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Conceptualizing neurodevelopmental disorders through a mechanistic understanding of fragile X syndrome and Williams syndrome

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Abstract

Purpose of review—The overarching goal of this review is to compare and contrast the cognitive-behavioral features of fragile X syndrome (FraX) and Williams syndrome and to review the putative neural and molecular underpinnings of these features. Information is presented in a framework that provides guiding principles for conceptualizing gene-brain-behavior associations in neurodevelopmental disorders.

Recent findings—Abnormalities, in particular cognitive-behavioral domains with similarities in underlying neurodevelopmental correlates, occur in both FraX and Williams syndrome including aberrant frontostriatal pathways leading to executive function deficits, and magnocellular/dorsal visual stream, superior parietal lobe, inferior parietal lobe, and postcentral gyrus abnormalities contributing to deficits in visuospatial function. Compelling cognitive–behavioral and neurodevelopmental contrasts also exist in these two disorders, for example, aberrant amygdala and fusiform cortex structure and function occurring in the context of contrasting social behavioral phenotypes, and temporal cortical and cerebellar abnormalities potentially underlying differences in language function. Abnormal dendritic development is a shared neurodevelopmental morphologic feature between FraX and Williams syndrome. Commonalities in molecular machinery and processes across FraX and Williams syndrome occur as well – microRNAs involved in translational regulation of major synaptic proteins; scaffolding proteins in excitatory synapses; and proteins involved in axonal development.

Summary—Although the genetic variations leading to FraX and Williams syndrome are different, important similarities and contrasts in the phenotype, neurocircuitry, molecular machinery, and cellular processes in these two disorders allow for a unique approach to conceptualizing gene–brain–behavior links occurring in neurodevelopmental disorders.

Keywords

fragile X syndrome; genetic; neuroimaging; Williams syndrome

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INTRODUCTION

Recent developments in molecular biology and neuroimaging have allowed for an unprecedented opportunity to explore the pathophysiology of neurodevelopmental disorders with greatly improved level of mechanistic detail. In this article, we will compare and contrast the phenotypes, neurocircuitry and molecular mechanisms associated with two specific neurodevelopmental conditions: fragile X syndrome (FraX) and Williams syndrome. FraX is the most common inherited cause of intellectual disability [1] and autism [2]. Mutations of the responsible gene (*FMR1*) in the X-chromosome are associated with significantly reduced levels of *FMR1* protein (FMRP). Absent or attenuated levels of FMRP, such as that observed in individuals with full mutations, are associated with intellectual disability [2–4], sensorimotor aberrations [5,6▪, 7], cognitive difficulties [6▪, 8,9], and behavioral impairments, including a particularly high prevalence of autistic behavior [10]. Williams syndrome is a more rare neurogenetic disorder, caused by deletion of a region on chromosome 7 consisting of approximately 26–28 genes including *CYLN2, GTF2I,* and *LIMK1* As is the case for FraX, the Williams syndrome cognitive–behavioral profile includes intellectual disability, attention deficits, and aberrant social behavior [11,12]. Although the genetic alterations of the two disorders are different, similar key domains of cognitive–behavioral function are affected, and similar molecular processes may be involved in the pathophysiology of the disorders. In this review, we will compare and contrast the deficits in social behaviors, executive function, visuospatial functioning and language processing and ability, as well as the associated putative neurocircuitry for these domains. We will also discuss the recent developments of the molecular mechanisms that may be shared by FraX and Williams syndrome. This review will conclude with a discussion of new insights and ideas regarding future directions for conceptualizing neurodevelopmental and neurogenetic disorders.

NEUROCIRCUITRY AND COGNITIVE-BEHAVIORAL PHENOTYPES IN FRAGILE X SYNDROME AND WILLIAMS SYNDROME

One of the most remarkable contrasts between FraX and Williams syndrome relates to their respective social phenotypes (Table 1). Social abilities observed in these disorders tend to fall along a continuum with increased social avoidance in FraX [13] and elevated social approach in Williams syndrome [14]. In particular, FraX is characterized by social withdrawal, poor eye contact [15], gaze aversion [16], and increased social anxiety [15], whereas Williams syndrome is characterized by social disinhibition [17,18], increased approachability [19], increased attention and fixation on social cues such as faces and eyes [20] (especially happy faces [21]), dissociation between social and physical threat [22], and increased generalized anxiety [23]. Despite these distinct differences, individuals with both FraX and Williams syndrome show difficulty in maintaining appropriate social interactions in terms of relating effectively to peers as well as making and maintaining social bonds.

These contrasting social phenotypes can potentially be linked to aberrations in brain regions involved in social behavior: theamygdala (emotional and social salience) and the fusiform cortex (face processing). Remarkably, while persons with FraX exhibit abnormally small amygdala volumes [24▪, 25], individuals with Williams syndrome exhibit abnormally large volumes [26,27]. Similarly, while FraX is associated with greater sensitization in the left amygdala with successive exposure to direct gaze [16], Williams syndrome is associated with reduced amygdala response to fearful facial expressions [28,29]. FraX is associated with a relatively reduced response to facial expressions within the fusiform gyrus [30▪], whereas Williams syndrome is associated with an abnormally greater response (specifically, greater volume of the functionally defined fusiform face area) to facial expressions [31▪].

Like many neurodevelopmental disorders, deficits in executive function are common to both FraX and Williams syndrome (Table 1). For example, response inhibition, a core feature of executive function that consists of the ability to inhibit an inappropriate or maladaptive behavior, is aberrant in both FraX [34,35] and Williams syndrome [36]. In one of the few studies comparing visual attention in FraX and Williams syndrome, Scerif *et al.* [37] showed that, on the same task, toddlers with FraX made more preservative errors, whereas toddlers with Williams syndrome confused distractors and targets. This suggests that early manifestations of inhibitory deficits seem to affect disengaging and set-shifting abilities in FraX and selective attention in Williams syndrome. Efficient inhibition abilities are essential for 'higher-order' executive functioning abilities including impulsivity control, executive working memory, and organization of thoughts and behavior to reach a goal (planning, self-correcting, verifying, and adapting).

The frontal lobe and frontostriatal circuits play an important role in executive function. In FraX, executive functioning deficits may be associated with reduced volume of frontal lobe [30▪], aberrant maturation of the prefrontal cortex [68▪], reduced activation in the left orbitofrontal gyrus [69], and atypical frontostriatal circuitry [38,60]. FMRP deficiencies may lead to aberrant development of white matter within the frontostriatal pathway [38,60]. Dramatically increased caudate nucleus volume has been documented in FraX [25,40,41, 42▪▪,43], often in association with decreased frontal lobe volume [30▪]. In Williams syndrome, inhibition/executive function deficits may be associated with reduced volume of the caudate nucleus [45], disproportionately large frontal areas [44], aberrant orbitofrontal activation [33], as well as dysfunction of the frontostriatal pathway [39].

Executive function also contributes to visuospatial and visuoconstructive processing, that is, the ability to process, manipulate, and organize visual information in space. Individuals with both disorders show impairments in visuospatial processing (FraX [8]; Williams syndrome, [46]) and visuomotor coordination (FraX [2]; Williams syndrome [47,48]). Boys with FraX and young adult men with Williams syndrome show deficits in tasks requiring manipulations of spatial information in memory, while the ability to remember spatial locations is spared in Williams syndrome (FraX [8]; Williams syndrome [63]).

Several regions within the parietal-temporal-occipital cortex are implicated in visual processing. Visual-perceptual processing primarily involves the parvocellular/ventral pathway (the 'what' stream of processing), whereas visuospatial processing is principally based in the magnocellular/dorsal pathway (the 'where' stream of processing). Structures relevant for visuospatial processing include the superior parietal lobe (SPL), inferior parietal lobe (IPL), and postcentral gyrus (PCG). There is evidence of functional abnormalities in the magnocellular/ dorsal pathway of individuals with FraX [49,50] and persons with Williams syndrome exhibit abnormal structural integrity in white matter tracts [specifically the superior longitudinal fasciculus (SLF)] of this pathway [51,52]. Further, reduced activation in the SPL during visuospatial working memory tasks was observed in both FraX [53] and Williams syndrome [54]. Although increased size [25,30▪] and reduced activation of the IPL during visuospatial working memory has been reported in FraX [53], this structure appears to be unaffected in Williams syndrome [61,70]. Finally, decreased white matter connectivity in the PCG was reported in FraX [60], whereas greater gray matter density occurs within the PCG in Williams syndrome [62].

In the language domain, persons with both FraX [8] and Williams syndrome [63] exhibit deficits in verbal working memory. However, while individuals with Williams syndrome show excessive paralinguistic language content (e.g. high level of emotional content/hooks) [64], those with FraX show delayed development in many domains of language (vocabulary, morphosyntax, and pragmatics) [71]. Interestingly, volumes of superior temporal gyrus are

small in FraX [32], while disproportionately large [26,27,45] and asymmetric [66] in Williams syndrome. Phonological memory, which entails maintaining and manipulating linguistic information, is impaired in FraX [72–74] and has not been studied extensively in Williams syndrome, although auditory working memory is abnormal in Williams syndrome [75]. Phonological memory is thought to require functional participation of the cerebellar vermis and caudate and their connections to the frontal lobe [76]. Individuals with FraX and Williams syndrome exhibit abnormal structure of the cerebellar vermis. A decrease in size of the cerebellar fastigial nucleus is found in *Fmr1* -knockout mice [*77*], which is consistent with reduced size of the posterior cerebellar vermis in humans with FraX [65]. Decreased number of Purkinje cells in the cerebellar vermis have also been documented in postmortem histologic analysis of tissue in FraX [78▪]. In contrast, the cerebellar vermis is significantly enlarged in Williams syndrome [67].

Taken together, we have described specific cognitive-behavioral abnormalities that are common to both FraX and Williams syndrome, and provided information as to the neurocircuitry potentially associated with such deficits – frontostriatal pathways for response inhibition/executive function; and magnocellular/dorsal pathway, SPL, IPL, and PCGfor visuospatial function. We have also described prominent contrasts in cognitive–behavioral function, oftenwith correspondingcontrasts in putativeneural correlates – for example, amygdala and fusiform cortex for social behavior; STG and cerebellar vermis for language. This critical analysis provides a basis for understanding the relationship between brain structure and human behavior, and may provide opportunities to use neuroimaging findings as biomarkers for specific cognitive–behavioral problems in neurodevelopmental disorders in general.

ADVANCES IN MOLECULAR BIOLOGY OF FRAGILE X SYNDROME AND WILLIAMS SYNDROME

Studying cellular and molecular mechanisms in FraX and Williams syndrome complements our understanding of the neural correlates of cognitive – behavioral profiles in these disorders. The common defective mechanism in many neurodevelopmental disorders appears to reside at the synapse. FMRP serves as an mRNA-binding protein regulating synaptic plasticity, dendritic pruning, and axonal development (Table 2). In *Fmr1* -knockout mice, loss of FMRP results in dysregulation of glutamatergic signaling maturation and alters the timing of the critical period for synaptic plasticity in the somatosensory cortex [96] and hippocampus [97]. These synaptic processes are believed to be critical in brain development and cognitive–behavioral functions. Emerging evidence supports the contention that microRNAs are involved in the translational regulation of major synaptic proteins in both FraX and Williams syndrome [80▪,98]. In hippocampal neurons of *Fmr1*-knockout mice, microRNA 125b (miR-125b) and FMRP regulate the expression of an important subunit of *N*-methyl D-aspartate receptor (NMDAR) [80▪], which controls a type of long-term potentiation (LTP) important for memory and learning. In Williams syndrome, miR-134 inhibits the translation of *LIMK1* [98], which is important in synaptic plasticity [99]. It is likely that microRNAs are important in the pathogenesis of other neurodevelopmental disorders as well.

Synapse formation is essential for neurotransmission. Glutamatergic pathways control the majority of excitatory neurotransmission and GABAergic pathways represent the major form of inhibitory neurotransmission. Aberrations of these systems can deviate the balance between overall excitatory and inhibitory synaptic activity [100]. In addition to this excitation/inhibition imbalance, these pathways serve other important functions in learning, memory and behavior [e.g. long-term depression (LTD), LTP, and dendritic pruning]. mGluR5-dependent LTD is a well established form of synaptic plasticity and putative

molecular mechanism involved in FraX [101]. Activation of mG1uR1/5 leads to cascades of signaling events driving the activation of protein synthesis involved in the internalization of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs), a process involving an assembly of Arc/ Arg3.1 and other proteins [102]. FMRP binds to the mRNA of Arc/Arg3.1 and other synaptic proteins, and is an essential part of cellular survival mechanisms through the modulation of signaling pathways [103]. mGluR5 is associated with scaffolding proteins [83] and cell adhesion proteins [91,104]. FMRP co-expresses with and silences the translation of mRNAs encoding postsynaptic density (PSD) components, including PSD-95 [82▪,83]. Impairment of PSD-95 may be involved in hippocampal-dependent learning defects [87], which are common in individuals with FraX [105]. Interestingly, knocking out the mRNA for PSD-95 results in decrease in *Cyln2*, which is a candidate gene for motor and cognitive deficits in Williams syndrome [106▪]. Various mGluR antagonists have been developed for the potential treatment of symptoms of FraX (see Table 3 and Table 4 [107–110,114,115▪▪,120,121]).

In addition to glutamatergic mechanisms, growing evidence supports the putative role of the GABAergic circuit dysfunction in FraX [122] and Williams syndrome [123▪]. Recent evidence suggests that the GABAergic system undergoes complex patterns of changes during brain development in FraX [85]. On the basis of the premise that individuals with FraX exhibit decreased GABAergic activity, $GABA_A$ receptor agonists have been tested in animals (Table 3; [113]) with human trials likely to occur in the near future. Interestingly, *GTF2I*, a candidate gene for Williams syndrome, is a regulator of *Dlx*, which is involved in the differentiation of GABAergic projection neurons [123▪]. An important class of protein involved in the migration of GABAergic neurons, semaphorin [95], is associated with both *FMR1* [124] and *GTF2I* [125]. Collectively, modulation of glutamatergic and GABAergic pathways presents opportunities for pharmacologic interventions in both of these disorders.

In summary, we have identified three levels of molecular machinery common to FraX and Williams syndrome: microRNAs involved in translational regulation of major synaptic proteins; scaffolding proteins in excitatory synapses; and proteins contributing to axonal development. Abnormal dendritic pruning is a shared morphologic feature between FraX [126,127] and Williams syndrome [106▪] as well.

INTEGRATION OF NEUROIMAGING AND MOLECULAR MECHANISMS: AN EXAMPLE

As shown above, significant deficits in executive function in FraX are associated with frontostriatal dysfunction. In addition, our group has shown significantly less activation in the hippocampus and basal forebrain in women with FraX during functional MRI [105]. These brain regions are known to have particularly high levels of *FMR1* transcription during fetal development and are involved in cholinergic neurotransmission. Evidence of cholinergic dysfunction in the dorsolateral prefrontal cortex of men with FraX was also suggested from a ^1H magnetic resonance spectroscopy study [117]. These data led us to hypothesize that deficits in executive function in FraX may be associated with cholinergic dysfunction in the frontostriatal pathway. Other lines of evidence also support this hypothesis. In *Fmr1* -knockout mice, the α subunit of the large conductance Ca^{2+}-activated potassium (BK) channel was among the proteins most reduced in the animal [94]. BK channels play an important role in cholinergic interneurons of the striatum [128], a brain region shown to be abnormal in FraX through multimodal imaging studies performed by our group [25]. Interestingly, BK channels are also important regulators of the hypothalamic–pituitary–adrenal axis, a system that regulates hormonal response to stress, a function that appears abnormal in both individuals with FraX and the mouse model of this disorder [129]. Finally, mutations in the gene coding for the a subunit of the BK channel have been

implicated in the pathogenesis of non-FraX autism [130]. Taken together, we hypothesize that correcting a deficit in neurotransmission within cholinergic striatal interneurons and striatal–cortical 'tone' (by using an acetylcholinesterase inhibitor such as donepezil) might be helpful in treating executive function-related symptoms (hyperactivity, impairments in cognitive and behavioral inhibition) in FraX. In an open-label, pilot trial of donepezil, five patients with FraX showed significantly improved cognitive–behavioral function [117]. Results of this open-label study were extended to 12 patients with significant benefits of donepezil shown in Fig. 1 and Table 4. (An NIMH funded, double-blind, placebo-controlled trial of donepezil is currently ongoing at our center.)

Although initial results from our open donepezil trial suggest that increased cholinergic neurotransmission may be beneficial to individuals with FraX, antagonism of cholinergic Ml [111] and M4 [112] receptors in *Fmr1*-knockout mice have been associated with decreased perseverative behaviors (Table 3). This conflicting information is puzzling, but may be related to interspecies differences, receptor subtype specificities, and complex interactions among G_q-coupled G-protein coupled receptors (GPCRs) [131–135]. More research in this area is clearly needed to resolve this issue and to address the impact of treatments targeting the cholinergic pathway for potential cognitive enhancement and reduction of inappropriate behaviors in FraX.

FUTURE DIRECTIONS

Advances in our understanding of neurocircuitry and molecular processes involved in neurogenetic conditions have allowed us to gain insight into the pathogenesis of cognitive–behavioral profiles of these disorders and to design pharmacologic interventions. As outlined above, we have illustrated this strategy through the example of cholinergic dysfunction in the frontostriatal pathway in FraX. In this review article, we have summarized commonalities and differences between FraX and Williams syndrome (Table 1 and Table 5). Executive function deficits associated with aberrant frontostriatal pathway are observed in these known neurogenetic disorders, as well as other neurodevelopmental disorders such as velocardiofacial syndrome [136,137] and idiopathic autism [24▪]. This observation supports the examination of cholinergic function in these syndromes, as modulating the cholinergic pathway may be helpful in treating symptoms related to deficits in executive functions and other behaviors.

In terms of developing a more accurate picture of the pathophysiology of cognitive–behavioral phenotypes in neurodevelopmental disorders, further defining neurocircuitry by linking molecular biomarkers with neuroimaging (e.g. positron emission tomography with functional MRI) will likely lead to new insights, thus setting the stage for improved circuit-based and molecular-based treatment strategies for specific symptoms. Longitudinal studies of both FraX and Williams syndrome during early development are also necessary to better understand the complex relationships among cognitive–behavioral profiles, brain development, and molecular mechanisms, particularly with respect to establishing cause. Such information has critical implications for early behavioral and pharmaceutical interventions.

CONCLUSION

The genetic variations leading to FraX and Williams syndrome are different, yet important similarities and contrasts in phenotype, neurocircuitry, molecular machinery, and cellular processes occur in these disorders. This permits a unique approach to conceptualizing gene–brain–behavior links in FraX and Williams syndrome. This approach could be applied to

other neurodevelopmental disorders, such as the many currently unknown conditions comprising the category of idiopathic autism.

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KEY POINTS

- Contrasting cognitive-behavioral and social profiles in FraX and Williams syndrome and their putative neural correlates include amygdala and fusiform cortex for social behavior, superior temporal gyrus and cerebellar vermis contributing to language.
- Similarities in cognitive-behavioral features and underlying neurocircuitry in FraX and Williams syndrome include frontostriatal pathways for executive function, and magnocellular/dorsal pathway, superior parietal lobe, inferior parietal lobe, and postcentral gyrus for visuospatial function.
- Research focused on gene-brain-behavior relationships in FraX has resulted in improved circuit-based and molecular-based understanding and experimental treatments of major target symptoms. Similar insights are expected to result from additional investigation of Williams syndrome.

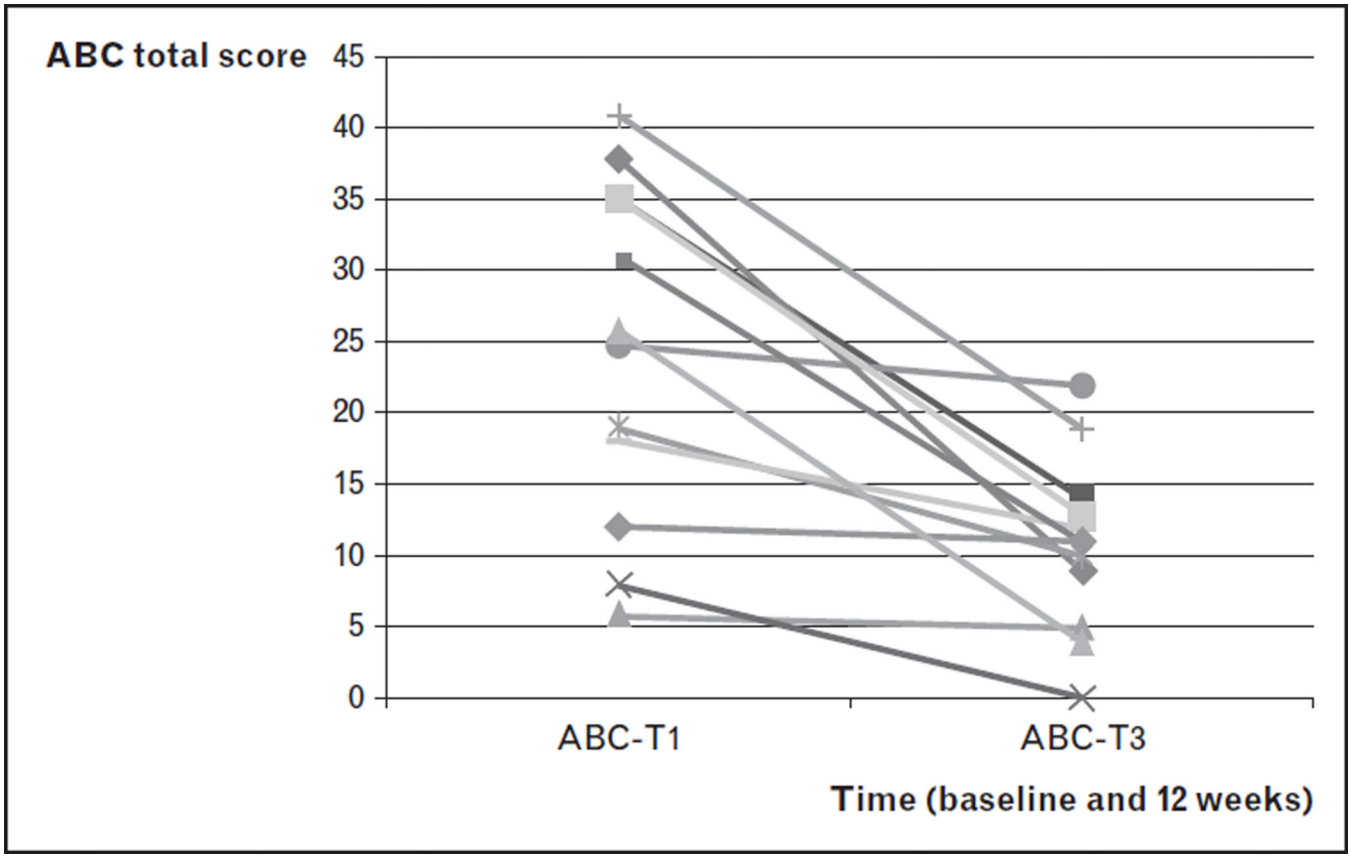

FIGURE 1.
Change in Aberrant Behavior Checklist (ABC) total score by subject in an open-label trial of donepezil for the treatment of behavioral problems in fragile X syndrome.

Table 1

Cognitive/behavioral phenotypes and putative neural correlates of fragile X syndrome and Williams syndrome

	Cognitive/behavioral features		**Putative neural correlate**	
	Fragile X syndrome	**Williams syndrome**	**Fragile X syndrome**	**Williams syndrome**
Social	*Similarities:*		*Similarities:*	
	Deficits in recognizing subtle social cues and impaired effectiveness in social interaction with peers.		Amygdala and fusiform cortex are affected, albeit in different directions.	
	Contrasts:		*Contrasts:*	
	Avoidance of social interactions [13]. Poor eye contact [15]; gaze aversion [16]. hcreased social anxiety [15].	Hypersociability [17,18]; approachable [19]; greater attention bias towards happy faces than angry faces [21]. Difficulty in disengaging eye contact in children and adolescents [20]. Ieased phobic like-fears and general anxiety [23].	Smaller amygdala [24▪,25]. Greater sensitization in the left amygdala with successive exposure to direct gaze [16]. Reduced response to facial expressions within the fusiform cortex [32].	Larger amygdala [26,27]. Reduced amygdala response to fearful facial expressions [28,29]. Abnormally greater response to facial expressions within fusiform cortex face area [31▪]. Right lateral OFC activation in response to positive faces [33]; right medial OFC activation in response to negative faces [33].
Response inhibition	*Similarities:*		*Similarities:*	
	Both FraX [34,35] and WS [36] show deficits in response inhibition.		Dysfunction of frontostriatal circuitry (FXS [38]; WS[39]), albeit in opposite directions.	
	Contrasts:		*Contrasts:*	
	Response inhibition is dysfunctional in male [35] and female [34] adolescents. Deficits in disengaging attention and set-shifting in toddlers [37].	Difficulty inhibiting inappropriately high appetitive drive towards social interaction [36]. Deficits in selective attention in toddlers [37].	Reduced volume of frontal lobe [30▪]. Dramatically increased caudate nucleus volume [25,40,41,42▪▪,43]. Ineased density of white matter tracts in left ventral frontostriatal pathway [38]. Significant correlation between FMRP and neural responses in right	Disproportionately large frontal areas [44]. Reduced volume of caudate nucleus [45].

	Cognitive/behavioral features		Putative neural correlate	
	Fragile X syndrome	**Williams syndrome**	**Fragile X syndrome**	**Williams syndrome**
			VLPFC and both left and right striatum [34].	
Visuospatial	*Similarities:*		*Similarities:*	
	Impairments in visuospatial working memory tasks (FraX [8]; WS [46]) and visuomotor coordination (FraX [2]; WS [47,48]).		Deficits in the magnocellular/dorsal pathway functioning (FraX [49,50]; WS [51,52]). Decreased activation in SPL during visuospatial working memory task (FraX [53]; WS [54]).	
	Contrasts:		*Contrasts:*	
	Deficits in lower level visual processing have been rarely documented, except for aberrant saccade behavior [55], which may confound assessment of visuospatial functioning.	Deficits in lower level visualprocessing (strabismus [56], reduced visual acuity [57], reduced stereopsis [58], and impairment in making simple saccades [59]) may confound assessment of visuospatial functioning.	Deficits on tasks with stimuli targeting the magnocellular pathway [49,50], Increased size of IPL [25,30▪]. Reduced IPL activation during visuospatial working memory tasks [53]. White matter connectivity in postcentral gyrus is decreased [60].	DTI reveals that white matter tracts within the magnocellular pathway such as the SLF exhibit an abnormal structural integrity [51,52]. Visuomotor abilities are associated with gray matter density of left IPL [61]. Greater gray matter density within the postcentral gyrus [62].
Language	*Similarities:*		*Similarities:*	
	Impairments in auditory working memory (FraX [8]; WS [63])		Abnormalities in size of STG and cerebellum, although the deviations from normal are in opposite directions.	
	Contrasts:		*Contrasts:*	
	Atypical speech, limited expressive communication.	Unusually loquacious and highly expressive [64].	Small STG volume [32]. Reduced volume of cerebellar vermis [65].	Asymmetric STG [66] and disproportionately larger STG volume [45]. Enlarged cerebellar vermis [67].

DTI, diffusion tensor imaging; FraX, fragile X syndrome; IFC, inferior prefrontal cortex; IPL, inferior parietal lobe; OFC, orbitofrontal cortex; SLF, superior longitudinal fasciculus; SPL, superior parietal lobe; STG, superior temporal gyrus; VLPFC, ventral lateral prefrontal cortex; WS, Williams syndrome.

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Table 2

Partial list of FMRP target mRNAs and associated molecules in fragile X syndrome or *Fmr1* knock-out mice

Category of function	Molecule	mRNA	Location of altered expression studied	Expression	References
Transcriptional regulator	MeCP2	*Mecp2*	Cerebellum; hippocampus, cortex, diencephalon, brainstem	↑mRNA; ↓mRNA	[79]
Translational regulator	miRNA-125b	–	Hippocampus	↑miRNA	[80▪]
Translational regulator	miRNA-132	–	Hippocampus	↑miRNA	[80▪]
mGlu receptor	mGluR1/2	*GαluR1/2*	Hippocampus, cortex, dentate gyrus	↑mRNA, ↑protein	[81]
NMDA receptor component	NR1	*Grin 1*	Prefrontal cortex; PSD of neocortex, hippocampus	↓protein; ↑protein	[82▪,83]
NMDA receptor component	NR2A	*Grin2A*	Prefrontal cortex	↓protein	[82▪]
NMDA receptor component	NR2B	*Grin2B*	Prefrontal cortex; PSD of neocortex, hippocampus	↓protein; ↑protein	[82▪,83]
GABA receptor component	$GABA_AR$ δ subunit	*Gaba-Aδ*	Cortex, subiculum, hippocampus	↓mRNA, ↓protein	[84,85]
Glucocorticoid receptor α	GRα	*NR3CI*	CA1 of hippocampus	↓protein	[86]
Signal transduction (G_q)	RGS5	*Rgs5*	–	↑mRNA	[84]
Scaffolding protein	PSD-95	*Psd95*	Hippocampus, prefrontal cortex	↓mRNA, ↓protein	[81,82▪,83,87]
Scaffolding protein	SAPAP3	*Sapap3/4*	Prefrontal cortex	↓mRNA, ↓protein	[82▪, 83,84]
Scaffolding protein	Shankl	*Shank 1*	Neocortex, hippocampus	↑mRNA	[83]
Scaffolding protein	APP	*App*	Cortex	↑mRNA, ↓protein	[88]
Plasticity-related protein	Arc/Arg3.1	*Arc*	Hippocampus, cortex	↓mRNA, ↓protein	[82▪, 89]
Scaffolding protein	Gephyrin	*Gphn*	Cortex	↓mRNA	[90]
Cell adhesion	Neuroligin 1	*Neuroligin 1*	Hippocampus	↑protein	[91]
Cell adhesion	Neuroligin 2	*Neuroligin 2*	Hippocampus	↑protein	[91]
GABA metabolism	GABAT	*Abat*	Cortex	↓mRNA, ↓protein	[85]
GABA metabolism	SSADH	*ALDH5A1*	Cortex, cerebellum	↓mRNA, ↓protein	[85]
GABA and glutamate metabolism	GAD	*Gad*	Cortex, cerebellum; amygdala; whole forebrain, cortex	↓mRNA; ↓protein; ↑protein	[92]
GABA transporter	GAT	*Slc6a12*	Whole forebrain, cortex, cerebellum	↓mRNA, ↓protein	[85]
Neurotransmitter	GABA	–	Amygdala	↓release	[92]
Microtubule dynamics, neurite extension	MAP1B	*Map 1b*	–	–	[93]
Component of Big potassium	BK channel a subunit	*KCNMA1*	Cortex	↓protein	[94]

Category of function	Molecule	mRNA	Location of altered expression studied	Expression	References
channel					
Calcium signaling	CaMK llα	*CamKllα*	Hippocampus	↑mRNA, ↑protein	[81]
Axonal development	Sema3A and Sema3F	*Sema3A* and *Sema3F*	–	–	[95]

APP, amyloid precursor protein; Arc, activity-regulated cytoskeleton-associated protein; CaMK llα, calcium/calmodulin-dependent protein kinases llα t; GABA-T, GABA transaminase; GAD, glutamate decarboxylase; MAPI B, microtubule-associated protein 1B; MeCP2, methyl CpG-binding protein 2; mGluR1/2, metabotropic glutamate receptor type 1/2; PI3K, phosphatidyl inositol 3-kinases; RGS5, regulator of G-protein signaling 5; Sema, semaphorin; SSADH, succinic semialdehyde dehydrogenase.

Table 3

Fragile X syndrome treatments targeting specific pathways in animals

Compound	Target	Animal model	Effects in animal model	References
JNJ1 6259685	mGluR1 antagonist	*Fmr 1*-knockout mice	Decreased marble burying; decreased audiogenic seizures; no effect on prepulse inhibition and motor coordination.	[107]
2-Methyl-6-(phenylethynyl)-pyridine (MPEP)	mGluR5 antagonist	*Fmr 1*-knockout mice	Decreased marble burying; improved motor learning; completely abolished the manifestation of audiogenic seizures; no effect on prepulse inhibition.	[107]
		Balb/c and Swiss Webster mice	Impaired some measures of sociability in both tested species, while reduced the intensity of some spontaneous measures of stereotypic behaviors emerging during free social interaction in Swiss Webster mice.	[108]
2-Chloro-4-((2,5-dimethyl-1-(4-(trifluoromethoxy)phenyl)-1 *H*-imidazol-4-yl)ethynyl) pyridine (CTEP)	mGluR5 antagonist	Sprague-Dawley rats and NMRI mice	Active in the stress-induced hyperthermia procedure in mice and the Vogel conflict drinking test in rats with minimal effective doses of 0.1 and 0.3 mg/kg, respectively. Long half-life of approximately 18 h and high oral bioavailability.	[109]
AFQ056	mGluR5 antagonist	*Fmr 1*-knockout mice	Rescued a deficit in inhibition of the startle response after a prepulse.	[110]
Dicyclomine	M1 antagonist (G_q-coupled)	*Fmr 1*-knockout mice	Decreased marble burying; decreased audiogenic seizures.	[111]
Tropicamide	M4 antagonist (G_i-coupled)	*Fmr 1*-knockout mice	Decreased marble burying, increased activity in the open-field assay, improved performance in the passive avoidance assay, reduced audiogenic seizures.	[112]
Gaboxadol (THIP)	$GABA_A$ receptor agonist	*Fmr 1*-knockout mice	Reduced hyperactivity and prepulse inhibition. No effect on cued fear startle response.	[113]

Table 4

Recent clinical trials for treatments targeting specific molecular mechanisms of fragile X syndrome

Compound	Target and effect	Study, patients	Treatment outcomes	References
Acamprosate	mGluR5	Open-label trial with three male patients with FraX.	Improved linguistic communication and global clinical benefit.	[114]
AFQ056	mGluR5	Randomized, double-blind, two-treatment, two-period, crossover study of 30 male patients with FraX.	Did not improve primary outcome measure, ABC-C score. However, patients with full *FMR1* promoter methylation and no detectable *FMR1* messenger RNA improved. No response was found in patients with partial promoter methylation.	[115▪▪]
Memantine	NMDA antagonist	Open-label trial with six patients with FraX.	Symptom-specific rating scales showed no statistically significant improvement. However, four of six patients showed global clinical benefit on ratings with the CGI-I.	[116]
Donepezil	Enhanced cholinergic neurotransmission	Open-label trial 12 adolescent and young adult patients with FraX for 6 weeks.	Increased CNT scores and decreased ABC Total, Hyperactivity, and Irritability scores as well as decreased CBCL/ABCL Attention Problems scores.	[117]
Riluzole	Agonist of $GABA_A$ receptors, synaptic and extrasynaptic; inhibitor of GABA transporters (GAT)	Six-week open-label prospective pilot study of riluzolein with six adults with FraX.	No significant clinical response was detected.	[118]
Valproic acid	Histone deacetylase inhibitor	Open-label study with 10 boys with FraX and ADHD.	Reduced ADHD symptoms as measured by CPRS.	[119]

ABC, Aberrant Behavior Checklist; ABCL, Adult Behavior Checklist; CBCL, Child Behavior Checklist; CGI-I, Clinical Global Impression – Improvement; CNT, Contingency Naming Task; CPRS, Conner′s Parent Rating Scale – Revised.

Table 5

Commonalities in molecular mechanisms between Fragile X syndrome and Williams syndrome

	Fragile X syndrome	Williams syndrome
Gene mutation	*FMR 1* at Xq27.3	Microdeletion at 7q1 1.23. Candidate genes involved: *CL1P2, CYLN2, ELN, GTF21, GTF21RD1*, and *L1MK1.*
Translational regulation	miRNA-125b inhibits translation of NR2A in *Fmr 1*-knockout mice [80▪].	miRNA-134 inhibits translation of Limk1 [96].
Scaffolding proteins	In the *Fmr 1*-knockout mice, FMRP co-expresses with mRNAs encoding PSD-95, and also silences the translation of its mRNAs [83].	*Dlg4* encodes PSD-95. *Dlg4* $^{-/-}$ mice showed altered forebrain expression of various synaptic genes, including *Cyln2*, which regulates cytoskeletal dynamics and is a candidate gene for WS [106▪].
Dendritic spine development	Overexpression of miR-1 25b induces long narrow spines in hippocampal neurons of *Fmr 1*-knockout mice, which correlated with a reduction in mEPSC amplitude [80▪]. In contrast, overexpressing miR-1 32 increased dendritic protrusion width and increased mEPSC amplitude [80▪].	D/g*4* $^{-/-}$ mice had subtle dysmorphology of amygdale dendritic spines [106▪].
Axonal development	Sema3F is a target of FMRP [124].	*GTF2I*, a candidate gene of WS, regulates *Dlx* gene expression [123▪]. *Dlx* homeobox genes promote cortical interneuron migration from the basal forebrain by direct repression of the class 3 semaphorin receptor neuropilin-2 [125].

WS, Williams syndrome.