Kallmann syndrome (KS) is a rare inherited disorder clinically characterized by the association of hypogonadotropic hypogonadism and hypo/anosmia. At conventional brain imaging, KS patients are featured by olfactory bulb hypo/aplasia and typical forebrain and anterior skull base morphological changes. Among male KS patients, about 40% present with a peculiar phenomenon consisting of insuppressible involuntary movements that mirror voluntary contralateral hand movements (mirror movements, MMs). Although MMs in KS have usually scarce clinical impact, their existence is intriguing as they unveil a genetically determined derangement of the complex circuitry committed to planning and execution of unilateral voluntary hand movement. Mild MMs are considered a physiological phenomenon before the age of 10, likely as a result of an incomplete brain myelination. Non physiological MMs have been reported in congenital (e.g. KS, Klippel-Feil disease, congenital cerebral palsy, corpus callosum agenesis, Joubert syndrome) and acquired conditions (Parkinson's disease, corticobasal syndrome, essential tremor, focal hand dystonia, Creutzfeld-Jakob disease, Huntington disease, stroke), thus highlighting the heterogeneous spectrum of diseases that might present this phenomenon. So far, the main pathogenic hypotheses of MM are: 1) abnormal persistence of the ipsilateral cortico-spinal tract, 2) abnormal interhemispheric transcallosal inhibition between the two motor cortices and/or 3) functional alteration of motor planning and motor execution. All these mechanisms should entail morphological, volumetric or ultrastructural brain changes such as cervical
spine neuroschisis, corpus callosum volume reduction due to defective transcallosal inhibitory fibers, or cortical-subcortical gray matter structure abnormalities.

Indeed, despite the early and rich description of MM since the 1930s (Bauman, 1932; Guttmann et al., 1939), the underlying neurological pathogenic mechanisms remain elusive and likely differ according to the associated disease. In KS, several authors suggest an involvement of the cortico-spinal tract mostly because cortico-spinal tract abnormalities have been observed in other inherited disorders, such as Klippel-Feil disease and Joubert syndrome, or the involvement of transcallosal networks based on the increased detection of midline abnormalities in KS (e.g. corpus callosum agenesis). The evidence for both hypotheses is however scarce.

On a large KS cohort, we recently showed with novel MRI techniques (including VBM, cortical thickness, curvature, sulcation and DTI based analyses), that KS patients present with specific structural forebrain cortical changes consistent with a localized profound derangement of cortex development. In the present study, besides all the abovementioned techniques, we applied MRI-based analyses focused on the motor cortical and subcortical brain structures to investigate whether KSMM + patients show specific brain anatomical and ultrastructural changes able to shed light on the intriguing phenomenon of MM.

The present study showed that KS patients with MM phenomenon have distinctive cortical and subcortical changes, mostly in regions involved in motor function (globus pallidus and both primary and secondary motor areas) by VBM and cortical thickness analyses. As the neural anatomical and functional underpinnings of MM have not yet been completely understood and several pathogenic hypotheses have been proposed (Galléa et al., 2011), in the paper will be discussed which theory best fits with the presence of MM in KS, according to the literature and our findings.

The results of our multimodality MRI study revealed a composite array of brain changes in KSMM+ that might represent the anatomical substrate of the mirror movement phenomenon in Kallmann syndrome.
Regarding the theories present in the literature our data: 1) seem to contrast the hypothesis of cortico-spinal tract abnormalities, 2) do not support the existence of abnormal transcallosal inhibitory pathways, and 3) sustain the presence of a rather complex motor (primary and secondary) cortical and subcortical (globus pallidus) reorganization that warrants focused functional studies to unravel the fascinating phenomenon of mirror movements.

**Brain anatomical substrates of mirror movements in Kallmann syndrome.**


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