



Gender Differences in the Cognitive Functions Sensitive to the Level of Dopamine in Prefrontal Cortex.

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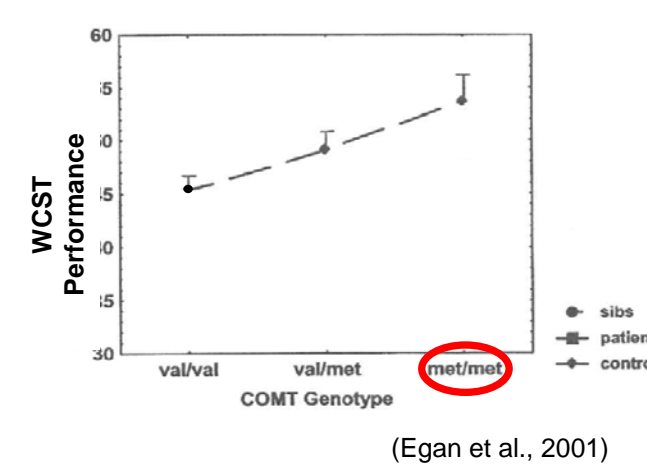
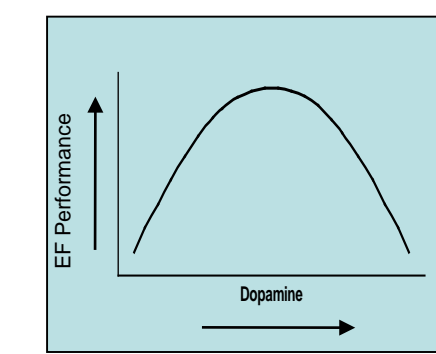


PURPOSE

- We obtained evidence that a gender difference might exist with respect to how a single nucleotide polymorphism (SNP) in the catechol-o-methyltransferase gene affects executive function performance^{1,2}. While one version of the gene might be more beneficial for males, the other version may be more beneficial for females. The current research attempted to A) replicate the gender by genotype interaction found by Diamond and colleagues, and B) further investigate why such a gender difference might exist, by examining how differences in estrogen levels between males and females might be involved in mediating the interaction.

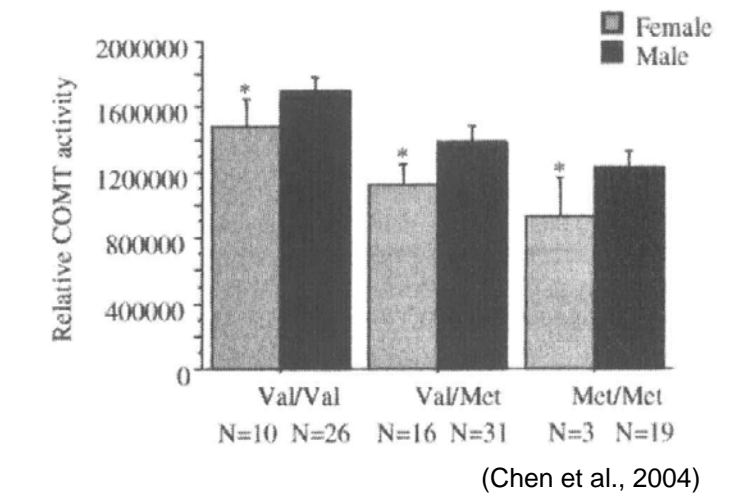
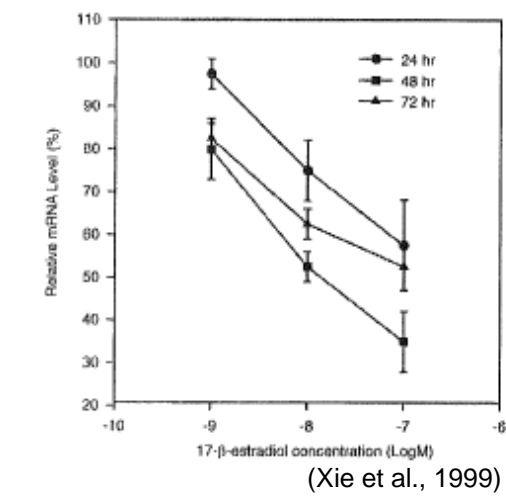
BACKGROUND

- Some executive functions have been shown to be sensitive to the level of dopamine (DA) in prefrontal cortex (PFC)^{3,4,5}. Indeed, reducing DA in PFC impairs performance on many EF measures (which depend upon PFC).
- An inverted U-shaped curve represents the relationship between the level of DA in PFC and performance of EF^{6,7,8,9}.
- PFC critically depends on 2nd mechanisms for the clearance of extracellular DA, such as the activity of catechol-o-methyltransferase (COMT)¹⁰, due to a relative dearth of dopamine transporters (DAT; the 1st mechanism for removal of extracellular DA in other brain regions).
- Variations in the enzymatic activity of COMT (due to variations in the gene which codes for the COMT) would therefore be expected to importantly impact PFC functions sensitive to the level of DA in PFC.
- Past research has shown that being homozygous the Methionine (Met) version of COMT, which results in a more sluggish COMT enzyme, results in better EF performance than being homozygous for the Valine (Val; more efficient) version of COMT, presumably due to higher levels of DA^{3, 11, 12, 13}.
- However, this result was not found by Diamond and colleagues with older females^{1,2}.



HYPOTHESIS

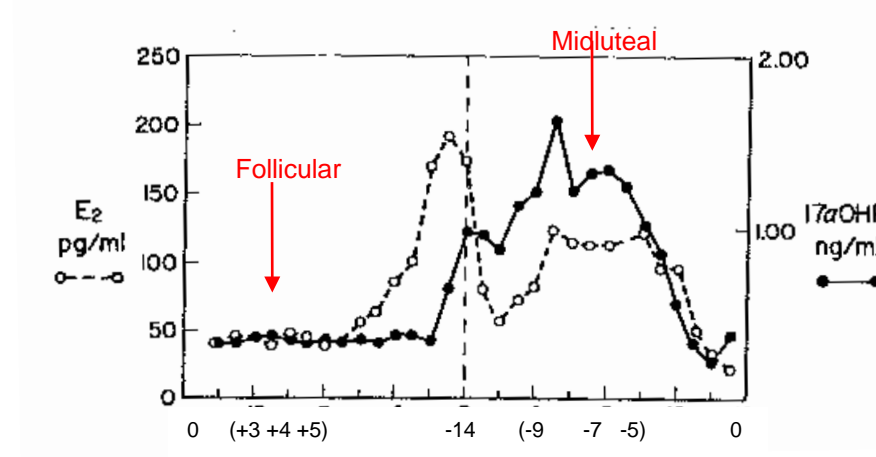
- The role of estradiol:
Estradiol has been shown to down-regulate the expression of the COMT gene^{14, 15}. COMT activity is ~30% lower in females than in males (independent of COMT genotype)¹⁶.
- We hypothesized that gender differences in the relative benefit of the Met and Val COMT genotypes should be greater in young adults (with circulating estrogen in women) than in older adults, and that the gender difference should be greatest at times during the menstrual cycle when estradiol levels are high.



METHODS

PARTICIPANTS: - 30 participants between the ages of 19-35.
- Homozygous for either Met or Val (genotype assessed using PCR, following collection of saliva during a pre-screening session (130 participants).

GROUPS: - Each female genotype group was further divided so half of the women were tested when their estradiol levels were high and half when their estradiol levels were low (different phases of the menstrual cycle).
- Groups were matched for ethnicity, age, IQ and levels of personal and parental education. The required information was collected during the pre-screening session, including administration of the Kaufmann Brief Intelligence Test II.



INCLUSION CRITERIA:
- Fluent in English.
- No hearing/visual impairments (unless corrected);
- No known neurological impairments, learning disorders, diagnoses of psychological syndromes, or history of brain injury;
- Caucasian ethnicity (due to the scarcity of the Met allele in certain populations^{17, 18}).
- Not taking any medications that affect thinking, memory, or mental clarity.
- Not in a physical state or taking medications known to disrupt the natural cyclicity of gonadal hormone (such as during pregnancy, nursing, or when taking oral contraceptive pills).

TESTING SESSION
- 3 tests of cognitive function (presented here).
- Salivary sample for progesterone assay (a relative indicator of estradiol levels).

COGNITIVE TESTS (METHODS CONT.)

- 1) **Hearts + Flowers:** - Participants are instructed to press a button on either the same side (hearts) or opposite side (flowers) to where a stimulus appears on a screen.

2) **F-A-S Verbal Fluency Test:** - Participants are given 1 min. to say as many different words as they can think of that begin with a specified letter (F, then A, & finally S)^{20, 21}.
- Involves the creative generation of words, holding in mind the responses you have already made, and inhibiting the tendency to repeat words^{22, 23}.
- Dependent primarily upon the left frontal lobe²⁴.
- May or may not depend upon DA in PFC^{25, 26}.
3) **Self-Ordered Pointing:** - Participants are instructed to touch one stimulus at a time in any order from a set of nine stimuli presented on a touch-screen monitor, without repeating a choice. However, after each response the screen refreshes and, while the same stimuli return presented in the same grid, the locations of individual stimuli have changed.
- Requires working memory (participants must encode the stimuli by appearance—not location) and inhibition to prevent repeating responses.
- Dependent upon dorsolateral prefrontal cortex^{27, 28, 29}.
- Independent of the level of DA in PFC^{30, 31}.

RESULTS

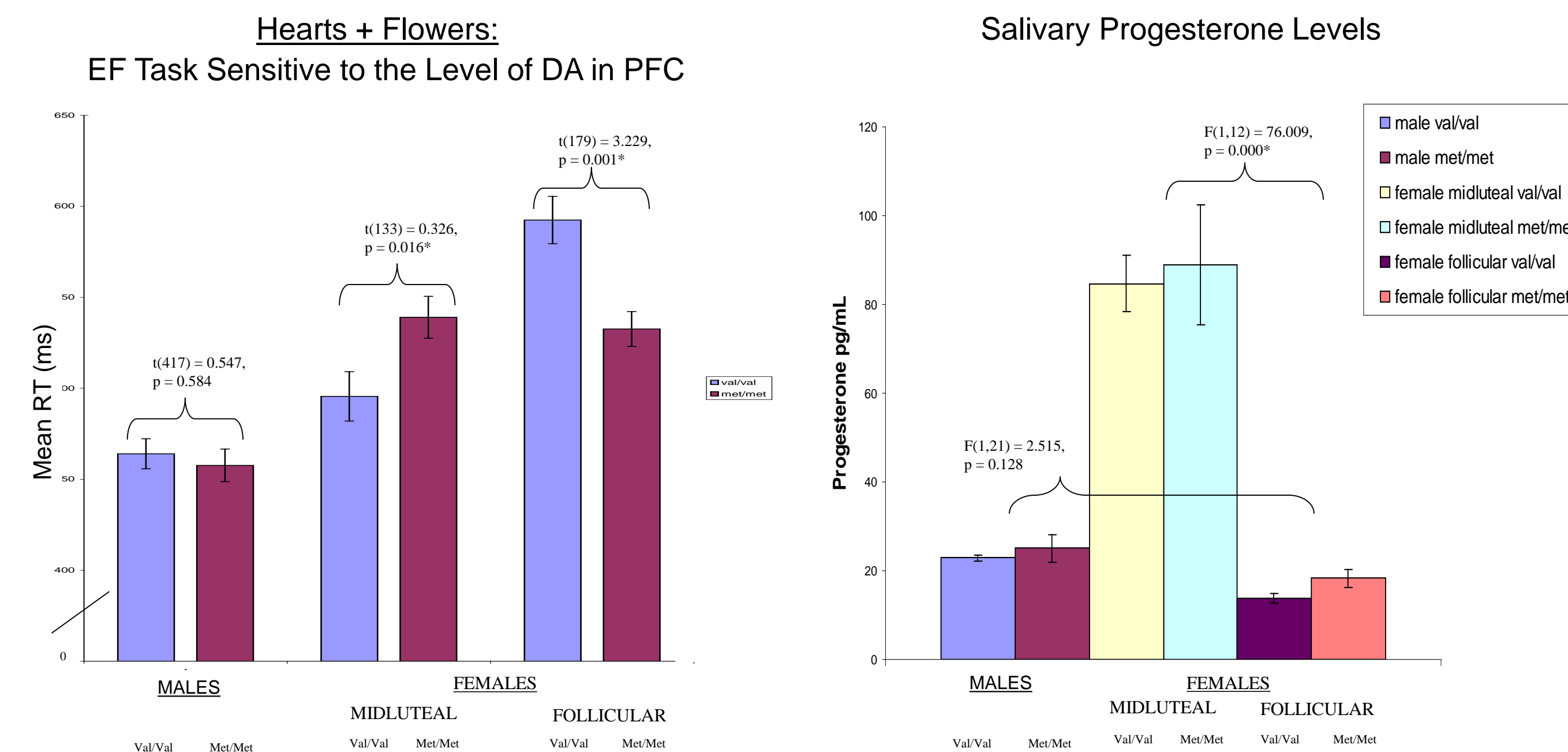


Figure 1. For the Hearts + Flowers task, the dependent measure was the average reaction time (measured in milliseconds) for the block of mixed heart & flower trials. Error bars represent standard error.
Figure 2. Average salivary progesterone levels for each group (measured in picograms/millilitre). Error bars represent standard error.

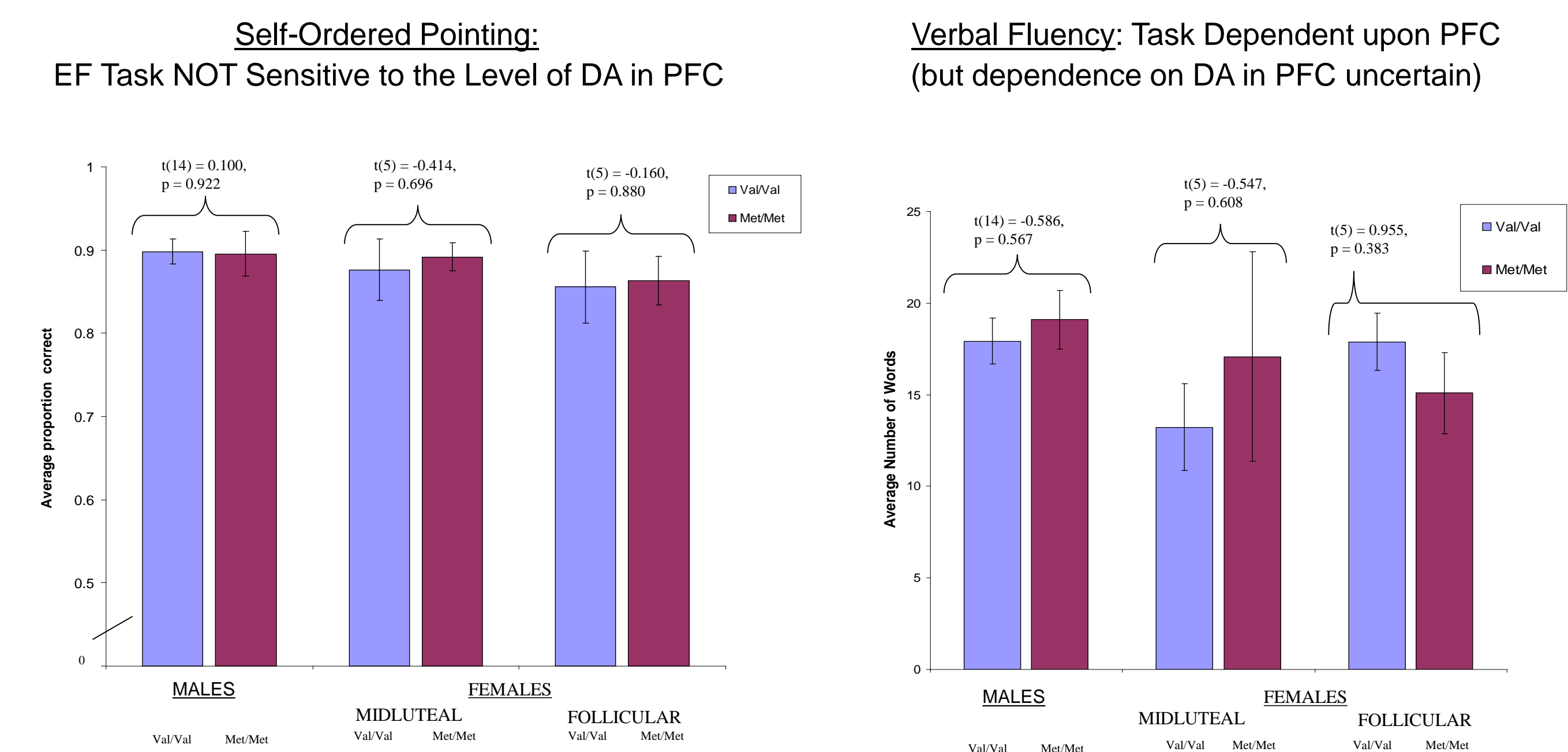


Figure 3. For Self-Ordered Pointing, the dependent measure was the average proportion of unique responses averaged across blocks 2 and 3. Error bars represent standard error.
Figure 4. Average of the mean number of words produced per person within one minute for each of the letters F-, A-, and S-. Error bars represent standard error.

CONCLUSIONS

- Females homozygous for Val performed better on the Hearts + Flowers task (an EF task dependent upon DA in PFC) than females homozygous for Met when estradiol levels were high.
- The results provide further support for the possibility of a gender difference in the effect of COMT genotype on EF performance.
- Estradiol likely plays a role in establishing the benefit of having the Val version of COMT in females, as the advantage of being homozygous for Val over being homozygous for Met was not as great during the phase of the menstrual cycle when estradiol levels are low.

IMPLICATIONS

- Many of the neuropsychiatric disorders implicating DA in PFC demonstrate gender differences in their manifestation, including prevalence, time course, treatment responses, etc.^{32, 33, 34}.
- The results of the current study may:
A) provide a framework for studying some of the gender differences in the manifestation of these disorders.
B) have implications for how medications that affect DA neurotransmission in PFC are prescribed (many of which are currently prescribed on the basis of clinical trials conducted exclusively using males³⁵).

LIMITATIONS & REMEDIATIONS

- 1) **Limitation:** Small sample size.
Remediation: The current results are part of a larger ongoing study for which more participants are being recruited.
2) **Limitation:** Estradiol levels were not measured directly.
Remediation: As part of the larger ongoing study, salivary estradiol levels will be assessed.
3) **Limitation:** The effect of high and low estradiol levels was assessed on a between-subject basis.
Remediation: As part of the larger ongoing study, each participant is being tested twice on comparable A- and B- versions of each cognitive task.
Each female is tested once when estradiol levels are low and once when estradiol levels are high (with females counterbalanced for order of menstrual cycle phase).
4) **Limitation:** Even mild stress has been shown to increase the level of DA in PFC.
Remediation: The level of salivary cortisol at the time of testing is being measured in the overall study in order to control for stress levels at the time of testing.

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