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Sleeping in the context of Fragile X syndrome, a complex relationship.

The effects of Fragile X syndrome and sleep deprivation on the glutamatergic signaling pathway

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Summary

Fragile X syndrome FXS is a genetic disorder primarily caused by a mutation in the Fragile X Mental Retardation 1 (FMR1) gene, characterized by a large number of CGG triplet repeats. Individuals affected by the disorder can suffer from a range of different physical and cognitive abnormalities. In addition to the cognitive impairment already seen in FXS patients, the disorder also causes sleep deprivation (SD). SD can also lead to cognitive impairments to some degree, which might add to the severity of symptoms in FXS patients. In this review, the molecular pathways underlying the cognitive impairment caused by FXS and SD will be discussed. Furthermore, the cause of SD in FXS patients will be evaluated to understand the relationship between the two conditions and to assess possible additive effects. FXS cognitive impairment is likely caused by its effect on metabotropic glutamate receptors (mGluRs), through the absence of FMRP. Dysregulation of mGluRs leads to altered long-term depression (LTD) and long-term potentiation (LTP). AMPA receptors critical for fast excitatory transmission and synaptic plasticity are also affected by FMRP absence. These factors together have a major negative impact on cognition by altering neural signaling. SD also negatively affects cognitive function by compromising long-term potentiation (LTP) and long-term depression (LTD) in the hippocampus. SD alters glutamatergic signaling, reduces NMDA-mediated LTP, increases GABA receptor expression, and affects FMRP levels, contributing to cognitive impairment. The fact that both SD and FXS significantly affect cognition is interesting as SD is more prevalent in FXS patients. The absence of FMRP likely contributes to sleep disturbances in FXS patients, which could then cause additional loss of cognitive ability. Current research explores various treatment approaches for FXS, including restoring FMRP levels or targeting affected neural pathways. While promising, these treatments have yet to yield significant clinical success. Treating symptoms like SD may offer interim solutions while researchers continue to investigate underlying mechanisms and potential therapies for FXS.

Introduction

Fragile X syndrome (FXS) is a genetic X-linked disorder first described in 1943 (Martin & Bell, 1943) for its significant effect on behavior and cognitive development and behavior. It is the most prevalent inherited cause of mental disability and autism spectrum disorder (ASD), and it affects about 1 in 7,000 males and 1 in 11,000 females. Affected individuals can show a range of symptoms including hyperactivity, impulsivity and anxiety, seizures, and poor language development (Hagerman et al., 2017). FXS also causes several abnormal physical features for example flat feet, a long face, and hyperextensible joints (Dew-Hughes, 2003; Hagerman et al., 2017). Males typically show more severe mental disability and physical abnormality, whereas females more often show symptoms linked with learning disabilities or social-emotional difficulties (Bartholomay et al., 2019). The difference in expression of the disorder has to do with the alternative X chromosome that females possess which males do not. The syndrome is primarily caused by a mutation in the Fragile X Mental Retardation 1 (FMR1) gene, which is characterized by a large number of CGG triplet repeats. These repeats range from 5 to 54 in normal alleles, 55 to 200 in pre-mutation alleles, and over 200 repeats in alleles in the full mutation range (Bagni et al., 2012). The severity of symptoms strongly correlates with the number of repeats, and therefore also with the levels of FMRP. Individuals in the pre-mutation range mostly have normal intellectual functioning, whereas individuals possessing a complete mutation leading to the manifestation of FXS often show severe cognitive impairment. Full mutation FXS comes with a high likelihood of developing ASD or pervasive developmental disorder—not otherwise specified (PDD-NOS) (Harris et al., 2008). Individuals with a pre-mutation also have a predisposition to suffer from developmental disorders however the disorders are generally not as frequent or severe as the full mutation (Hagerman et al., 2011; Hagerman et al., 1992). We have now seen that FXS is a serious genetic condition with many morphological and developmental abnormalities. Besides these symptoms, FXS patients also suffer from sleep deprivation (SD) at a higher rate than normal (Kronk et al., 2010; Gould et al., 2000). Abnormal sleep behavior has been linked to many health deficits including increased risk for cardiovascular diseases and cancer (Faith et al., 2012). Sleep is also one of the most important processes in the brain that facilitates normal cognitive functioning and SD or a deviation from normal sleep patterns causes impaired memory consolidation, attention deficits, and a lower IQ (Graves et al., 2003; Abel et al., 2013; van Dongen et al., 2003; Wang et al., 2013). These symptoms of SD largely overlap with symptoms of FXS and therefore could add to its detrimental effects. This suggests minimizing SD in FXS patients might reduce some of the detrimental effects seen in FXS. While a cure for FXS would certainly be better, research has to this day been unsuccessful in providing effective clinical treatment (Jalnapurkar et al., 2019). On the other hand,

research on SD is well-established and there are many known methods to improve sleep quality. The reason that this type of research is very prevalent is that besides FXS patients many more people in today's population would benefit from a remedy for SD. A great number of individuals in modern society suffer from sleep deprivation (SD) and it has become an increasingly large problem in the past decades. There are various reasons for SD to occur, irregular work hours or night shifts, stress, and sleep apnea just to name a few. From 1910 to 1963 adolescents in America slept on average 1,5 hours less (Webb & Agnew, 1975). Additionally, >30% of Americans 30-64 years of age slept less than 6 hours per night on average (Faith et al., 2012). Now we know that SD and FXS both have a large impact on society, especially the cognitive deficits that can severely affect normal functioning in society, and diminishing the negative effects of these conditions would therefore help the general population to function better. As understanding a condition lies at the basis of finding a clinical solution, much research shows the mechanisms underlying both SD and FXS. As of now the best supported hypothesis for the cognitive impairments seen in FXS are likely caused mostly by a defect in the glutamatergic system. Interestingly this is also one of the many signaling pathways negatively affected by SD (Havekes et al., 2012; Havekes & Abel.,2017). This signaling system works through the neurotransmitter glutamate which binds to two main types of receptors: N-methyl-d-aspartate (NMDA) and alpha amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPA). The system has a core function in learning and memory formation, synaptic plasticity, and long-term potentiation (Fairman & Amara, 1999; Alix & De Jesus Domingues, 2011), and many brain pathologies have been linked to the glutamatergic signaling pathway including neurodegenerative diseases like Alzheimer's and Parkinson's disease (Ribeiro et al., 2010). It is important to understand the relationship between FXS and SD by looking at the mechanisms through which FXS could induce SD. This can tell us whether SD is caused on a molecular level by the genetic defect, or on a behavioral basis, and is crucial for developing a treatment for SD in FXS individuals. Combined with a better understanding of the way the glutamatergic system is affected this provides insight into how cognitive functioning is impaired. This will allow us to compare similarities and differences between the effects of SD and FXS at the molecular level, which will help to unravel the relationship between the two. In this review, the effects of FXS and SD on cognition and glutamatergic signaling will be discussed. Additionally, the mechanisms through which FXS could induce SD will also be discussed. The relationship between the two conditions will be evaluated and the possible additive negative effects will be discussed.

The effects of Fragile X Syndrome on brain function

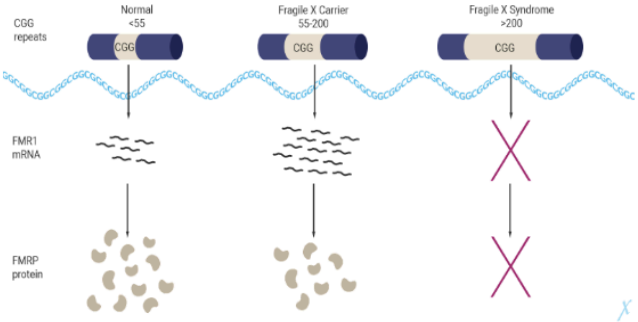
To understand the relationship between FXS and SD we must have an overview of the effects that FXS and SD have on cognition. For understanding the effects of FXS it is important to first understand the underlying genetic defect and the implications of this defect at the molecular level in the brain. First, we will look at the genetic cause of the disease, then we will look at the effect this genetic defect has on brain signaling. This is important if we want to say something about the differences and similarities between the pathology of SD and FXS.

FXS is a genetic disease caused by a mutation of the FMR1 gene, the gene is located on the X chromosome coinciding with a folate-sensitive Fragile site (Fryns et al 1984). FMR1 is a region consisting of CGG triplet repeats, an abnormally large number of repeats can disrupt gene expression, and for >200 repeats the genetic defect leads to FXS (Figure 1). In the wildtype allele, the cytosine nucleotides in the FMR1 gene are methylated in the promoter region but not near the CGG repeat region. There appears to be a 'boundary' for methylation close to the CGG repeat region in the FMR1 gene (Naumann et al., 2009). Individuals affected by FXS are characterized by cytosine methylation from the CGG repeat region up until the promoter region; this additional methylation causes gene transcription to malfunction at an early age (Pieretti et al., 1991). This malfunction results in the lack of the corresponding protein product, FMRP (Js et al., 1992). FMRP is a protein that affects many molecular processes both inside and outside the brain and its expression is largely conserved throughout the animal kingdom (Mcbride et al., 2005). Many mRNAs within the neuronal cytoplasm that code for both pre and postsynaptic proteins are not regulated in the absence of FMRP (De Rubeis et al., 2012). The FMRP absence causes an increase in multiple proteins that play a role in receptor internalization and cytoskeleton remodeling, while simultaneously also causing a decrease in the translation of other proteins in the brain due to impaired stability of their mRNAs (Figure 2). This change in receptor distribution and protein synthesis results in changes in signal transduction thus also changing the way the brain processes information.

The most well-described theory of how the absence of FMRP diminishes brain function is the mGlur theory of fragile x mental retardation. mGluRs are metabotropic glutamate receptors, group 1 mGluRs are influenced by FMRP presence and are therefore often used for research on FXS, this group consists of mGluR1 and mGluR5. The areas of expression of these two subtypes differ significantly, MGluR1 staining is most intense in Purkinje cells of the Cerebellar cortex, and in tufted cells in the olfactory bulb. Alternatively, mGluR5 is found mostly in the cerebral cortex, hippocampus, and the olfactory bulb.

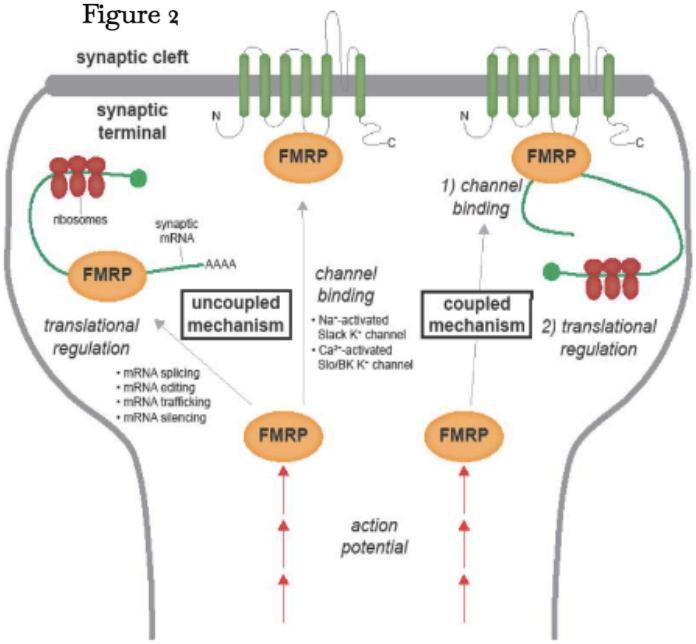
mGluRs play an important role in regulating receptor expression in the postsynaptic membrane and are shown to facilitate both long-term depression (LTD) and Long-term potentiation (LTP), two processes at the center of memory formation (Lüscher & Huber, 2010; Bailey & Kandel, 1993). These processes cause long-term reversible changes in the structure of a synapse and are widely accepted as molecular processes important for memory and learning. Additionally, the absence of FMRP can negatively affect AMPA receptor insertion and function. AMPA receptors are complex structures located in the postsynaptic membrane composed of four subunits, each of which can bind to the neurotransmitter glutamate. These receptors play a key role in fast excitatory transmission within the central nervous system and are intricately linked to processes related to memory and synaptic plasticity in the hippocampus (Dubiela et al., 2013; Lynch, 2004). AMPA receptors play an important role in the normal development of the synapse and disruption of AMPA signaling pathways can lead to impaired neuronal plasticity, and subsequently to learning disabilities (Guo et al., 2011; Muddashetty et al., 2007; Wu et al., 2007). The increase of mGluR1 and mGluR5 and the reduction of glutamatergic AMPA receptors in the postsynaptic membrane in the CA1 region of the hippocampus and the cerebellum leads to enhanced mGluR LTD in the hippocampus and the cerebellum (Nakamoto et al., 2007). This is supported by the observation that a reduction of mGluR5 in Fmr1 KO mice partly reverses cognitive deficits seen in Fmr1 KO mice (Dölen et al., 2007). Nagamoto et al (2007) show that the absence of FMRP also causes AMPA receptor internalization in the postsynaptic membrane, which could lower the excitability of a neuron. Furthermore, Danesi et al (2019) demonstrate that changes in Ca_{2+} influx and AMPA receptor function alterations may contribute to the pathology of FXS. This is further supported by Achuta et al. (2018), who show that AMPA receptor permeability to Ca_{2+} is increased in FXS due to a decreased expression of subunit $GluA_2$ in human neuronal progenitor cells. The study also reveals that blocking AMPA receptors lacking this subunit restores neuronal function. Combined these findings tell us that the absence of FMRP due to FXS has a major impact on the function and localization of the AMPA receptor. FMRP absence causes a lot of dysfunctions in the body and the brain, and both mGlur and AMPA receptor expression are severely affected. This indicates that the glutamatergic pathway is severely affected by FXS and that this pathway is at the basis of its brain pathology.

Figure 1



A schematic representation of the DNA structure of healthy individuals compared to FXS individuals. From FRAXA Research Foundation. (2023, March 31). What causes Fragile X Syndrome: Understanding the genetic and molecular basis of the condition. https://www.fraxa.org/fragile-x-syndrome/cause/

Figure 2



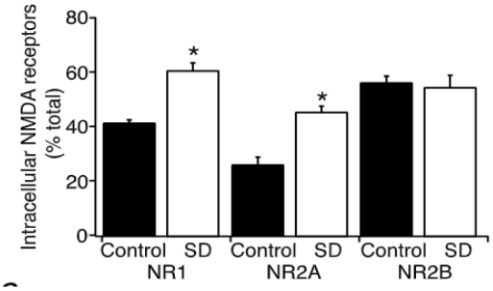
A schematic showing different roles FMRP plays in channel binding and translational regulation at the synaptic terminal. On the left side, the mRNA and channel binding are separate processes, on the right FMRP works by simultaneously binding to mRNA and the channel. From Davis, J. K., & Broadie, K. (2017). Multifarious Functions of the Fragile X Mental Retardation Protein. Trends in genetics: TIG, 33(10), 703–714. https://doi.org/10.1016/j.tig.2017.07.008

The effects of sleep deprivation on brain function

For us to understand the relationship between SD and FXS, it is important to get an understanding of how the two affect brain function separately before we can say something about the association between the two conditions. Therefore, we will first look at the effect SD has on glutamatergic signaling and cognition. Sleep helps to keep the brain and the body functioning optimally, and it is universally conserved throughout the animal kingdom. It is of paramount importance to various processes including hormone release, glucose management, and neural plasticity (Gorgoni et al., 2013; Van Cauter et al., 2008). SD disrupts these critical processes and can therefore lead to several physical and mental issues. One of the best-described complications SD has on humans is the negative effects it has on human brain function. One of the affected brain areas which is of particular interest is the hippocampus. The hippocampus is involved in the formation of new memories and working memory and therefore central to a normally functioning human brain. An array of studies show that SD harms learning and memory in the hippocampus (S. J. Martin et al., 2000). The disrupted mechanisms in the hippocampus include LTP and LTD, which are paramount to memory formation and consolidation. Total SD or sleep fragmentation diminishes LTP in rats,
using recordings of hippocampal Schaffer collateral CA1 synapses (Tartar et al., 2006; Campbell et al., 2002). LTP is also diminished when only REM SD occurs using the multiple-platform technique. One of the mechanisms behind this is NMDA-mediated LTP. NMDA is a calcium ion channel that binds glutamate, and it is central to the induction of LTP in neurons. This type of LTP is induced by activating kinases that cause an increase of AMPA receptors in the membrane, or an increase in channel conductivity (Hayashi et al., 2000; Poncer et al., 2002). Increased internalization of this receptor type consequently causes

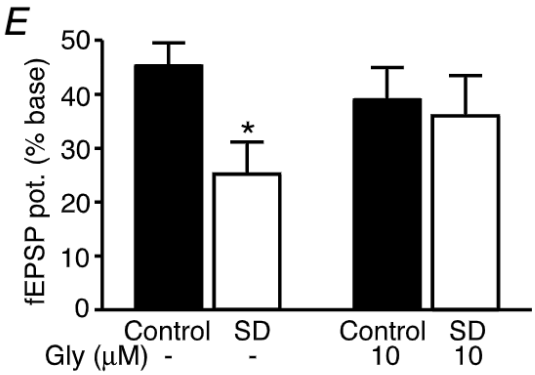
diminished LTP. McDermott et al. (2006) show that NMDA receptor internalization was increased after 72h SD and that an NMDA receptor agonist reversed the negative effects of SD on LTP in rats (figures 3 and 4). This is further supported by Hagewoud et al. (2009) who showed a reduction in phosphorylation of AMPA receptors in the hippocampus. (figure 5) AMPA phosphorylation is important for successfully incorporating the receptors into the membrane, and a reduction therefore causes a decrease of AMPA in the membrane. Lastly, McDermott et al (2006) show that NMDA receptor internalization was increased after 72h SD.

Figure 3



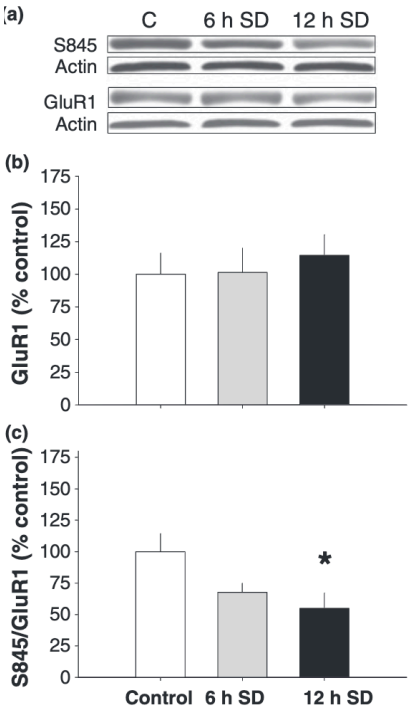
Concentration of intracellular NMDA receptors in the hippocampus of SD and control rats. Three different NMDA subunits are assessed with the NR1 and NR2A subunits showing a significant difference with the control. From McDermott, C. M., Hardy, M., Bazán, N. G., & Magee, J. C. (2006). Sleep deprivation-induced alterations in excitatory synaptic transmission in the CA1 region of the rat hippocampus. The Journal of Physiology, 570(3), 553–565. https://doi.org/10.1113/jphysiol.2005.093781

Figure 4



*fEPSP pot. of sleep-deprived rats with and without glycine treatment. The untreated SD rats show a significant decrease, while the treated SD rats do not differ significantly from the control group. *P<0.05 from McDermott, C. M., Hardy, M., Bazán, N. G., & Magee, J. C. (2006). Sleep deprivation-induced alterations in excitatory synaptic transmission in the CA1 region of the rat hippocampus. The Journal of Physiology, 570(3), 553–565. https://doi.org/10.1113/jphysiol.2005.093781*

Figure 5



(a) immunoreactive bands forGluR1 and S845 phosphorylation in the membrane fraction. (b) 6h and 12h SD show no significant effect on GluR1 subunit levels. (c)

6h and 12h SD effects on phosphorylation at the GluR1-S845 site. 12h SD shows a significant decrease. *p<0.05. *From Hagewoud, R., Havekes, R., Novati, A., Keijser, J., Van Der Zee, E. A., & Meerlo, P. (2009). Sleep deprivation impairs spatial working memory and reduces hippocampal AMPA receptor phosphorylation. Journal of Sleep Research, 19(2), 280–288.* https://doi.org/10.1111/j.1365-2869.2009.00799.x

Besides LTP, SD enhances LTD in the CA1 region of the hippocampus. SD increases the expression of subtypes of γ- Aminobutyric acid (GABA) receptors, and increases the expression of subtype mGlu1αR in the hippocampus. GABA receptors induce inhibition in the CNS by activation of metabotropic GABAb receptors, and ionotropic GABAa/GABAc receptors. Both these subtypes have a significant negative effect on the excitability of a neuron. Additionally, the increased expression of subtype mGlu1αR can also lead to enhanced mGlur-LTD (Tadavarty et al., 2009; Stelzer, 1992). SD also appears to affect FMRP concentration. Kwon et al. (2015) showed that FMRP levels are reduced in the hippocampus of sleep-deprived rats. As mentioned before, a lower amount of FMRP could be a leading cause of enhanced mGluR-LTD, contributing to the lower levels of AMPA receptors in the postsynaptic membrane.
Lastly, SD might affect the cholinergic signaling pathway as well. Cholinergic signaling is significant for memory formation and there are two types of cholinergic receptors present in the body, muscarinic receptors, and nicotinic receptors. Of these two types, the muscarinic receptors are particularly important for memory (Havekes et al., 2011). Salín-Pascual et al. (1998) show that the amount of cholinergic muscarinic M2 receptors in the pons and hippocampus is reduced after REM SD. While this implies that SD affects Cholinergic signaling, different studies show conflicting evidence (Ca et al., 1995; Moreira et al., 2003; Nunes et al., 1994). These differences might result from how the experiments were set up. In any case, more research is needed to find more reliable results. Collectively these studies show that SD has a diminishing effect on multiple important pathways at the basis of synaptic plasticity and memory.

Sleep deprivation in Fragile X Syndrome patients

We have now looked at FXS and SD as two separate conditions that affect cognitive functioning and several molecular mechanisms. To be able to better understand the relationship between the two, we must understand the pathology of SD in FXS patients. This allows us to see whether SD in FXS is directly caused by the disorder or if different mechanisms are at play. As mentioned before, FXS phenotypes struggle with sleep abnormalities at an above-average rate. The abnormalities include SD, frequent wakefulness, and trouble falling asleep. These abnormalities severely reduce sleep quality which is detrimental to cognitive performance (Alhusseini et al., 2022). This could add to the cognitive malfunctioning already seen in FXS patients. The absence of FMRP due to FXS likely is one of the major factors causing sleep abnormalities. Bushey et al. (2009) found that FMR1 amorphs or

hypermorphs in drosophila show altered sleep homeostasis, impaired waking performance, and lack of rebound sleep after SD. In addition, FMR1 defects cause altered circadian behavior in mice models (Zhang et al., 2008). This is further supported by a recent study that showed that a human FMRP isoform injected into postnatal mice partly reduced the fear response, seizures, and sleep abnormalities observed in untreated Fmr1 KO mice (Wong et al., 2023). Lastly, Weigend et al (2019) imply that mGluR5 and FMRP play an important role in the sleep-wakefulness cycle. A possible mechanism through which FXS could cause SD is through melatonin regulation. Melatonin is a hormone produced primarily in the pineal gland, its most important function in humans is the regulation of circadian rhythms. Its release is regulated in the suprachiasmatic nucleus (Barrenetxe et al., 2004), and besides regulating the sleep-wakefulness cycle, melatonin also plays a key role in the regulation of sex hormones (Yu et al., 2018). Numerous chronobiological studies have shown that the disruption of melatonin release can result in compromised sleep quality (Boyko et al., 2017; Ahmad et al., 2020; Vitale et al., 2014). Gould et al. (2000) show that FXS individuals have significantly higher levels of melatonin in the blood during nighttime. FXS individuals also show much greater variation in melatonin levels than normal individuals. Gould et al. (2000) propose various mechanisms through which FXS could cause heightened melatonin secretion. The first proposed mechanism is receptor insensitivity due to Immature spine morphology caused by FMRP absence. Another hypothesis is that hyperactivity of the sympathetic nervous system seen in FXS patients causes an increase in melatonin secretion. The third proposed mechanism through which FXS may induce SD is through its possible effect on the transcriptional regulation of serotonin N-acetyltransferase. FMRP absence could alter the transcription of proteins involved in this pathway. These are however speculations, and more research is needed to be able to confirm one of these hypotheses. Lastly, a study done by Kronk et al. (2010) on FXS individuals and their sleep patterns revealed that the individuals with more severe behavioral and physiological symptoms consequently have a higher chance of sleep abnormalities. As we know the severity of symptoms is correlated with FMRP levels, this further supports the connection between lowered levels of FMRP and sleep abnormalities. Together, these findings suggest that a large part of the SD seen in FXS patients is indeed caused by the absence of the FMRP protein. And possible clinical solutions for FXS will likely also abolish the sleep abnormalities seen in FXS. As a clinical solution for FXS is not in sight yet, looking at the mechanisms through which FXS induces SD to devise a treatment for SD in FXS patients might be a better alternative for now.

Discussion

We have discussed the impact of both SD and FXS on molecular signaling pathways in the brain, with an emphasis on glutamatergic signaling. The relationship between FXS and SD is outlined ultimately to better understand the combined effects of SD and FXS on the glutamatergic system. Both conditions are detrimental to cognitive function and harm glutamatergic signaling (figure 6). SD negatively affects LTP and LTD by compromising NMDA and AMPA receptor function by increased internalization of both. Additionally, SD also causes an increase in expression of GABA receptors which significantly decreases the excitability of a neuron. Lastly, SD influences FMRP levels in the Hippocampus which could contribute to lower amounts of AMPA incorporated into the membrane.
The best-described hypothesis which describes the detrimental effects of FXS on cognitive performance is the mGlur theory of fragile x mental retardation. The theory is supported by research showing an increase in mGlur1 and mGlur5 in the membrane, and an increase in AMPA receptor internalization through the absence of FMRP. This leads to enhanced mGlur-LTD.
SD and FXS are intricately linked as sleep problems are more prevalent in FXS individuals. Furthermore, there appears to be a correlation between the severity of FXS symptoms and the degree of SD. Both SD and FXS Negatively affect LTP and LTD through increased internalization of AMPA receptors. This is caused by an increased phosphorylation of AMPA receptors and a decrease in NMDA-mediated LTP. Along with this comes a decrease in FMRP which might cause additional AMPA internalization. For FXS the increase in mGlur1 and mGlur5, and the decrease of AMPA in the postsynaptic membrane through the absence of FMRP are thought to be the main reasons for disrupted LTP and LTD.
Important to point out is that FMRP levels seem to be affected in healthy individuals due to SD. Interestingly, in FXS individuals there is no FMRP present. Therefore, the reduction in FMRP due to SD is impossible for FXS patients and the effects of FXS negate the effect of SD on FMRP levels. This means that FXS might limit the negative effects of SD on the brain to some degree. We have looked at the effects of both SD and FXS separately on brain pathways, and there seem to be some differences in the mechanisms that are affected. An interesting difference between FXS and SD is that as of now research shows that FXS mainly influences the glutamatergic signaling through increasing mGlur prevalence in the postsynaptic membrane, alongside its effect on AMPA receptors. SD on the other hand, mainly influences the glutamatergic system through a reduction of NMDA-mediated LTP, and an increase in the expression of GABA receptors, besides its effects on AMPA receptors. Important to note here is that SD and FXS act on different mechanisms through which LTP and LTD are affected. Therefore, the effects could act alongside one another and can lead to additive negative effects on cognitive function.

We have seen that SD is likely caused by FXS to some degree and that SD partly works on different pathways in the brain that affect cognitive function. This means that FXS-induced SD is another mechanism through which the genetic defect diminishes cognitive function. However, more research is needed on SD in combination with FXS to confirm this. This finding can also be considered when looking into treatment options. As of now, there are no effective treatments for FXS, and looking into treatment of the symptoms rather than the root cause of the disease might be more within reach. Currently, there are two possible methods described; reactivation of the fmr1 gene, or rescuing pathways affected by the absence of FMRP in the brain (Kumari et al., 2019). Restoring the FMRP deficit if achieved will likely be a better treatment option than rescuing the pathways affected. However, this has been proven to be a difficult feat as no treatment has shown a significant effect as of yet. One key aspect to note here is that most of the research on SD and FXS is performed using animal models, while they have shown promising results with some treatments, the findings do not always translate to humans. When looking at human trials, treatment of SD might prove more achievable, and will also help to diminish some of the cognitive defects seen in FXS patients. An example of this is a study done by Wirojanan et al. (2009), in which melatonin treatment of SD shows promising results in FXS patients. While the cognitive deficits might be diminished to some degree, the signaling defects caused by the absence of FMRP will still be present.

For us to fully understand the depths of the effects of FMRP on cognitive function more research needs to be done. For this reason, it is important to note some of the limitations of this essay. First, this literature review focused mainly on the glutamatergic system, and as mentioned before FMRP is very important for the transcription and translation of an array of proteins in the brain and body. Therefore, it does not only affect the glutamatergic system but also other important molecular pathways in the body. This means that FMRP absence dysregulates cognitive functioning through alternative pathways that have not been described as of now. Therefore, it is important to keep a broader perspective when looking at FXS ultimately to better understand the disorder. The same can be said for SD, as mentioned earlier not only the glutamatergic signaling pathway is negatively affected, but also cholinergic and GABA-ergic signaling is compromised because of SD. Especially for SD in FXS individuals, more research is needed, as the lack of FMRP might result in a different reaction to SD in FXS patients compared to healthy individuals. Another point to consider is that the citations in this review focus mainly on the hippocampus as a target area while both SD and FXS are known to affect other brain regions like the amygdala and the forebrain as well. These regions might respond differently to FMRP absence of SD and might have resulted in different conclusions. The hippocampus is used because this is the most well-described

region important for learning and memory, which is crucial for normal cognitive function.

In conclusion, research has shown that FXS and SD both have a significant effect on cognitive ability. Both have a significant negative effect on glutamatergic signaling, although the mechanisms through which this effect is reached are different between the two. We have seen that FXS patients struggle with SD at an above-average rate which shows that the two are interlocked, and it is likely that FMRP absence directly causes the sleep abnormalities seen in the patients. The relationship is interesting when looking at clinical treatment for FXS. Current studies are investigating the possible substitution of FMRP in the brain, or targeting affected neural pathways which are affected by the absence of FMRP. While some of these studies show promising results, they have shown no clinical success yet, and therefore a bottom-up approach where treatments of the symptoms of FXS, like SD, might be a better treatment option in the meantime.

Figure 6

Aspect	Sleep deprivation	Fragile X syndrome
FMRP levels	Reduced	Completely abolished
LTP	Decreased LTP through decreased AMPA and NMDA receptor incorporation in the postsynaptic membrane	Decreased LTP through decreased AMPA receptor insertion in the postsynaptic membrane
LTD	Enhanced LTD by increasing GABA and mGluıαR expression, decreased FMRP levels might also play a role	Enhanced through decreased AMPA receptors in the membrane and increased mGlurı and mGlur5 due to the absence of FMRP.
Behavioral effects	Lowered attention, decreased cognitive performance	Mental disability, often paired with ASD or PDD-NOS, Learning disabilities, Abnormal sleep

An overview of different aspects of SD and FXS

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