



# The Influence of the rs1229761G/C *FOXP2* Polymorphism on Gating, Cognition, Language / Thought and Affect in Healthy Males



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## INTRODUCTION

•Schizophrenia (SZ), and Attention deficit hyperactivity disorder (ADHD) may share common genetic risk variants.

•Forkhead box P2 (*FOXP2*) encodes a transcription factor involved in speech and language<sup>1</sup> and in the control of the corticobasal ganglia circuits<sup>1,3</sup>.

•There is evidence supporting a role for the *FOXP2* locus in schizophrenia<sup>1,2</sup>, autism<sup>1</sup> and ADHD<sup>4</sup>.

•Language impairment, inattention, impulsivity and abnormalities of corticobasal ganglia circuitry are central features of these disorders; however the impact of *FOXP2* risk polymorphisms on relevant intermediate phenotypes has not yet been studied.

•The rs1229761G/C *FOXP2* non-coding polymorphism has shown significant association with ADHD<sup>4</sup>.

•**Aim:** To assess the impact of rs1229761G/C *FOXP2* polymorphism on sensorimotor gating, cognition and personality traits.

## SUBJECTS & METHODS

**Subjects:** The rs1229761G/C *FOXP2* polymorphism was analyzed in 829 unrelated Greek/Caucasian healthy males. The mean of their age(±SD) was 26±4.2 (range18-35 years).

### Quantitative Trait Testing (phenotyping)

• Sensorimotor gating: Acoustic Startle and Prepulse Inhibition (PPI). PPI is a measure of inhibitory control of information processing in which a weak sensory stimulus (the prepulse) inhibits the startle response to a subsequent sudden intense stimulus (pulse).

• Neurocognition: Spatial working memory (SWM), Attention, Executive functions, Planning for problem solving and emotional decision making

• Personality traits: Behavioral Approach/Inhibition Systems (BIS/BAS) (Gray, J.A. 1981&1982), Schizotypy (STQ) (Claridge and Broks, 1984)

• Neuroticism, Extraversion, Psychoticism (EPQ) (Hans Jürgen Eysenck and Sybil B.G. Eysenck 1975) and Novelty seeking, Harm avoidance, Reward Dependence, Persistence(TCI) (Cloninger et al. 1994).

### Genotyping

Subjects were grouped according to genotype in three groups GG (n=276), GC (n=404) and CC (n=149).

### Statistical methods

ANOVAs and Kruskal-Wallis tests were used to analyse the phenotypic variables.

## CONCLUSIONS

•The G allele carriers (n=680) demonstrated a Gating deficit as evidenced by a significant (p<0.01) 3-way interaction in the ANOVA [reduced PPI at the short (30ms) interval with the 85dB prepulse].

•The G allele carriers performed worse (p<0.05) in Spatial Working Memory [Strategy, Total-, Within- and Between- Errors in the difficult 8-box condition).

•They scored higher (p<0.05) in measures of Schizotypy [STQ\_Magical Thinking and STQ\_Unusual Experiences (p<0.01)] and Impulsivity [BAS\_Fun seeking, TCI\_Novelty seeking, low scores in EPQ\_lie scale].

•The rs1229761 G allele, which has been associated with ADHD, impacts on important intermediate phenotypes such as short interval gating, working memory, strategic thinking, schizotypy and impulsivity in healthy males.

•These results elucidate the function of the *FOXP2* gene in the human brain and suggest that it may be a "hub" for pathological features (gating, cognition, language/thought, impulsivity) common to ADHD, schizophrenia and autism.

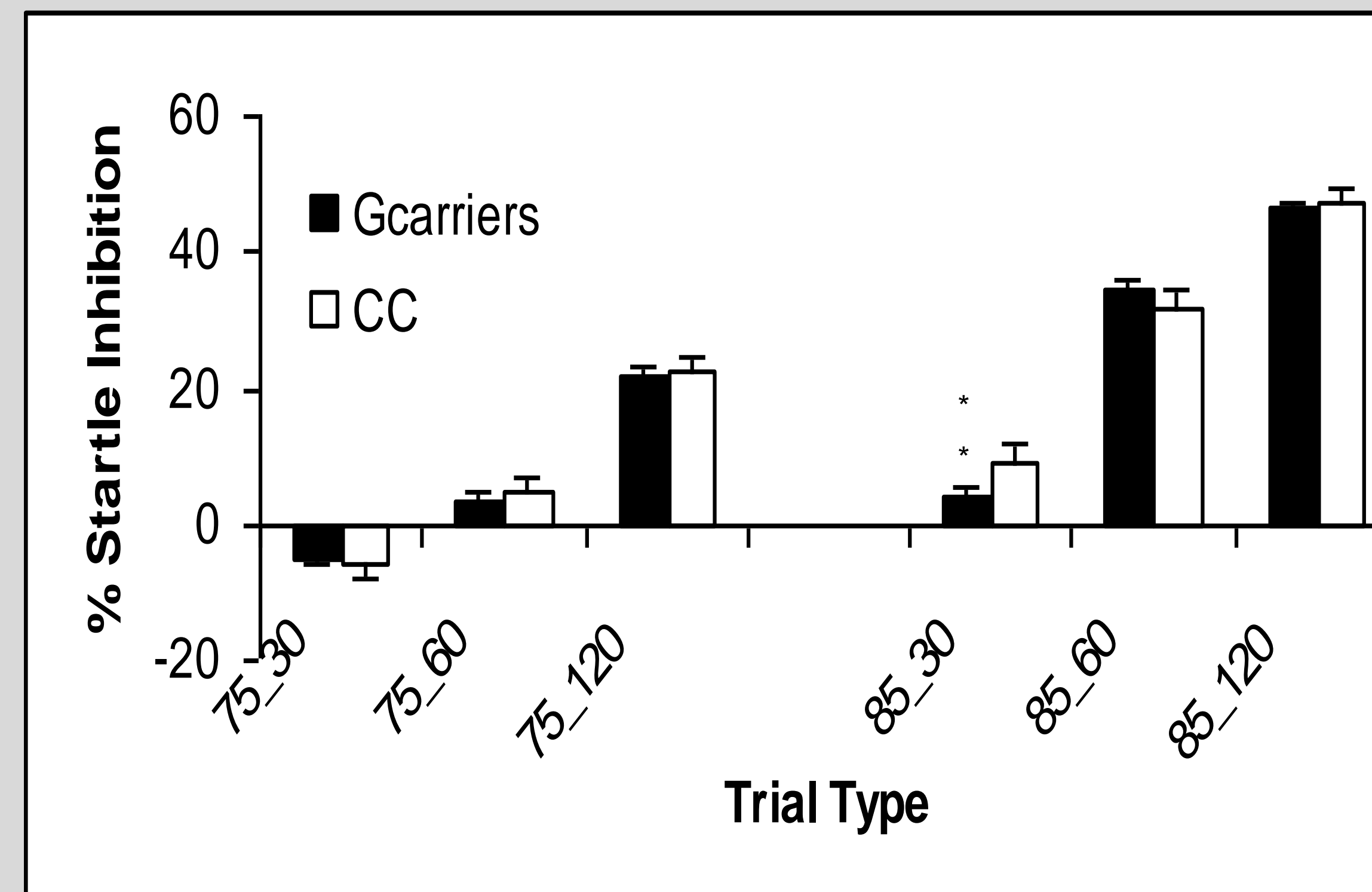
## RESULTS

**Table 1:** There were no demographic differences between the genotype groups, but because of trend level smoking effect, smoking status was taken as a covariate in all analyses.

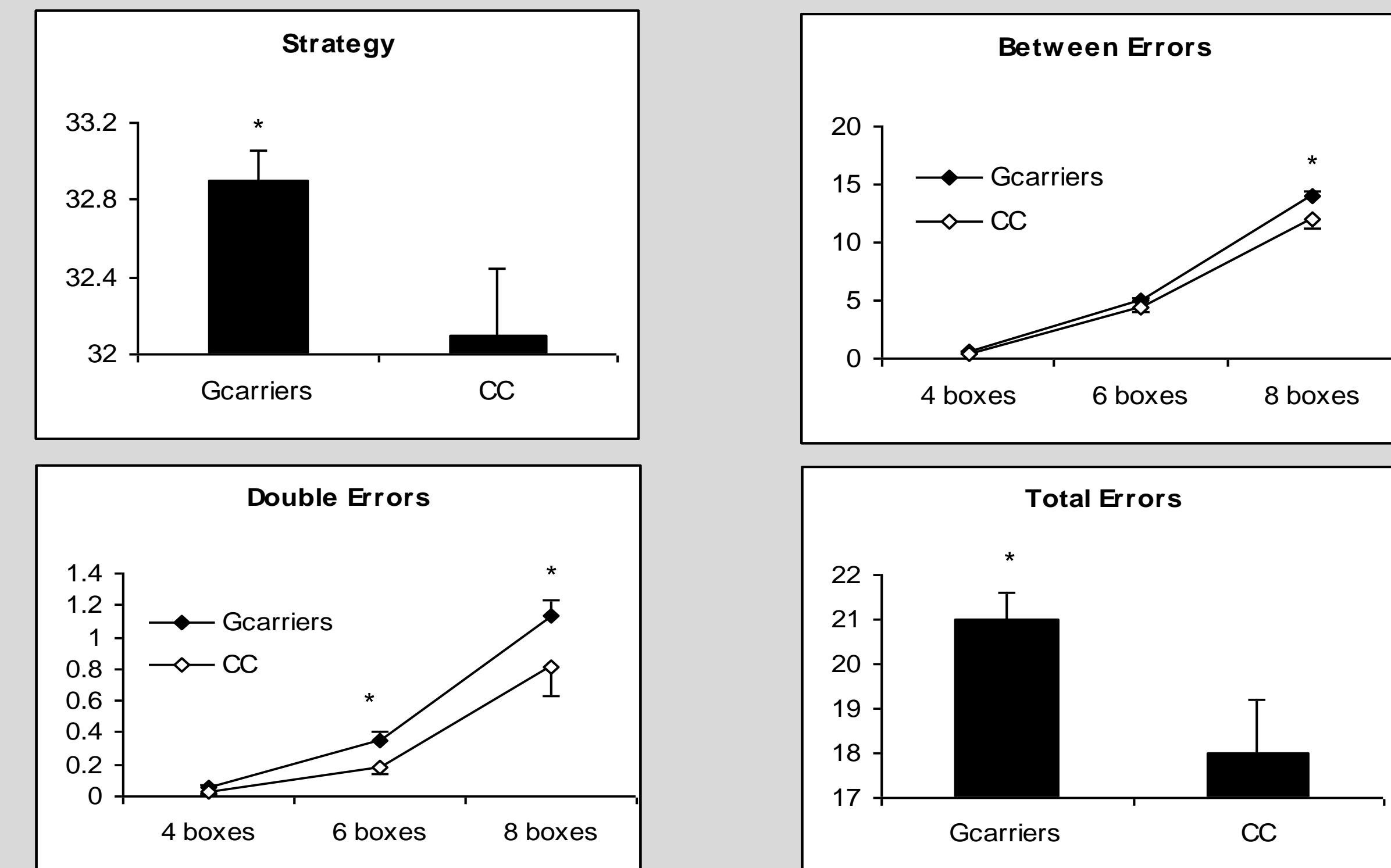
1 Kruskal-Wallis, 2 chi square

	GG	GC	CC	P
Age (years) <sup>1</sup>	22.4±3.7	22.9±4.2	22.5±3.8	>0.57
Estimated IQ <sup>1</sup>	112.6±10.2	113.1±10.0	112.9±11.2	>0.6
Education (years) <sup>1</sup>	14.7±2.6	14.8±2.6	14.7±2.6	>0.61
Smokers/Non-smokers <sup>2</sup>	136/140	162/242	62/87	=0.06
Smokers:cigarettes/day <sup>1</sup>	16.6±8.0	15.7±8.4	16.1±8.5	>0.51

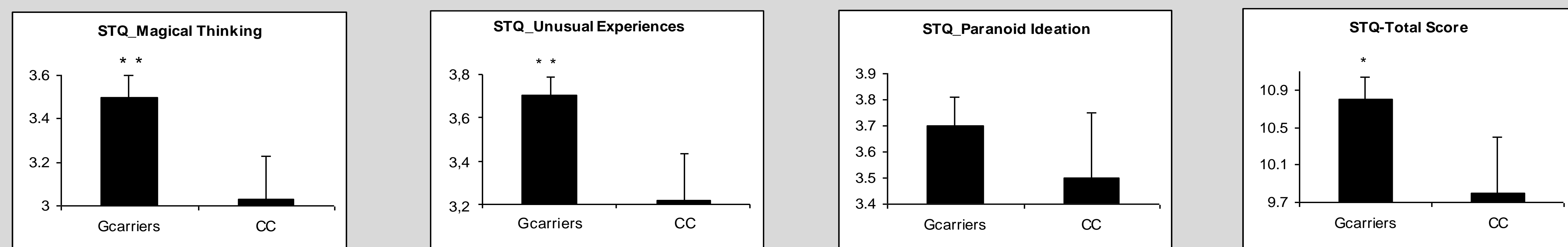
**Figure 1:** We found that G allele carriers had significantly less prepulse inhibition at the 85\_30 trial type as evidenced by a significant (p<0.01) group by prepulse by interval interaction and the post hoc gating tests. This suggests abnormalities in the short interval gating processes in G allele carriers.



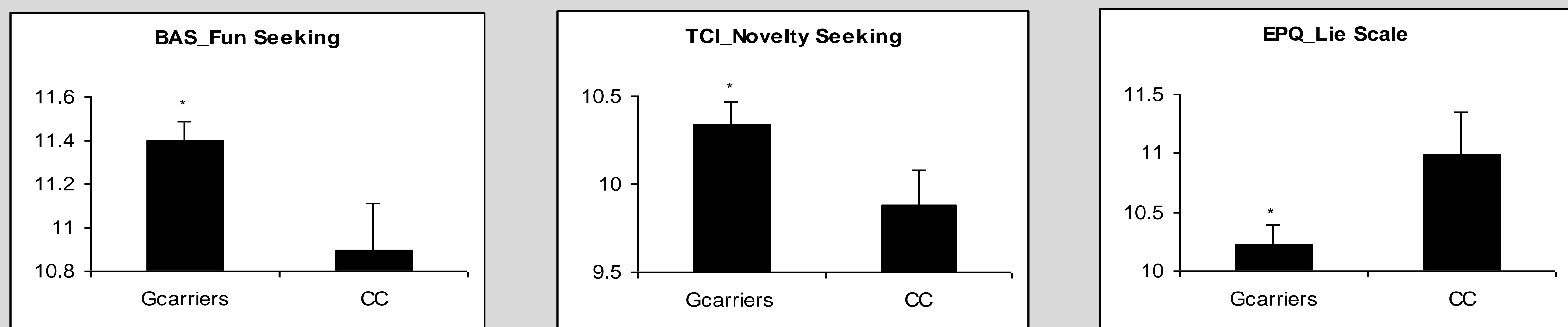
**Figure 2:** Cognitive measures revealed no significant differences among genotype groups except for Working Memory. G allele carriers had worse working memory performance as they had a worse strategy performance (indicated with a greater score in Strategy) and they made more Between errors in the difficult 8-box condition and errors more Double-, Within- and Total errors in this task.



**Figure 3:** From the personality measures, schizotypy stands out as the main measure with significant differences between genotype groups. The G allele carriers scored higher for Magical Thinking and Unusual Experiences at p<0.01 and total schizotypy score (p<0.05). These results suggest abnormalities in thought processes in G allele carriers.



**Figure 4:** The G allele carriers scored higher in measures on impulsivity (BAS\_Fun Seeking and TCI\_Novelty Seeking), with fewer lies in the EPQ Lie scale (all p<0.05).



References: 1.Hiroshi Takahashi , Kaoru Takahashi and Fu-Chin Liu. *Foxp* Genes , Neural Development, speech and Language Disorders. *Adv. Exp. Med. Biol.*,2010, Vol.665,Section III, 117-129  
2.Elizabeth Spiten , Genevieve Konopka , Giovanni Coppola et al. . Identification of the Transcriptional Targets of *Foxp2* , a Gene Linked to Speech and Language , in Developing Human Brain. *Am. J. Hum. Genet.* 2007;81:1144-1157  
3.Enard W. et al. . A humanized version of *Foxp2* affects cortico-basal ganglia circuits in mice. *Cell.* 2009 May 29;137(5):961-71  
4.Marta Ribases , Cristina Sanchez-Mora , Josep Antoni Ramos-Quiroga et al. . An association study of sequence variants in the forkhead box P2 ( *FOXP2*) gene and adulthood attention-deficit/hyperactivity disorder in two European samples . *Psychiatric Genetics* 2012 . 22:155-160