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Causes for the Impact of Klinefelter Syndrome (KS) on Neurodevelopment: A Literature Review

By Keerat Kalsi Virdi

AUTHOR BIOGRAPHY

Keerat Kalsi Virdi is a junior at Eden Prairie High School in Eden Prairie, Minnesota. He is extremely passionate in biology, neuroscience and anatomy.

ABSTRACT

Klinefelter Syndrome (KS) is a genetic disorder which affects 1 out of every 600 males in the United States. Previous studies indicate KS has significant differences in areas such as quality of life, testicular function, and learning, although little research exists to explain the neurodevelopmental implications. The purpose of this literature review was to synthesize existing literature on KS, which was primarily categorized into the impacts on memory, brain volume and activation, and endocrine function. Research focusing on the neurodevelopmental implications of KS were selected, with a preference for studies which performed statistical analysis through an observational or experimental design. Articles were collected from a multitude of countries. Across the existing literature, KS has been shown to produce significant impairments on working memory and explicit memory, with negative neurodevelopmental impacts. KS exhibits reduced gray matter in the brain and limited activation in areas crucial for processes such as learning. In terms of endocrine function, KS produces reduced levels of testosterone, halting growth in parts of the brain essential to neurodevelopment. It has also increased the prevalence of Follicle Stimulating Hormone (FSH) resulting in numerous mental health disorders. Limitations include a lack of statistical significance in some studies, uniformity across multiple countries and research groups, and small sample sizes. Future research must address these concerns and foster collaboration between different specialists in the field of KS. These actions are imperative to improving early diagnosis of KS and create effective intervention strategies, improving quality of life for KS men and their families.

Keywords: *Klinefelter syndrome, KS, cognitive, XXY, neurodevelopment, neuroanatomical, memory, testosterone*

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INTRODUCTION

Episodic memory is the ability to recall specific events from personal experiences, or, as Allen and Fortin (2013) described it, the ability to "'mentally time travel' to reexperience individual events". It is one of the primary types of memory and falls under the broader category of declarative memory. Declarative memory refers to knowledge that can be consciously recalled and expressed in words (Pause et al., 2013). It is commonly divided into two subtypes: episodic memory, which stores personal experiences tied to specific times and places, and semantic memory, which stores general facts and knowledge about the Klinefelter Syndrome (KS), also referred to as the 47 XXY karyotype, is a genetic disorder affecting approximately 1 in every 600 males worldwide (Butler et al., 2022). It is caused by the presence of an extra X chromosome in males and is known to have measurable effects on factors such as growth, testicular function, and learning. Recent findings suggest broader impacts as well. Jordan et al. (2023) reported that individuals with KS may experience reduced quality of life, with lowered levels of life satisfaction, physical activity, and peer relationships compared to non KS individuals.

The World Health Organization defines neurodevelopmental disorders as "behavioural and cognitive disorders that arise during the developmental period that involve significant difficulties in the acquisition and execution of specific intellectual, motor or social functions" (Patel & Derrick, 2020). Although KS is not officially classified as a neurodevelopmental disorder, research indicates that it can have multifaceted neurodevelopmental consequences, particularly through cognitive dysfunction. Compared to its well-documented physical symptoms, the neurophysiological basis of KS remains less studied. Moreover, its classification as a genetic rather than a neurodevelopmental disorder has limited investigation into its cognitive and behavioral effects.

Despite being one of the most common genetic disorders in males, KS often goes undiagnosed. Specifically, it is estimated that only 25-35% of affected individuals ever receive a medical diagnosis, with the majority of cases diagnosed in adulthood (Davis et al., 2016). Historical data further indicate a potential upward trend in KS diagnoses, rising from 1.09 to 1.72 cases per 1000 live births (Morris et al., 2007). These trends highlight the importance of understanding the neurodevelopmental outcomes of KS, as greater knowledge may support early diagnosis and improve rehabilitation strategies.

The purpose of this literature review is to synthesize current research on the neurodevelopmental implications of KS, with a primary focus on memory, brain volume, activation, and endocrine function.

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METHODOLOGY

This literature review examined existing research on the neurodevelopmental impacts of KS, with particular attention to memory, brain volume, brain activation, and endocrine function. Peer-reviewed academic research papers were identified through the databases PubMed, Science Direct, and Google Scholar.

Most of the selected papers were published between 2020-2025. However, older studies were included for valuable historical context, comparison between sources, and definitions of technical terms. Preference was given to original research articles, especially those employing statistical analysis and comparing KS patients with non-clinical controls in observational or experimental settings. Review papers were used sparingly and primarily for clarifying terminology.

Selection prioritized studies that specifically examined KS in relation to neurodevelopment or neuroanatomy, ensuring relevance to the review's focus. While a few studies were region-specific (e.g.,United States), the majority of papers represented a multitude of countries, including the United Kingdom, Brazil, and Australia. Geographic origin was not, however, a determining factor in inclusion.

LITERATURE REVIEW

Before examining the specific causes of why KS affects neurodevelopment, it is important to understand its broader impact. Research consistently indicates that KS negatively affects academic learning, social outcomes, effective communication, and language development. For example, Fjermstead et al. (2023), found that men with KS performed significantly worse than non-KS controls on neurophysiological and cognitive tests, scoring on average18 points lower across three standardized IQ tests, revealing clear differences in cognitive ability.

Regarding academic outcomes, Simonetti et al. (2022) found that in countries such as Brazil, the average education span among KS men was 6.9 years, with most participants having attended public school. Fjermstead et al. (2023) further demonstrated that adolescents and children with KS performed significantly poorer than their peers on tests focusing on math, spelling, and word identification. As a result, a majority of kindergarten-age children in the United States with KS receive early intervention services, including publicly funded or privately paid therapies before beginning school (Thompson et al., 2020).

Beyond academics, KS is associated with serious social challenges. Cross-sectional studies reveal that children and adolescents with KS often struggle with shyness, attention problems, and immaturity (Tartaglia et al., 2020). Young men with KS also scored significantly lower on empathy tests compared to high-functioning controls (van Rijn et al., 2014). These findings align with higher rates of comorbid diagnoses: up to 10% of individuals with KS are diagnosed with autism spectrum disorder (ASD), and as many as 40% with attention

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deficit hyperactivity disorder (ADHD) (Tartaglia et al., 2020). Consequently, KS students are more likely to require special education services and targeted social skills interventions (Thompson et al., 2020).

Similarly, communication and language development are additional areas of difficulty. Men with KS not only score lower on IQ tests compared to controls, but also exhibit deficits in verbal learning and fluency (Fjermstead et al., 2023). Specific deficits include inaccurate spelling and difficulty with word identification, suggesting a clear association between KS and language impairment. These challenges may be linked to lower working memory capacity and impaired fluid reasoning, although further research is needed to confirm these associations (Jordan et al., 2023).

Overall, the evidence demonstrates that KS affects multiple domains of development, including cognition, learning, social functioning, and communication. The following sections will examine the underlying causes of these impacts, organized into three categories: memory, brain volume and activation, and endocrine function.

MEMORY

Across the literature, memory is consistently cited as one of the most impacted cognitive processes in men with KS. Studies reveal the presence of slight differences in memory performance when comparing XXY men and matched controls, with further impairments observed in men diagnosed with both KS and ADHD (Lee et al., 2011). Although memory is a broad spectrum that encompasses several areas and multiple memory systems of the brain, research on KS's effect on memory can be grouped into two main categories: working memory and declarative memory.

Working Memory

Working memory, the cognitive system responsible for temporarily storing and processing information, is consistently impaired in individuals with KS (Baddeley, 1992). According to Jordan et al. (2023), KS children scored significantly lower than IQ-matched peers on word identification and spelling tests, widely used measures of working memory in adolescents. These results aligned with earlier work by Lee et al. (2011), who found that individuals with KS made more frequent errors on executive function tasks involving working memory. Similarly, Skakkebæk et al. (2014) demonstrated significantly lower scores on the Digit Span (DS) and Letter-Number Sequencing (LN) tests among KS men. Collectively, these results support the theory that weakened information processing leads to weaker memory formation and forgetfulness.

The importance of working memory extends far beyond KS. Its development is associated with psychological, structural, and electrophysiological changes from infancy to adulthood, while impairments are

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associated neurodevelopmental disorders such as ADHD and early-onset schizophrenia (Gomez et al., 2021). More broadly, working memory is essential for learning. Hassanzadeh et al. (2024) found that younger adults in Iran, who demonstrated stronger working memory capacity, outperformed middle-aged participants on reinforcement learning (RL) tasks, with performance declining alongside age-related reductions in working memory. One specific example includes handwriting. Truxius et al. (2025) showed that working memory plays a significant role in early handwriting fluency among 1st and 2nd -grade children by facilitating visuomotor integration skills. Over time, handwriting becomes less dependent on working memory, demonstrating developmental changes in the underlying neural processes (Truxius et al., 2025). Taken together, the literature suggests that KS-related deficits in working memory may help explain the broader learning difficulties observed in this population.

Declarative Memory

While working memory is the process of encoding, recalling and manipulating information, explicit memory, also known as declarative memory, is defined as information that can be consciously recalled, including facts and episodes. It is divided into several different categories, including episodic and semantic memory (Mujawar et al., 2021). Research indicates that individuals with KS experience impairments across several forms of explicit memory. Verbal memory, responsible for storing information in a linguistic form, is particularly affected. According to John et al. (2019), KS men performed below-average on literacy and language tests and frequently exhibited speech impairment, which may be attributed to deficits in verbal memory. Verbal memory is vital for neurodevelopment, as increased verbal memory activity is associated with heightened neural activation in the frontal and parietal cortices, frontal gyri and right cerebellum (Vogan et al., 2015).

Visual memory is similarly affected. Bruining et al. (2011) reported that boys with KS made significantly more mistakes and identified fewer objects than controls on visual memory tasks. Deficit in visual memory means subjects are less likely to remember and identify certain objects, leading to errors and reliance on guessing. Visual memory is also vital for neurodevelopment, as a recent study of school-age children in Norway found that lower visual memory capacity was associated with poorer executive function, slower motor skills, and delayed reaction times, underscoring the central role of visual memory in neurodevelopment. (Ingvaldsen et al., 2023). Several mechanisms may explain memory impairments in KS. Zhao et al. (2025) suggest altered neurogenesis, the process of creating new neurons and neurites, and higher susceptibility to glucose metabolism disorders, both of which negatively affect neurodevelopment and memory function. Another reason includes processing speed. According to Jordan et al. (2023), there is a potential trend between slower processing speed and KS, which leads to a lack of inductive and quantitative reasoning. Since processing speed is a strong predictor of explicit memory, slower rates may hinder both acquisition and retention of new information (Estelle & Voelbel, 2024). Finally, the high prevalence of ADHD in KS populations may further exacerbate memory difficulties, as impaired memory formation is among ADHD's core cognitive symptoms (Tartaglia et al., 2020).

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Brain Volume

Differing brain volume amounts and levels of neural activation are two peculiar differences seen in men with KS. These differences are a major cause for many of the cognitive effects of KS, which makes further research imperative for continued understanding of neurodevelopment in KS men.

Men with KS tend to display complex differences in brain volume. Gray matter is the outermost area of the brain responsible for processes such as movement, memory, and emotions. In regular brain development, the volume is supposed to continually increase until the age of eight (Mercadante & Tadi, 2023). According to Foland-Ross et al. (2021), when analyzing the brains of KS boys, some areas of the brain had increased cortical gray matter volume due to cortical thickness, while others had decreased volumes from decreased surface area. Moreover, deep screening and imaging reveal two regions in the right hemisphere of the brain which had significantly higher surface area because of KS. One region was believed to play a role in language processing and music perception, while the other is believed to be responsible for gaze control and visual attention, although the researchers emphasize that continued research is necessary to confirm these findings (Larsen et al., 2024). In terms of reductions, a more recent study by Foland-Ross et al. (2024) concluded that men with KS have significant decreases in frontal, temporal, subcortical, and cerebellar gray matter compared to controls, while also aligning with past studies by concluding parietal and occipital cortices have increased gray matter. These changes in brain volume have important implications regarding neurodevelopment. Foland-Ross et al. (2019) revealed a positive association between hippocampal volume and spatial memory test performance in men with KS, as well as a positive impact of androgen treatment on brain volume, which highlights a potential solution to deficits faced by lower brain volume. Broadly, Skakkebæk et al. (2014) found that not only is KS associated with reduced brain volumes in areas such as the hippocampus, but it has significant impacts on verbal fluency, processing speed, and IQ, which also leads to significant diagnoses of psychiatric disorders such as depression, anxiety, and SCL-8. While the study notes there is no correlation confirmed yet between reduced brain volume and these measures of cognitive ability in KS subjects, its findings necessitate further research on this subject.

Brain Activation

In addition to changing the volume of gray matter in the brain, KS also alters brain activation. Foland-Ross et al. (2023) analyzed adolescents with KS and found reduced brain activation in regions particularly crucial for executive function, such as the inferior frontal gyrus, which is responsible for speech production and working memory, and the dorsal anterior cingulate cortex, which controls error response and attention, highlighting key impacts on neurodevelopment. In addition, a study using fMRI discovered trends of KS increasing activation in response to motor output and auditory stimuli, which was likely due to increased and uncontrollable tremors. (Wallentin et al., 2016) These findings also align with newer studies. Facial emotion

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processing through fMRI technology reveals modified activation in KS men, with increases in activation in the frontal, temporal, and occipital cortices. Increases in these areas corresponded with symptoms of anxiety and depression, as well as significant social impairments (Vreeland et al., 2024). These trends indicate brain activation could be a leading cause of neurodevelopmental impacts in KS men.

One of the potential causes of the observed differences in brain volume and activation in KS can be due to differing pubertal development. Recent studies found significant support for potential associations between brain volume and activation and pubertal delays. However, researchers are unsure whether these associations are a result of testicular insufficiency or structural brain differences, emphasizing the need for continued research (Foland-Ross et al., 2024). Another potential explanation for the differences could be from altered networks. Zhao et al. (2025) uncovered the altering of glutamate receptor signaling pathways, synaptogenesis—the creation of new connections, or synapses in the brain—and CREB signaling pathways. The altering of these pathways is believed to impair neurotransmitter release and synaptic transmission, halting neurodevelopment and overall neuronal growth. These trends indicate potential causes of brain volume and activation which would benefit from further research.

Endocrine Function

KS significantly affects the hormones and glands of the endocrine system. This is particularly important because evidence from animal models indicate an association between endocrine system disruption and impaired neurodevelopment. For instance, severe chemical interference created by endocrine impairments has been associated with neuroanatomical abnormalities in children, including deficits in information processing, short-term memory, and overall IQ (Colborn, 2004). Although research directly examining the neurodevelopmental implications of endocrine dysfunction in KS is more limited, the available evidence indicates that it plays a substantial role in cognitive outcomes. These effects are primarily characterized by altered testosterone levels, impaired testicular function, and elevated follicle-stimulating hormone (FSH).

It is commonly agreed throughout the literature that KS leads to significant impacts on testosterone and testicular function. According to Spaziani et al. (2021), although testosterone levels in infants remain elevated, they plummet to undetectable levels during and after puberty, which researchers associated with an altered hypothalamus-pituitary-gonadal (HPG) axis in KS. In addition, men with KS often encounter hypogonadism, which is associated with lower testosterone and significantly lower testes volume (Foland-Ross et al., 2023). Overall, lower testosterone levels through hypogonadism have a multifaceted effect on neurodevelopment. In mice, for instance, blocking the infant surge of testosterone leads to differences in brain DNA formation (Tartaglia et al., 2020), which leads to permanent changes in brain structure. One example of this includes the amygdala, which is a structure in the brain that controls emotional responses and affects social functioning. According to Kogler et al. (2023), cognitive control of the amygdala is dependent on steady testosterone levels, as

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these levels create functional connectivity with the right middle occipital gyrus. Testosterone levels were also positively correlated with social function. In testicular volume, a significant association was recorded between attention difficulties and lowered testicular volume in children with KS (Tartaglia et al., 2020). To prevent further damage, androgen and testosterone replacement therapies are often recommended for KS men, as previous studies show there is improvement in brain development and psychosocial outcomes (Tartaglia et al., 2020). Overall, maintaining stable testosterone levels and testicular volume is imperative for long-term neurodevelopment.

Follicle-stimulating hormone (FSH) is a hormone that is involved in sexual development and reproduction in males and females (Orlowski & Sarao, 2023). However, men with KS have a significantly higher level of FSH as infants due to lower testosterone, which normally suppresses the production of FSH. (Spaziani et al., 2021). While having a balance of this hormone aids sexual development, elevated levels have negative effects on neurodevelopment. For instance, mice with high levels of FSH not only have impaired cognitive function, but they also display symptoms of Alzheimer's disease (Xiong et al., 2022). While Alzheimer's disease is not necessarily classified as a neurodevelopmental disorder, these neurophysiological changes must be considered to prevent its onset later in life. Furthermore, historical data indicate a relationship between FSH levels and depression-like symptoms in men (Castanho et al., 2014), which in adolescents contributes to lower hippocampal volume compared to healthy controls and delayed brain maturation, demonstrating clear impacts on neurodevelopment (Straub et al., 2019).

DISCUSSION

Weaknesses

Although the field of KS has made tangible progress in understanding its neurodevelopmental implications, several weaknesses have limited the conclusions that can be made of this literature review. In many selected papers, researchers highlight a potential association or general trend seen in KS, but a number of these studies lack statistical significance and do not provide conclusive evidence for the neurodevelopmental impacts of KS. Moreover, while there are numerous studies researching a certain impairment of KS (e.g. working memory), the majority do not research the foundation of these effects, or why they occur. This weakness limits current research because it prevents explanation of how the effects occur, curbing the possibility of future solutions. Within the studies themselves, it is difficult to establish a generalized conclusion of the impact of KS on neurodevelopment. Most studies took place in different countries with vastly different educational systems and research expertise on the subject, which may skew results in favor of a certain result. Broadly, all experimental studies were cross-sectional with relatively small sample sizes, limiting their scope. Overall, these weaknesses demonstrate the necessity for continued research on the causes of the neurophysiological differences in KS men, which would build upon existing findings and establish conclusive evidence.

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Strengths

This literature review highlights several consistent strengths in current research. For instance, the ability of multiple countries to reach similar results regarding neuroanatomical differences in KS indicates the universality of KS's effects, considering different countries with different systems are arriving at the same conclusions. Moreover, there has been increased collaboration between prominent researchers of KS in recent years, which has delivered several new findings (e.g. neurogenesis differences) that significantly boost our current understanding of the disorder.

CONCLUSION

This literature review synthesized existing knowledge on the causes of the neurodevelopmental implications observed in KS, focusing on memory impairments in both working and explicit memory, altered brain volume and activation, and endocrine dysfunction through reduced testosterone and increased FSH. The review used research papers with statistical analysis to back findings and demonstrate associations in key areas of difference. Limitations of this review included a lack of uniformity among conclusions, statistical significance in studies, and small sample sizes. Overall, these results have successfully concluded that memory impairments and altered neurodevelopment are the root cause of worsened academic performance by KS children and adolescents. These deficits are not isolated instances; rather, they are multifaceted, drawing upon impairments from several regions of the brain, and have been consistently proven in multiple settings across multiple countries and patient samples. Moving forward, researchers should seek to address existing experimental design issues, as well as continue joint collaboration between research teams to reveal new findings. These efforts are imperative, as further understanding of KS's neuroanatomical differences may lead to earlier diagnoses and increased clinical interventions, which may improve quality of life and reduce stigma around KS. In academic settings, educators may implement targeted approaches to best aid KS students in regard to their level of learning.

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