

# Androgen treatment in Klinefelter syndrome and its effects on hippocampal structure

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## Introduction

- Klinefelter syndrome (KS; 47,XXY), caused by supernumerary X chromosomes, is the most common sex chromosome aneuploidy in males
- Standard treatment for KS consists of testosterone replacement therapy starting at or around puberty
- Whether this treatment influences the brain and corresponding behavior is unknown

### Current Study Goal

- To assess the effect of testosterone replacement therapy on hippocampal structure, an area of the brain:
  - known to show volume decreases in boys with KS relative to age-matched typically developing boys<sup>1, 2</sup>
  - containing dense populations of androgen receptors<sup>3, 4</sup>

## Participants

- A subset of participants from a 2 year, randomized, double-blind clinical trial of Oxandrolone<sup>5</sup> were scanned on a 3T MRI scanner
- KS participants had karyotyped diagnosed XXY, <10% mosaicism for 46,XY cell line, no evidence of spontaneous onset of puberty, and no treatment with androgen in the year before the study

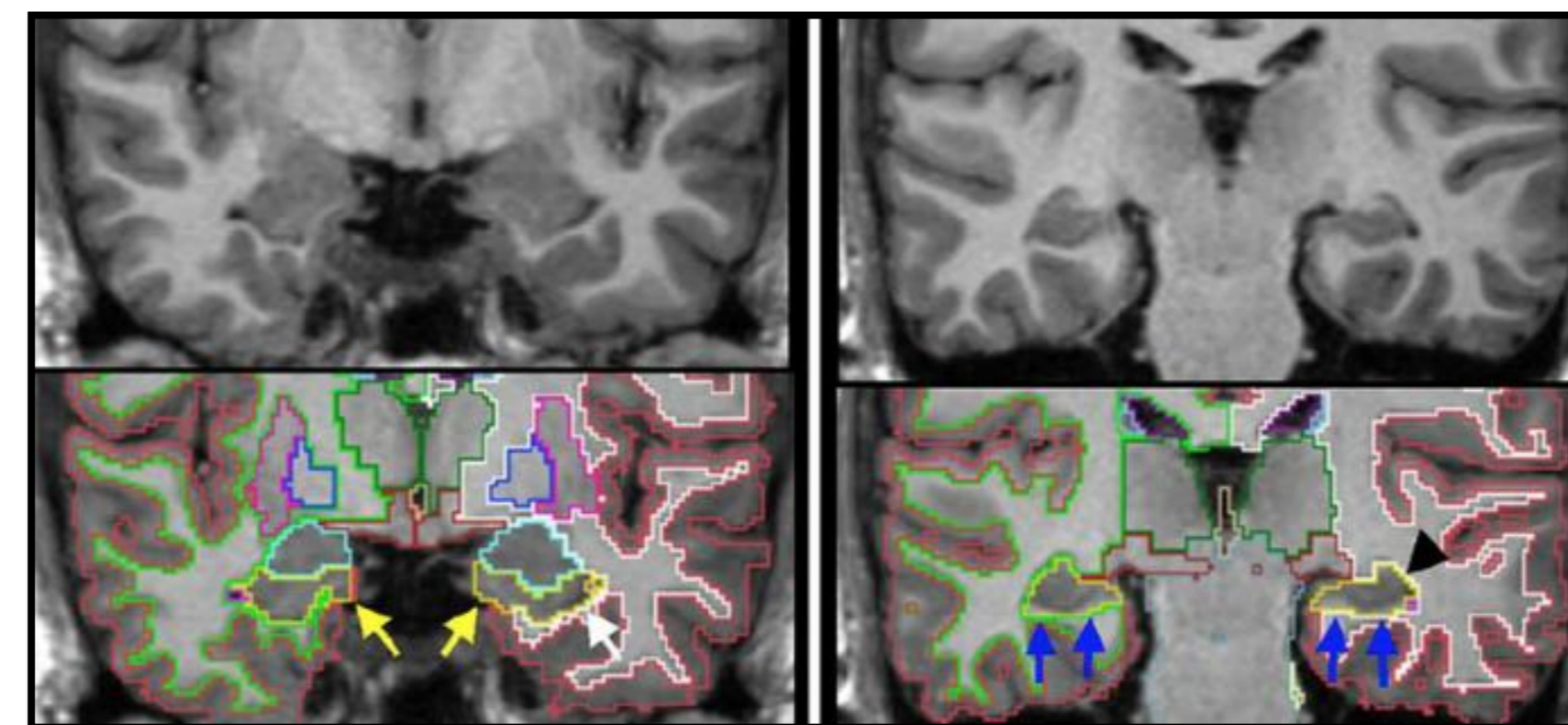
	Treatment	Placebo	TD Control	P
N	10	13	12	-
Oxandrolone dose (mg/kg/day)	0.06	0	-	-
Age at scan (years)	10.9 (1.3)	11.6 (1.5)	11.1 (2.0)	0.581
TGMV (cm <sup>3</sup> )	638.0 (37.2)	611.4 (44.7)	632.0 (42.5)	0.210
Performance IQ	102.0 (14.0)	104.4 (19.6)	115.1 (10.0)	0.125
Verbal IQ	94.3 (12.2)	96.2 (17.4)	116.7 (11.0)	0.002
FSIQ	97.5 (12.8)	98.4 (19.9)	118.0 (12.6)	0.010

TD, typically developing; TGMV, total gray matter volume; FSIQ, Full-scale intelligence quotient. Values indicate means and standards deviations

## Analysis

### Hippocampus delineation

- An automated MRI analysis tool (FreeSurfer)<sup>6</sup> was used to complete initial segmentation of the hippocampus
- The automated segmentations were then manually reviewed and corrected by a rater who was blinded to participant group

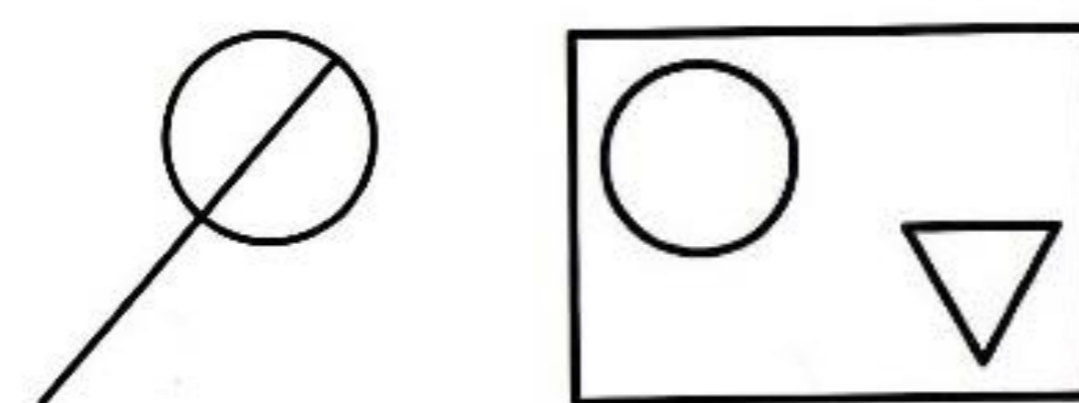


### Statistical analysis of hippocampal volumes

- Regional volumes were compared between groups (placebo, oxandrolone, TD control), while controlling for total gray matter volume (TGMV) and age

### Statistical analysis between hippocampus volume and spatial memory

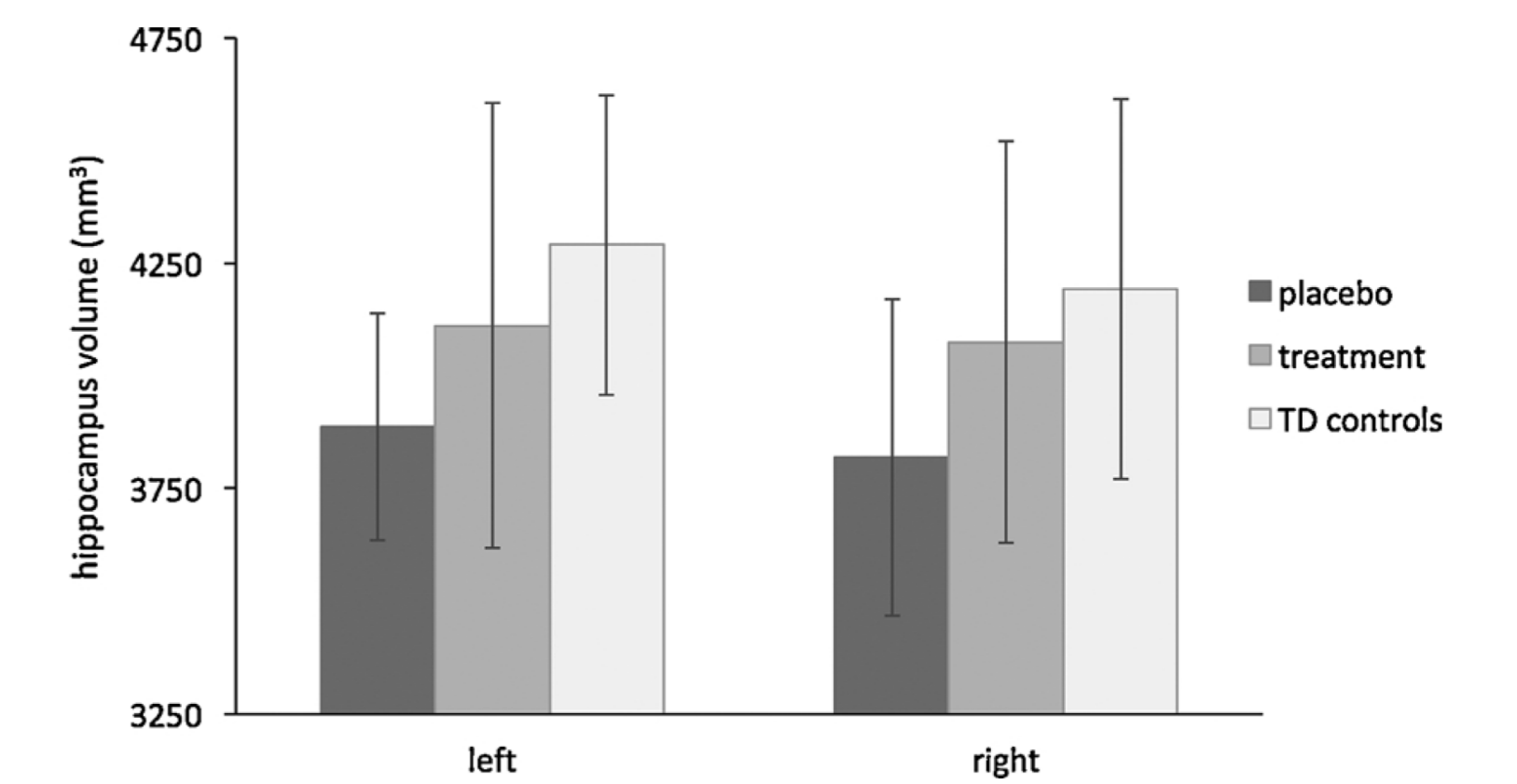
- To explore behavioral associations of hippocampal differences, correlations between hippocampal structure and age-adjusted (scaled) scores on the Recall of Designs subtest of the Differential Ability Scales (DAS)<sup>7</sup> were conducted



- This subtest involves cognitive functions that are known to be hippocampus-dependent<sup>8</sup>

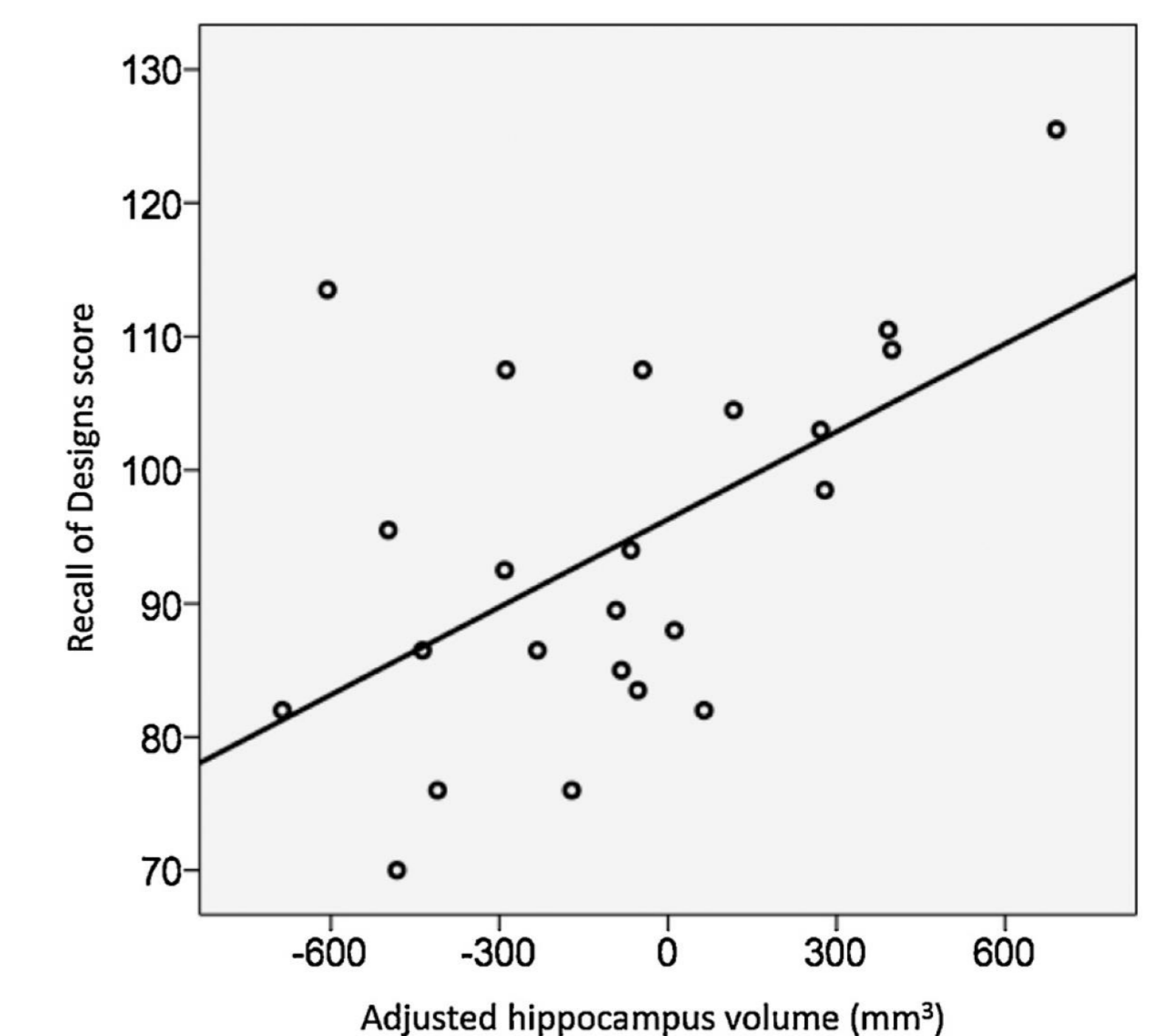
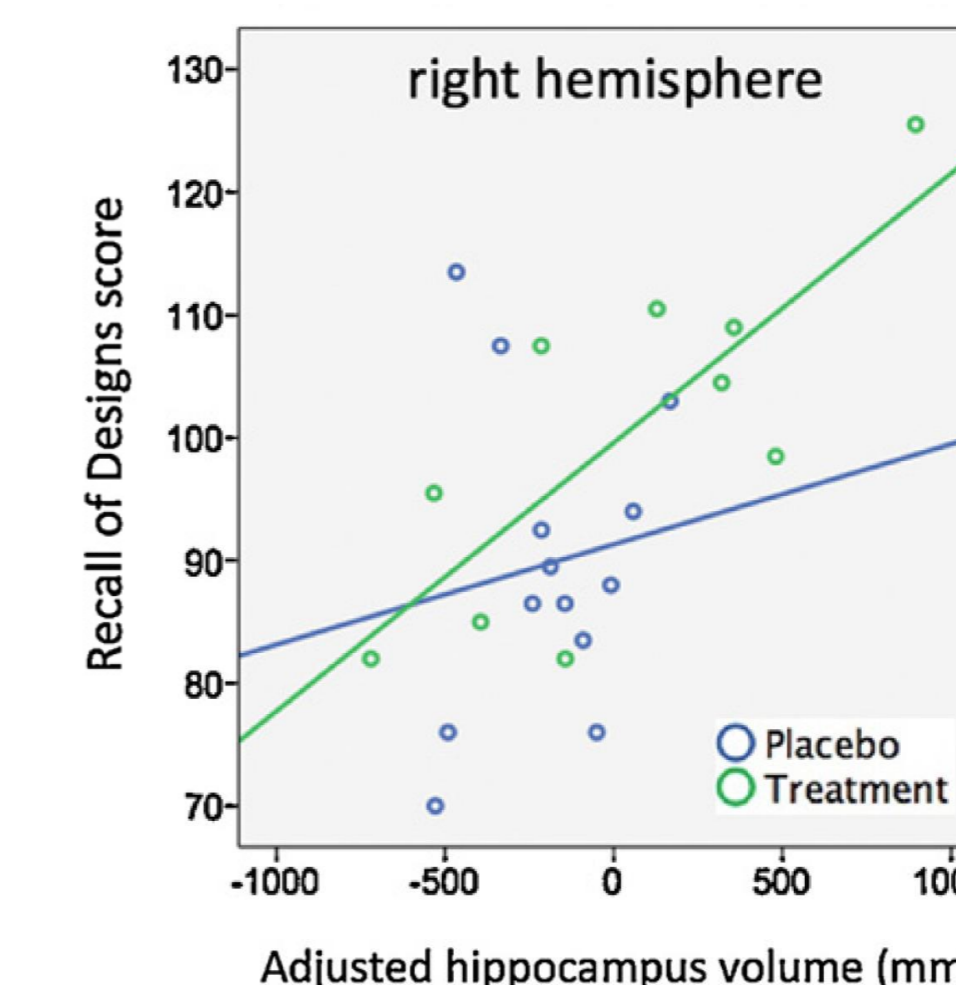
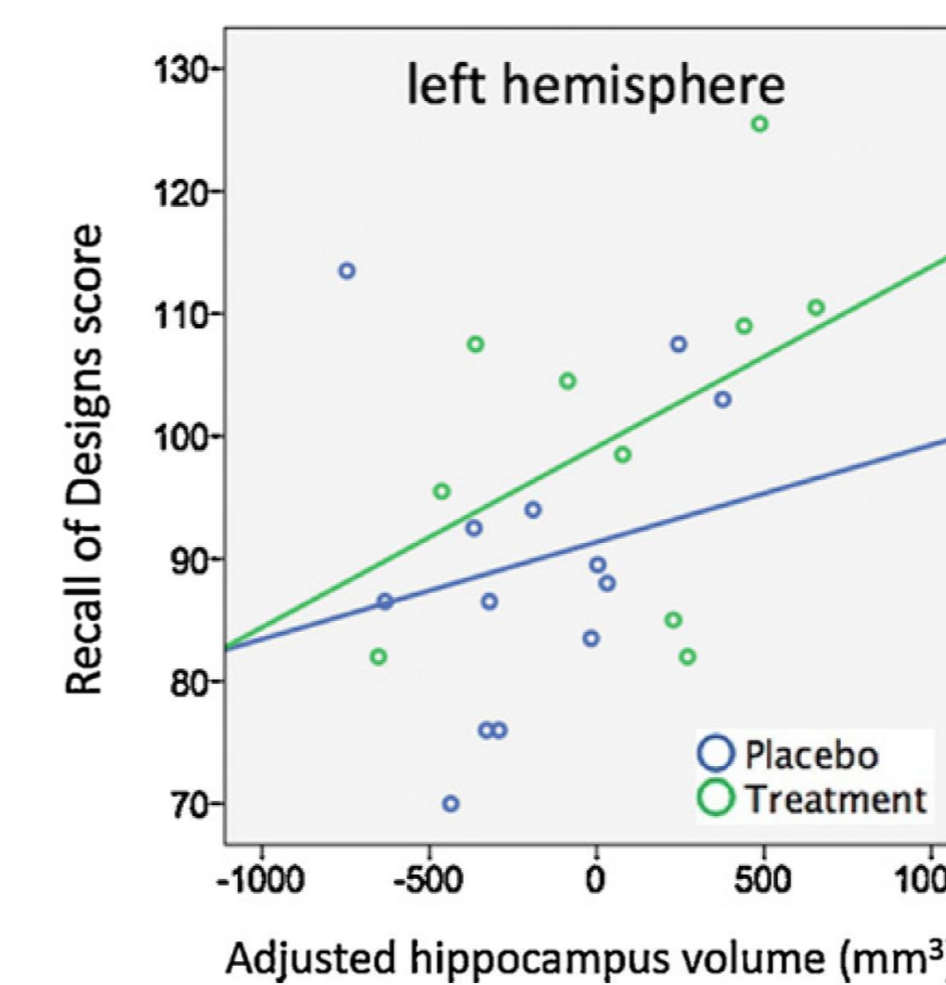
## Hippocampus Volume Results

- Right hippocampal volumes were significantly increased in the oxandrolone group relative to the placebo group ( $p=0.012$ )
- Left hemisphere differences were marginally significant ( $p=0.055$ )
- Hippocampal volumes were significantly decreased in the placebo group relative to the TD group ( $p=0.007$ )
- No hippocampal volume differences were observed between the oxandrolone group and the TD group ( $ps>0.05$ )



## Association Between Hippocampus Volume and Spatial Memory Results

- A significant association between hippocampus volume and scores on the Recall of Designs subtest were observed across KS subgroups (oxandrolone and placebo;  $p=0.0007$ )
- These associations were primarily driven by the left hemisphere



## Conclusions

- Treatment with low doses of oxandrolone in boys with KS is associated with increased hippocampal volume
- These differences have direct ties with behavior, as indexed by a spatial memory task
- These findings suggest a possible mechanism through which testosterone replacement therapy may exert the beneficial improvements to cognition and behavior found in other research

## Acknowledgements & References

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<sup>1</sup>Bryant et al., 2011; <sup>2</sup>Hong et al., 2014; <sup>3</sup>Frankfurt and Luine, 2015; <sup>4</sup>Leranth et al., 2003; <sup>5</sup>Ross et al., 2017;

<sup>6</sup>Version 5.3, <http://surfer.nmr.mgh.harvard.edu>; <sup>7</sup>Elliott, 1990; <sup>8</sup>Shrager et al., 2007