



Cell-Subtype Changes in Adenosine Receptor Expression in Schizophrenia

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INTRODUCTION

Schizophrenia is a debilitating neuropsychiatric disorder affecting approximately 0.6% of the U.S. population and is characterized by altered thought processes, hallucinations, and delusions. Dysregulation of the glutamate and dopamine neurotransmitter systems are implicated in the pathophysiology of schizophrenia.

The adenosine system is an important neuroregulatory system in the brain that modulates glutamate and dopamine signaling via the ubiquitously expressed adenosine receptors. However, adenosine A_1 and A_{2A} receptor (A_1R and $A_{2A}R$) expression is poorly understood in specific cell-subtypes in Frontal cortical brain regions implicated in this disorder.

In this study, we assayed A_1R and $A_{2A}R$ mRNA expression by qPCR in enriched populations of pyramidal neurons, isolated from postmortem anterior cingulate cortex (ACC) tissue from age and sex-matched schizophrenia ($n=20$) and control ($n=20$) subjects, using laser microdissection (LMD).

METHODS

Enriched populations of pyramidal neurons were isolated from the postmortem ACC tissue of schizophrenia ($n = 20$) and control ($n = 20$) subjects using (LMD).

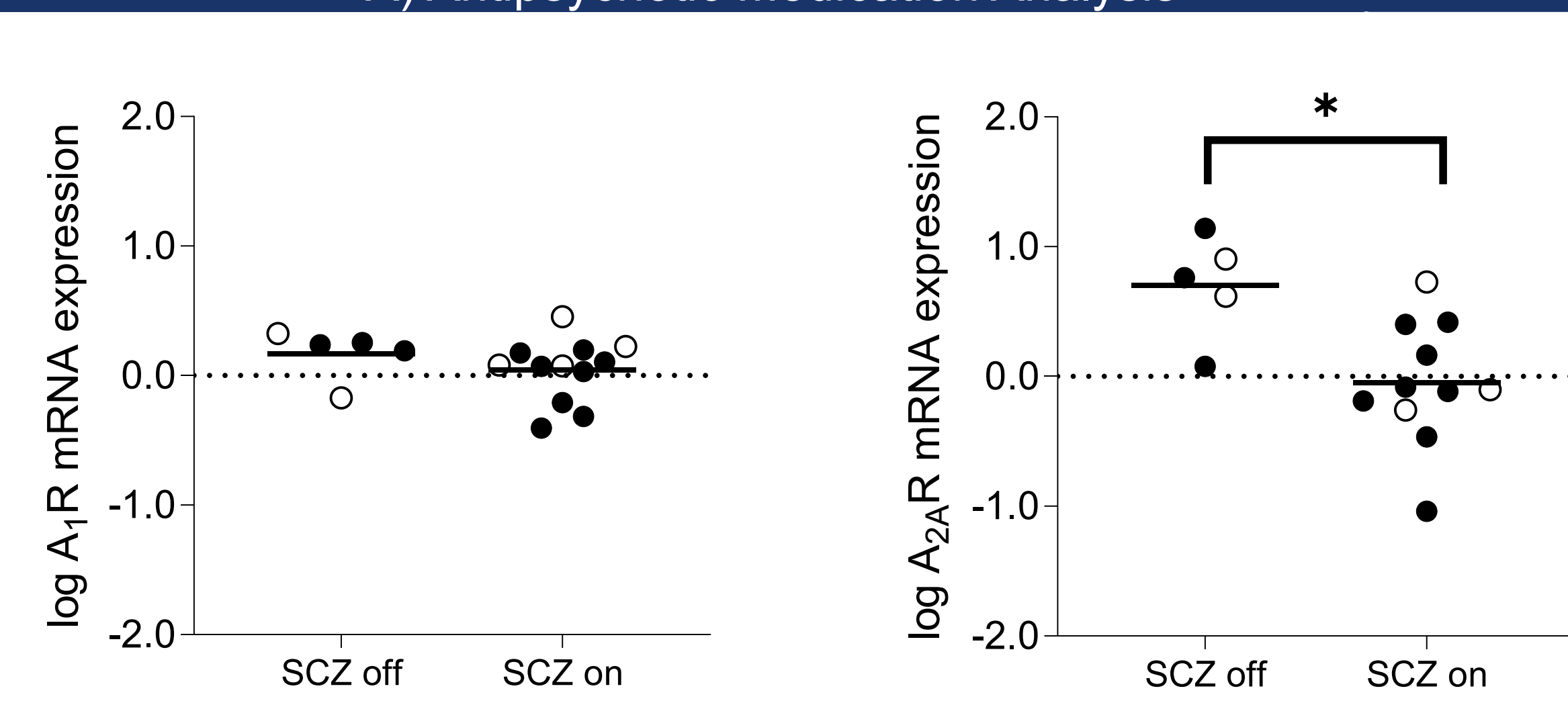
Expression of A_1Rs and $A_{2A}Rs$ was assayed using quantitative polymerase chain reaction (qPCR). A_1R and $A_{2A}R$ expression was quantified and analyzed based on sex, clinical dementia rating (CDR) scores, and antipsychotic use.

ACKNOWLEDGMENTS

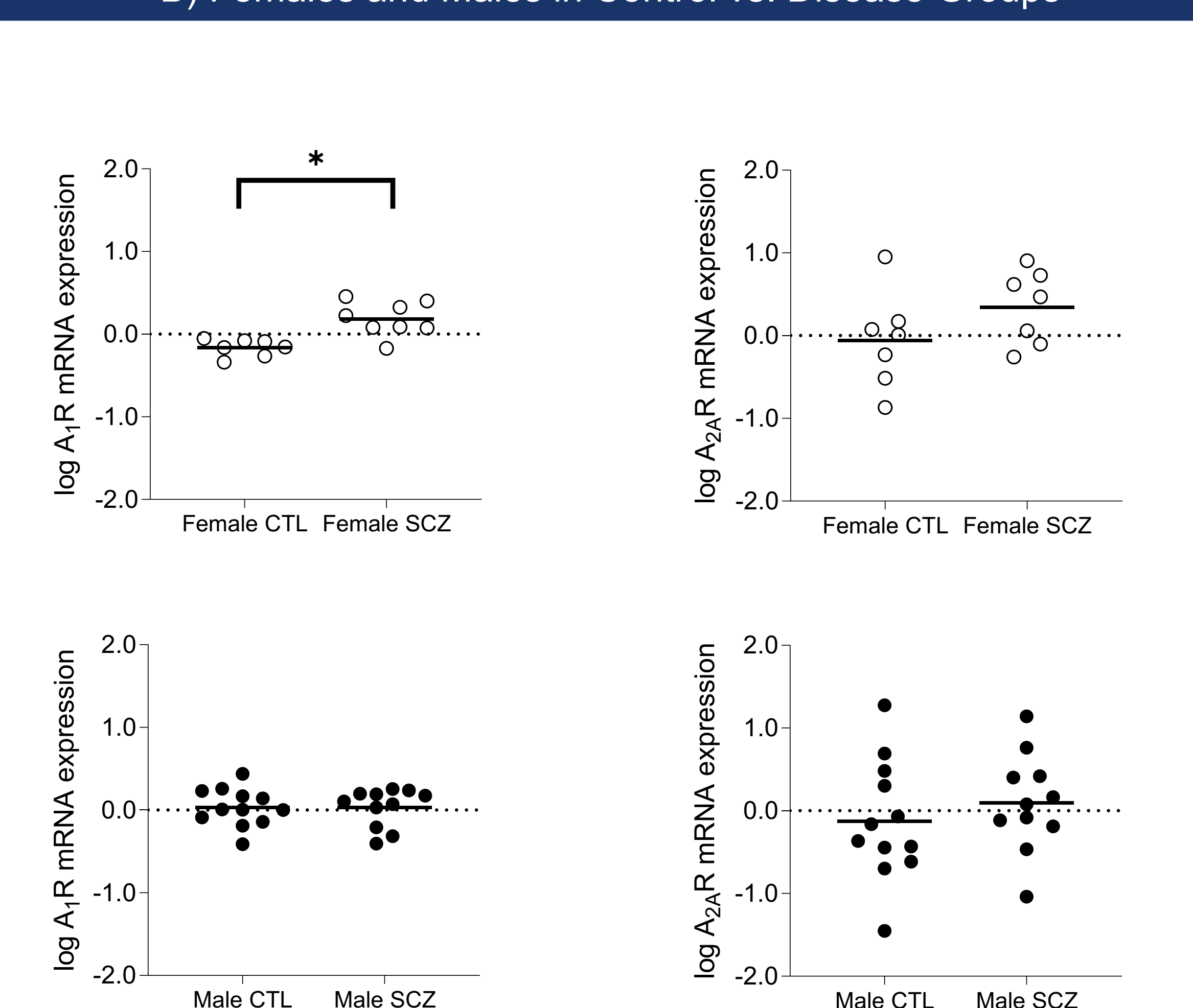
This research was funded by the National Institute of Mental Health (MH107487) and the American Foundation of Suicide Prevention (YIG-1-139-20).

RESULTS

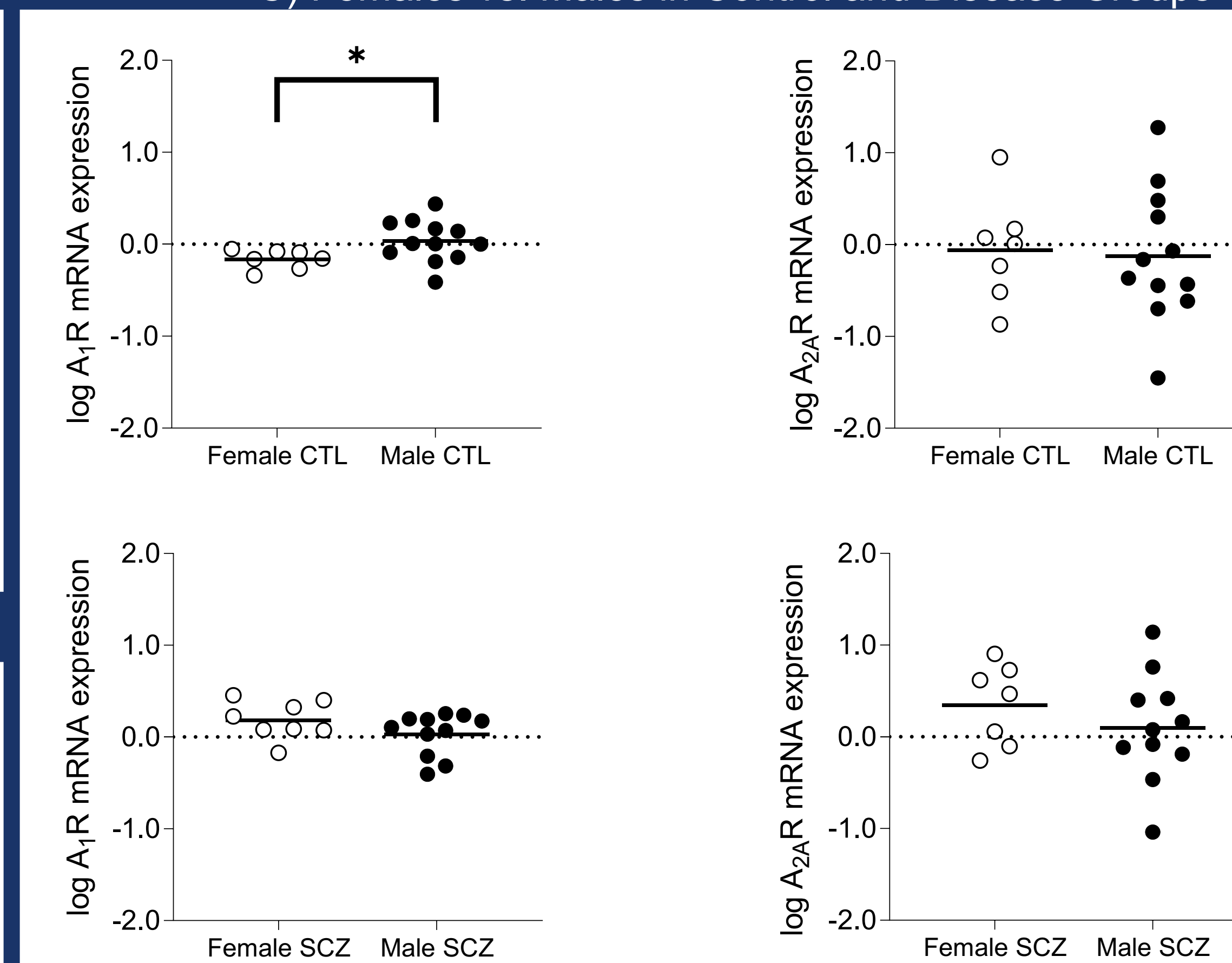
A) Antipsychotic Medication Analysis



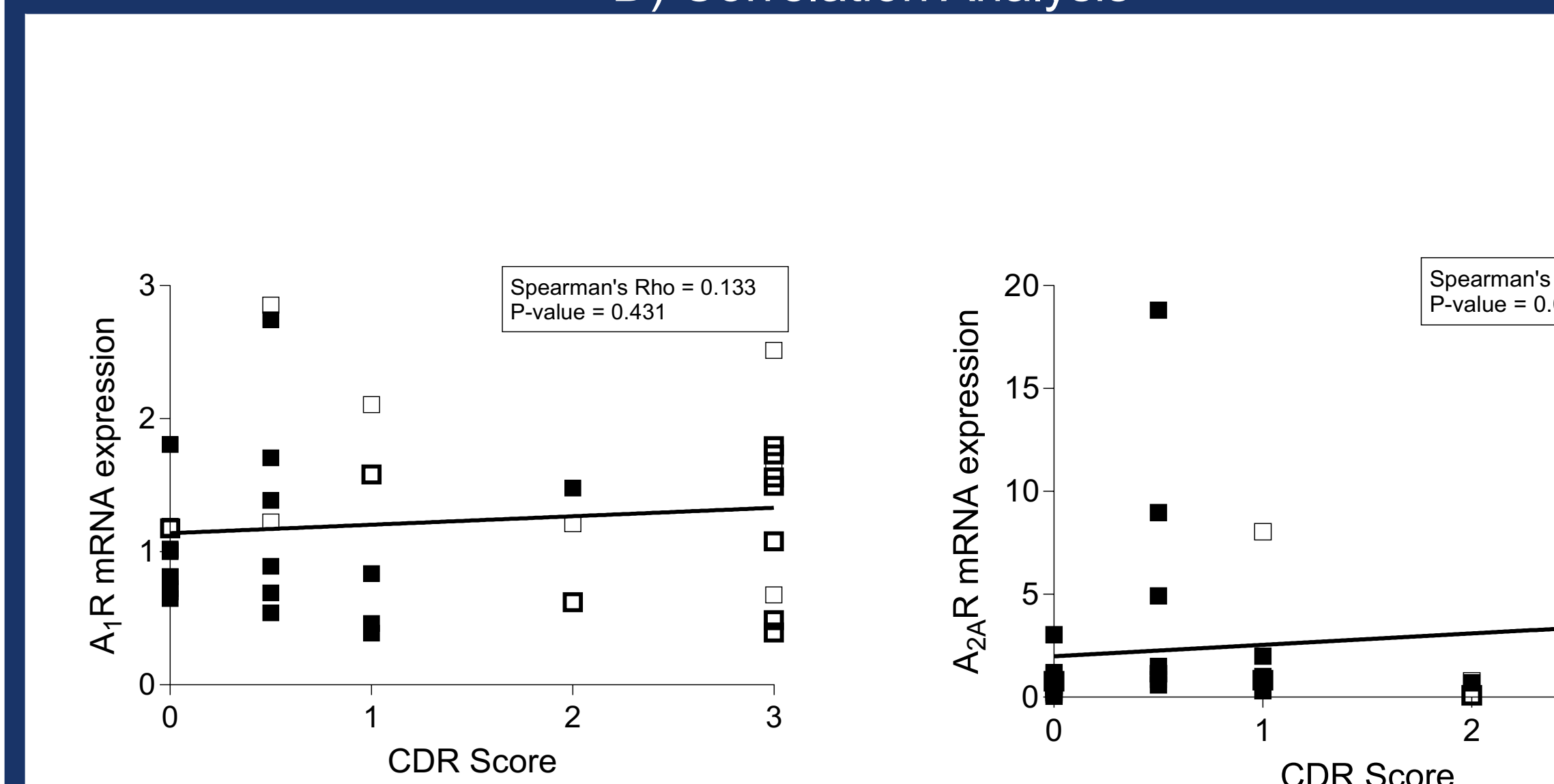
B) Females and Males in Control vs. Disease Groups



C) Females vs. Males in Control and Disease Groups



D) Correlation Analysis



A) $A_{2A}R$ mRNA expression was significantly increased in schizophrenia subjects who were off antipsychotic medication (ANCOVA: $F_{(1,12)}=6.444$, $p=0.026$).

B) A_1R expression was significantly increased in female schizophrenia subjects compared to female controls ($t_{(13)}=-4.008$, $p=0.001$).

C) A_1R expression was significantly decreased in female controls compared to male controls ($t_{(17)}=2.137$, $p=0.047$).

D) There was a significant positive association between dementia severity and $A_{2A}R$ mRNA expression (Spearman's $r=0.424$, $p=0.009$).

In Figures A-C, open circles indicate females, closed circles indicate males. In Figure D, open squares indicate schizophrenia, closed circles indicate controls.

DISCUSSION

- The results from our medication analysis indicate that $A_{2A}R$ expression may be normalized by antipsychotic treatment; however, a limitation of this analysis is the low number of subjects ($n = 5$) off antipsychotic medications.
- A_1R expression was increased in female schizophrenia subjects compared to female controls, indicating sex-specific increases in A_1R expression in this study.

- A_1R expression was significantly decreased in female controls compared to male controls, suggesting sex differences in basal A_1R expression.
- There is likely a relationship between dementia severity and $A_{2A}R$ mRNA expression, as subjects with more severe dementia have increased expression, regardless of sex.
- Overall, these results provide novel insights into the cell-subtype specific expression of adenosine receptors in the ACC in schizophrenia and suggest that changes in receptor mRNA expression may be sex-dependent and associated with dementia in these subjects.