XXY (Klinefelter Syndrom): A fMRI Study of Prepubertal Boys

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Introduction: An extra X chromosome in males, or Klinefelter Syndrome (KS) (also known as 47,XXY), is the most common sex-chromosome aneuploidy in humans. Serving as a homogeneous model for studying both androgen deficiency and learning disability in childhood, the KS phenotype is distinguished by testicular failure and childhood androgen deficiency [1], and the KS neurocognitive phenotype includes impaired motor function, language-based learning difficulties, and attention/working memory deficits [2]. The purpose of this study was to use BOLD fMRI to investigate the functional brain differences between boys with KS (8-12 years) and age-matched control boys, and to examine effects of androgen replacement therapy on brain function, in order to improve our understanding of cognitive deficits associated with KS and androgen deficiency, and understanding of mechanisms underlying androgen impact on cognition in male neurocognitive development.

Method: Participating subjects included 16 boys with KS and 12 age- and socioeconomic status-matched normal boys. All were prepubertal. We also conducted fMRI with verb generation and visual-motor tasks on 3 boys with KS before and after 6 months of androgen treatment (same dose of androgen as in our ongoing clinical trial). MR data were acquired using a Philips 3.0T whole-body clinical MRI system and a 8-channel SENSE head coil. Each fMRI scan lasted 5 minutes, collecting a time series of images of 120 time points, using a single-shot gradient echo EPI sequence sensitized to the BOLD contrast (TR/TE/α = 2.5s/35ms/90^o, 36 interleaved slices of 4mm thickness, zero inter-slice gap, 2mmx2mm in-plane resolution). Verb generation, and visual-motor tasks were employed to examine language, motor and visual functions in KS. The 5-min verb generation scan consisted of 5 cycles of "30s Control /30s Task" conditions. Each "Verb Generation Task" epoch consisted of 10 random nouns each of which was shown at the center of the screen for 2s, and a plus sign ("+") was shown on the screen for 1s in between two consecutive nouns. In each "Control" epoch, four pound signs ("####") were shown at the center of the screen for 2s, alternated with a plus sign ("+") shown for 1s. The subject was instructed to think about a verb related to each noun, while not to think about anything during the "Control" epochs. The 5-min visual-motor task scan consisted of 5 cycles of "30s Motor/30s Visual". Each "Motor" epoch consisted of 10 random numbers (1,2,3,4,5) each of which was shown at the center of the screen for 2s, and a plus sign ("+") was shown on the screen for 1s in between two consecutive numbers. The subject was instructed to press the fingers of both hands corresponding to the number shown on the screen. In each "Visual" epoch, a flashing checkerboard pattern was shown on the screen with a contrast reversal rate at 8Hz. The subject was instructed to focus on a red plus sign at the center of the screen. The red plus sign disappeared from time to time at a random rate, and the subject was instructed to press his index fingers when the red plus sign went away.

Results: 14 KS and 10 normal boys were able to finish all the fMRI scans, and their data were included in the analysis. There were no significant differences in age (p = 0.76) and motion (absolute: p = 0.76, relative: p = 0.70) between controls (N = 10, mean age = 10.6 years, 0 left-handed) and KS (N = 14, mean age = 10.1 years, 1 left-handed). Figure 1 revealed significantly reduced activation in brain regions implicated in articulation and semantic processing including the left insula and inferior frontal gyrus (IFG) in the KS compared to the control groups. In the comparison of the 3 boys with KS, pre- and post-androgen treatment for 6 months, we observed significantly increased bilateral activation in the insula and IFG. Figure 2 showed significantly reduced activation in the sensorimotor region and SMA in KS compared to controls. In the comparison of the 3 boys with KS, pre- and post-androgen treatment for 6 months, we observed significantly increased activation of the sensorimotor region and SMA after treatment. No significant difference in visual activation was observed between the groups. In the comparison of the 3 boys with KS, pre- and post-androgen treatment for 6 months, we observed no significant change in visual activation.

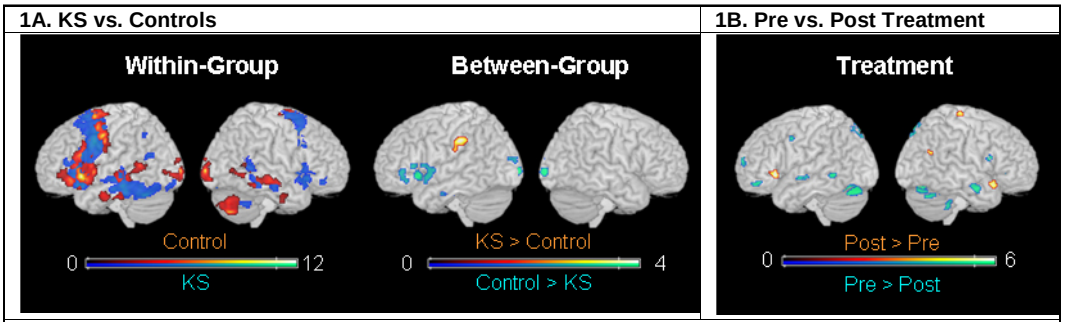

Figure 1. Brain activation patterns during a verb generation task: A. KS compared to controls and B. KS baseline and treated with androgen for 6 months. 1A. Brain activation patterns at baseline in KS (cold colors, left panel) and in Controls (warm colors, left panel) and comparing between KS and controls (KS > Controls, warm colors, right panel; Controls > KS, cold colors, right panel). 1B. Brain activation patterns that show significant differences before and after treatment (6 months) in three subjects with KS (mean age at baseline: 10.9 years; Post > Pre, warm colors; Pre > Post, cold colors). Statistical threshold was set at p = 0.001 for the baseline scan (random effects analyses) in KS and control boys, and p = 0.05 family-wise error (FWE), extent threshold (ET) = 10 for pre- post-treatment scans (fixed-effects analyses) in KS boys.

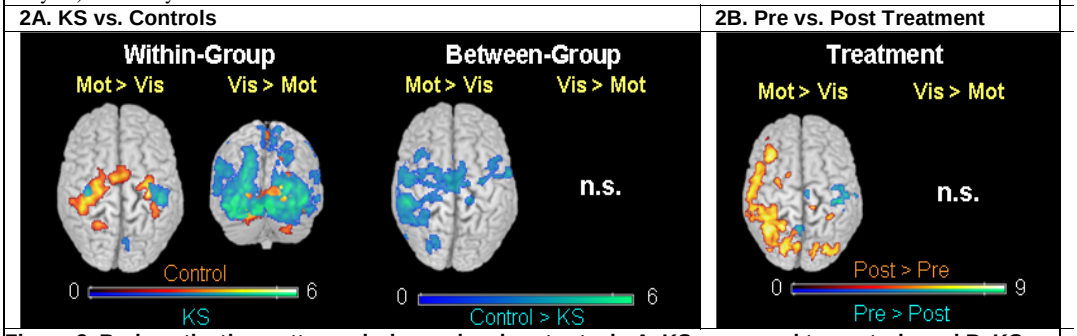

Figure 2. Brain activation patterns during a visual-motor task: A. KS compared to controls and B. KS baseline and treated with androgen for 6 months.
2A. Brain activation patterns at baseline in KS (cold colors, left panel) and in Controls (warm colors, left panel) and comparing between KS and controls (KS > Controls, warm colors, right panel; Controls > KS, cold colors, right panel) for the Motor > Visual and Visual > Motor contrasts. 2B. Brain activation patterns that show significant differences for the Motor > Visual contrast before versus after treatment (6 months) in three subjects with KS (mean age at baseline: 10.9 years; Post > Pre, warm colors; Pre > Post, cold colors). Pre- compared to post-treatment for Visual > Motor (control task) showed no significant change with treatment). Statistical threshold was set at p = 0.001 for the baseline scan (random effects analyses) in KS and control boys, and p = 0.05 corrected family-wise error (FWE), extent threshold (ET) = 10 for pre- post-treatment scans (fixed-effects analyses) in KS boys.

Discussion and Conclusion: Relative to the age-matched control group, boys with KS showed aberrant activation patterns in a regional specific manner, depending on the cognitive operation (language and motor functions). Our results are consistent with the known motor dysfunction, and deficits in language in KS [2]. Aberrant activation patterns showed 'normalization (i.e., increase in activation)' with androgen treatment, suggesting that androgen treatment may improve aspects of brain function in KS.

References: [1] J. Ross, et al., Horm Res, 2005. 64: 39-45. [2] C.L. Fales, et al., J Int Neuropsychol Soc, 2003. 9(6): 839-46.