Kallmann syndrome (KS) is a rare inherited disorder (affecting about 1 in 10,000 males), clinically characterized by the association of hypogonadotropic hypogonadism and hypo-/anosmia.

Both KS clinical hallmarks derive from a disturbed intrauterine migration process involving olfactory axons and gonadotropin-releasing hormone neurons from the olfactory placode to the hypothalamus.

The failure of the migration process results in hypo-/aplasia of the rhinencephalon (olfactory bulbs and tracts) and in altered gonadotropic axis function with low levels of sex hormones.

The most known morphologic brain feature is the reduction in depth and length of the olfactory sulcus, which typically turns medially, opening anteriorly into the interhemispheric fissure.

This sulcal abnormality is thought to be driven by the absence/hypoplasia of the olfactory bulbs and represents an intriguing model of genetically driven developmental brain abnormalities.

By conventional MR imaging and novel quantitative sulcation, curvature, cortical thickness, and tract-based spatial statistics (TBSS) analyses we have featured in a large sample of 45 male patients affected with KS the morphologic and structural brain involvement.

In particular, our study showed that patients with KS display surface cortical variations and gray and white matter volume changes, which clustered symmetrically in the frontal basal regions, close to the olfactory bulbs (gyrus rectus, medial orbital-frontal gyrus).

Changes in the frontal basal regions have been consistently described in the rhinencephalon and contiguous cerebral cortical and bone structures by pathology, conventional MR imaging, and CT studies in patients with KS. Increased volume of the corticospinal tracts and corpus callosum has been also depicted by conventional
MR imaging, suggesting the involvement of brain structures beyond the basal forebrain, though these findings have not been confirmed in larger series.

In our VBM whole-brain analysis, gray and white matter changes appeared fairly symmetric and limited to the frontal basal regions.

White matter volume changes (ie, decrease of white matter volume) were found exclusively in small subcortical areas of the medial orbital-frontal gyri close to the olfactory sulci. Similarly, VBM analysis disclosed small symmetric and contiguous areas of increased and decreased gray matter volume in the frontal basal regions close to the olfactory sulcus. The striking relationship between white and gray matter changes seems to suggest that these changes embody a fairly localized cortical-subcortical abnormal architectural development. Moreover, because all parenchymal changes are very close to the olfactory sulcus, they are most likely induced by the rhinencephalon hypo-/aplasia.

Except for these areas, by VBM analysis, cerebral gray and white matter did not differ between patients with KS and healthy controls. Similarly, TBSS analysis did not reveal any significant difference between patients with KS and controls, revealing that the ultrastructure of the white matter is preserved despite significant forebrain cortical changes. Nonetheless, KS genetic heterogeneity does not allow the exclusion of white matter hypertrophic or degenerative phenomena in specific subgroups of patients with KS because a strict genotypic/MR imaging phenotypic correlation requires a larger sample. Actually, no pathologic study reported brain parenchyma abnormalities in patients with KS, even though histologic data are very scarce. Peripheral axonal degeneration due to the absence of the olfactory bulbs has been shown in the olfactory mucosa, but concomitant significant processes of axonal degeneration within the brain are not supported by VBM and TBSS findings.

Consistently, the whole-brain curvature and sulcation analyses showed symmetric cortical abnormalities strictly confined to the frontal basal cortical regions (gyri recti and medial orbitalfrontal gyri). Olfactory sulcus abnormalities were expected because the reduction in depth and length of the olfactory sulcus at gross pathology and conventional MR imaging evaluation is a known morphologic feature of the brain in patients with KS.

Olfactory sulcus abnormalities have been associated with embryogenic olfactory bulb–inducted processes.

In patients with KS, the aplasia/hypoplasia of the olfactory bulbs is associated with an ipsilaterally decreased depth of the olfactory sulcus, which might turn medially, opening anteriorly into the interhemispheric fissure.

Indeed the olfactory sulcus presented with decreased sulcation and curvature, while the medial orbital-frontal sulcus showed a “compensatory-like” increased sulcation and curvature. The concomitant changes of the contiguous orbital-frontal regions seem to highlight a more extensive effect of the olfactory bulbs on forebrain morphogenesis.
Most interesting, patients with KS display increased cortical thickness very close to VBM, sulcation, and curvature forebrain anomalies, suggesting that olfactory bulb–induction failure might act not only on the sulcal but also on the structural organization of the cortex.

Regional gray matter increase has been associated with the absence of a sulcus, though so far no study investigated the correlation between cortical thickness and sulcation abnormalities, to our knowledge. We might speculate that a less deep sulcus results in an abnormal regional gray matter volume and cortical thickness as a consequence of overcrowding neurons migrated to this region. Alternatively, gray matter volume and cortical thickness changes might result from cortical functional differences between patients with KS and controls. The orbital-frontal cortex is deeply involved not only in olfaction (odor identification and olfactory memorization) but also in integrating emotion into cognition within decision-making processes.

KS is clinically characterized by the absence or reduction of olfaction, whereas few data are available on cognitive functioning and psychiatric risk, though schizophrenic disorders have been anecdotaly reported among patients with KS.

Nonetheless, the primary and secondary olfactory cortices correspond to piriform and periamygdalar cortices and the posterior orbital-frontal gyrus and insula, all areas that in our study did not present with gray matter and cortical thickness changes. Moreover, none of our patients presented with a history of overt psychiatric disease, even though a specific neuropsychological and psychiatric assessment was not performed. Focused neurocognitive studies are warranted to investigate the presence of basal forebrain function impairment due to the above-mentioned morphologic and structural brain changes.

Finally, the changes observed in our study might be at least partly ascribed to hormonal differences between patients with KS and controls. Most of KS phenotypic features (hypogonadism, small penis, sexual secondary characteristics) are due to low testosterone levels during infancy and adolescence, which could also induce a feminine brain development. Sex brain dimorphism includes brain size, white and gray matter volume and regional cortical thickness changes.

This study did not reveal significant differences in brain size between patients with KS and controls.

Moreover, sex- and testosterone-related brain differences do not seem to involve the medial orbital-frontal basal regions, thus restraining the direct role of hormonal dysfunction in determining the morphologic pattern observed in patients with KS. Longitudinal studies on patients with KS enrolled before hormone replacement therapy will help clarify the effects of testosterone in postnatal brain development, even though the effect of hormone milieu on prenatal and early brain development phases will remain difficult to unravel.

_Brain Changes in Kallmann Syndrome_