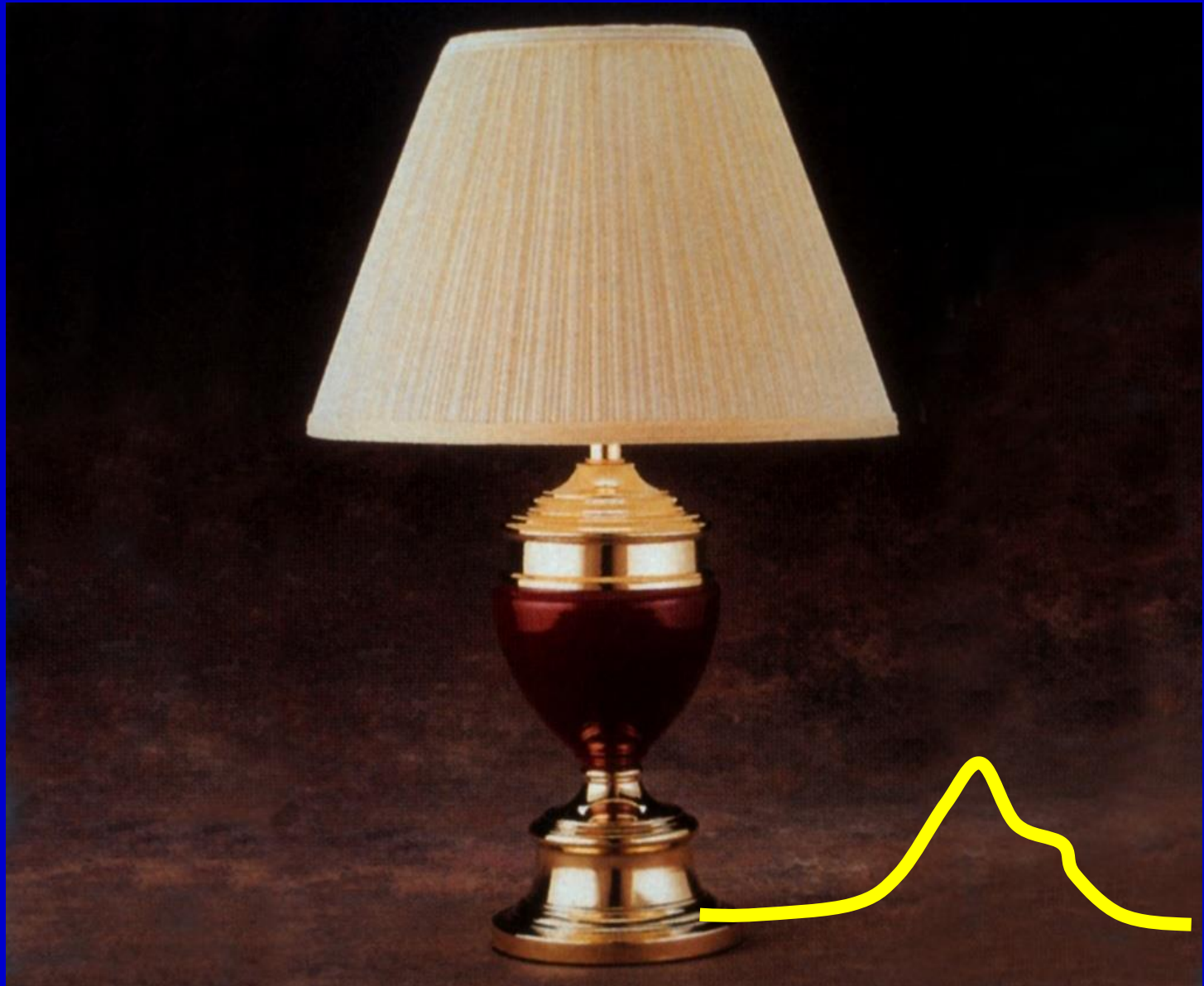
- Startle elicited by an acoustic probe during viewing of a picture with affective content
- IAPS (International Affective Picture System)
- An established paradigm for the study of human emotion (Lang et al 1990).

IAPS 6150: Neutral Picture



Affectively
neutral
pictures do
not affect
startle

IAPS 7175: Neutral Picture



IAPS 2340: Pleasant Picture



Affectively pleasant pictures inhibit the acoustic startle during picture viewing

IAPS 1920: Pleasant Picture



IAPS 3150: Unpleasant Picture

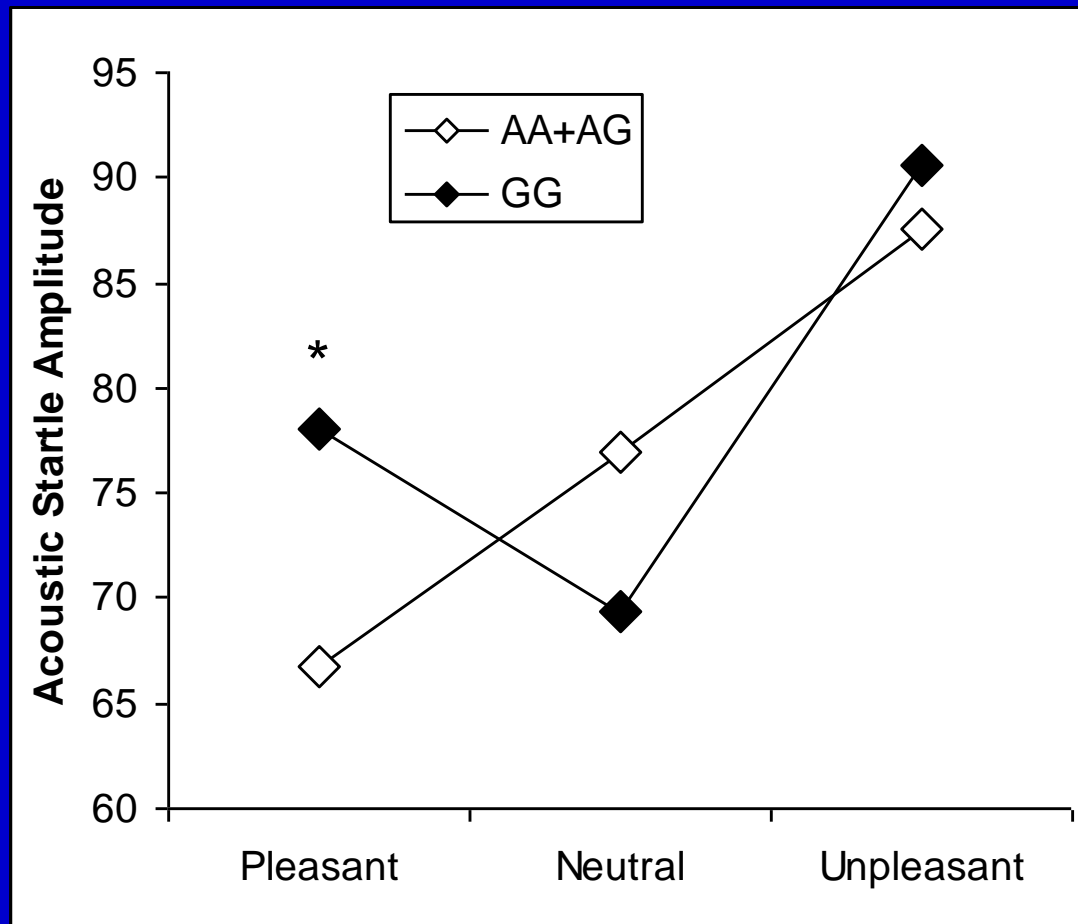


Affectively
unpleasant
pictures increase
the acoustic startle
during picture
viewing

IAPS 6313: Unpleasant Picture



Affective Startle Modulation



Significant ($p < 0.01$) group by valence interaction in the ANOVA

Summary

Healthy male G homozygotes present with abnormalities in:

- Working Memory and
- the Affective Processes underlying:
 - Language (Alexithymia)
 - Decision making (Iowa Gambling Task)
 - Pictorial contexts (Affective Startle)

Conclusions

The rs1358278G was previously shown to be part of a risk haplotype for schizophrenia

Our results suggest that one way for this *FOXP2* polymorphism (or another one in linkage disequilibrium with it) to increase risk for schizophrenia, may be through impairments in working memory and the processing of internal or external emotional material

Acknowledgements

Panos Bitsios

Erasmia Koiliari

Panos Roussos

Stella Giakoumaki