Universitat Autònoma de Barcelona

Síndrome de X-Frágil en niñas y adolescentes: descripción del fenotipo neurocognitivo y de su posible relación con la conducta adaptativa

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Síndrome de X-Frágil en niñas y adolescentes: descripción del fenotipo neurocognitivo y de su posible relación con la conducta adaptativa

Tesis doctoral presentada por

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“Los hombres geniales empiezan grandes obras,

los hombres trabajadores las terminan”

Leonardo Da Vinci

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ABAS-II	Sistema de Evaluación de la Conducta Adaptativa-II
ADHD	Attention Deficit Hyperactivity Disorder
AGG	Adenina-Guanina-Guanina
ARN	Ácido Ribonucleico
ARN_m	Ácido Ribonucleico mensajero
BAS-2	Batería de Socialización-2
BRIEF-2	Evaluación Conductual de la Función Ejecutiva-2
CGG	Citosina-Guanina-Guanina
CI	Capacidad Intelectual
CIT	Cociente Intelectual Total
DI	Discapacidad Intelectual
FE	Funciones Ejecutivas
FMR1	Fragile X Mental Retardation 1
FMRP	Fragile X Mental Retardation 1 Protein
FXAND	Fragile X-Associated Neuropsychiatric Disorders
FXPOI	Insuficiencia Ovárica Prematura Asociada al X Frágil
FXTAS	Síndrome de Temblor y Ataxia Asociado al X Frágil
GC	Grupo Control
MT	Memoria de Trabajo

NEPSY-II	Batería Neuropsicológica Infantil-II
OR	Odds Ratio
SB	Sustancia Blanca
SENA	Sistema de Evaluación de Niños y Adolescentes
SG	Sustancia Gris
SXF	Síndrome X Frágil
TDAH	Trastorno por Déficit de Atención con Hiperactividad
TEA	Trastorno del Espectro Autista
TMT	Teoría de la Mente Total
TMV	Teoría de la Mente Verbal
WISC-V	Escala de Inteligencia Wechsler para niños-V

RESUMEN

Resumen:

El Síndrome X Frágil (SXF) es la segunda causa más común de discapacidad intelectual de base genética, por detrás de la trisomía 21, y la primera causa de discapacidad intelectual hereditaria.

En el caso de los varones, al contar tan solo con un cromosoma X, el hecho de ser portadores de la mutación completa del gen *FMR1* provoca una ausencia total de la proteína FMRP mientras que, en el caso de las mujeres, conlleva una disminución parcial ya que el cromosoma con el gen *FMR1* sano será capaz de sintetizar cierta cantidad de FMRP. Todo esto implica que la clínica en varones suele expresarse de forma más grave que en las mujeres. Este hecho ha influido en que la gran mayoría de investigación científica se haya centrado en describir el fenotipo neurocognitivo de los varones afectos y que el número de investigaciones realizadas en mujeres sea significativamente inferior.

La presente tesis se estructura en base a 4 artículos. Éstos representan el núcleo de la investigación que tiene como objetivos principales estudiar la relación entre diferentes áreas del perfil neurocognitivo y la conducta adaptativa en chicas con el diagnóstico de SXF; así como el riesgo de sufrir acoso escolar en el papel de víctima y su relación con su nivel de adaptación funcional. Todos ellos cuentan con una muestra de 26 chicas con SXF y 14 chicas de grupo control emparejadas por edad y capacidad intelectual total, con edades comprendidas entre los 7 y los 16 años.

1. INTRODUCCIÓN

1. Introducción:

1.1. Historia del Síndrome X Frágil.

El Síndrome X Frágil (SXF) es la segunda causa más común de discapacidad intelectual (DI) de base genética, por detrás de la trisomía 21, y la primera causa de DI hereditaria.

La primera descripción del Síndrome fue realizada por Martín y Bell en el año 1943. Estos autores siguieron durante 17 años a una familia en la que había 11 miembros varones con DI, nacidos de una madre sana. Fueron los primeros en reportar una DI con herencia ligada al X. Más adelante, en el año 1969, Lubs describió un hallazgo sobre un cromosoma diferente que denominó “marcador cromosómico de constricción secundaria” en el cromosoma X, que diferenciaba a los miembros con DI de una misma familia. Estudios posteriores con varones mostraron una región frágil cercana a la porción distal del brazo largo del cromosoma X.

En un primer momento se pensó que el SXF era un trastorno genético recesivo ligado al X, pero los datos clínicos no corroboraban estas hipótesis. En el año 1991, equipos de científicos internacionales identificaron el gen *FMR1* y la mutación responsable de causar el SXF (Verker et al., 1991; Pieretti et al., 1991). Encontraron que en las familias con SXF había una porción del exón 1 sin traducir con una expansión en la repetición del triplete de nucleótidos Citosina-Guanina-Guanina (CGG). Descubrieron que en los varones con el fenotipo de SXF, la proteína FMRP estaba ausente, como resultado de un silenciamiento en la transcripción correspondiente del gen *FMR1,* lo cual se produce como consecuencia de la expansión del número de repeticiones del triplete CGG (> 200 repeticiones). Descubrieron que el SXF era el resultado de una ampliación en la longitud de un área de repetición CGG encontrada en la región promotora del gen *FMR1* (Reches et al., 2019).

Estudios epidemiológicos refieren una frecuencia estimada de SXF de 1,4:10.000 varones y 0,9:10.000 mujeres (Jorge P et al., 2018). Con una prevalencia de 1 cada 2.500 a 7.000 varones y 1 cada 2.500 a 11.000 mujeres (Bartholomay et al., 2019). Respecto a la prevalencia de la premutación se estima que oscila entre 1 de cada 148 - 204 mujeres y entre 1 de cada 290 - 468 varones (Wheeler, Raspa, Hagerman, Mailick, & Riley, 2017).

1.2. Bases genéticas del SXF.

La causa del SXF se debe a una deficiencia parcial o ausencia total de una proteína llamada “fragile X mental retardation 1 protein” (FMRP) también conocida como el regulador sináptico funcional *FMR1*. Es una proteína de unión del ARN con un papel importante en la regulación de un amplio número de ARN mensajero (ARN_m) en las neuronas postsinápticas. El SXF está causado por la expansión en la repetición de los trinucleótidos CGG en la región promotora no transcrita del gen (2019 Lozano et al., 2014; Reches et al.), localizado en Xq27.3 (Bennetto et al., 2001; Tassone et al., 2014), que lleva a una metilación, un silenciamiento en la transcripción y la ausencia total o déficit de FMRP (Hagerman et al., 2017; Tassanakijpanich et al., 2021).

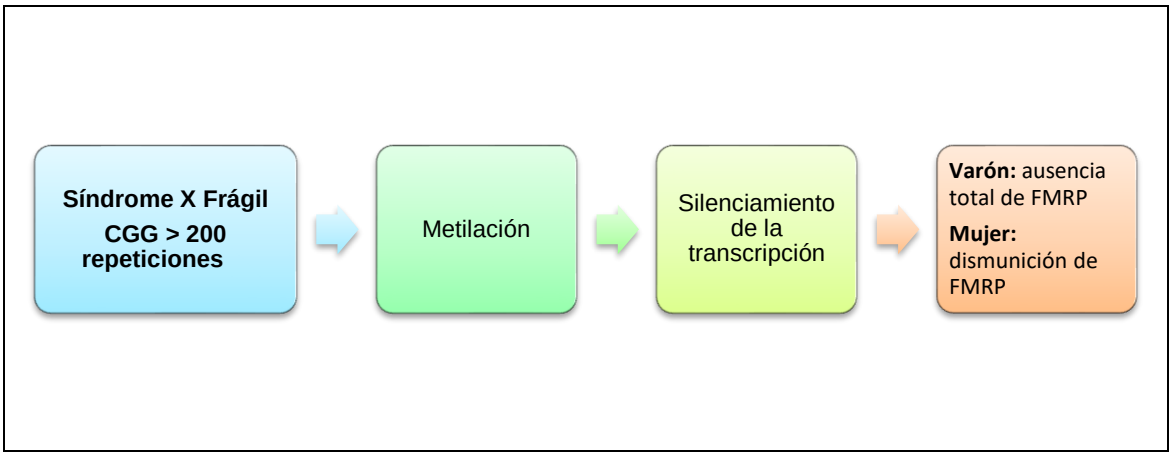
La FMRP es una proteína citoplasmática, también localizada en el nucleoplasma neuronal y en los poros nucleares. Está involucrada en la regulación del metabolismo post-transcripcional del ARN. Juega un papel importante en la plasticidad sináptica, el desarrollo dendrítico y axonal y en los procesos de aprendizaje y memoria. Actúa como agente organizador del ARN_m transportador y está involucrada en el control de sus propios niveles de proteína. En un alelo estable y normal la región CGG es interrumpida por un triplete Adenina-Guanina-Guanina (AGG) cada 9 o 10 repeticiones. Los alelos premutados tienen un número menor de interrupciones AGG en comparación

con los alelos de tamaño normal *FMR1*. En función del número de repeticiones se ha clasificado a los sujetos en cuatro categorías: individuos no afectados (6-44 repeticiones), individuos en la zona gris (45-54 repeticiones), individuos portadores de la premutación (55-200 repeticiones) e individuos con la mutación completa (>200 repeticiones) (Reches et al., 2019).

Tabla 1. Clasificación según el número de repeticiones.

	Número de repeticiones CGG
No afectados	6-44
Zona gris	45-54
Premutación	55-200
Mutación completa	>200

Figura 1. Resumen del mecanismo genético del Síndrome X Frágil



Nota. La figura resume el mecanismo gético del Síndrome X Frágil. Adaptado de *Fragile X premutation and associated health conditions: A review* (p. 5), por N. Tassanakijpanich et al., 2021. *Clinical Genetics*; 1-10.

Estudios realizados en población infantil con personas portadoras de la premutación muestran una gran variabilidad de resultados en función de la edad. Por lo general, no se han encontrado diferencias significativas al comparar personas portadoras de la premutación con un grupo control, especialmente en población femenina. En el caso de aquellas personas que sí presentan clínica, ésta suele ser de menor gravedad que en los casos con la mutación completa. Los portadores de la premutación con clínica suelen presentar algunos rasgos físicos y psicológicos, así como ciertos retrasos en el neurodesarrollo (Tassanakijpanich et al., 2021). En cuanto a los rasgos físicos se ha encontrado que los más comunes son la presencia de orejas prominentes y macroorquidismo (después de la pubertad). Respecto a su fenotipo cognitivo conductual, los estudios realizados muestran una mayor incidencia de síntomas de un trastorno por déficit de atención con hiperactividad (TDAH), timidez, dificultades en las relaciones sociales, agresividad y rasgos de un trastorno del espectro autista (TEA) (Lozano et al., 2014; Tassanakijpanich et al., 2021).

En población adulta se ha encontrado que la premutación suele asociarse con el síndrome de temblor y ataxia asociado al X Frágil (FXTAS, más frecuente en varones) y con la insuficiencia ovárica prematura asociada al X frágil en mujeres (FXPOI), así como con una amplia variedad de problemas médicos y psiquiátricos (FXAND) (Salcedo et al., 2019). Dentro de estos últimos se han descrito trastornos de ansiedad, trastornos del estado de ánimo (depresión), alteraciones del sueño, dolor crónico, alteraciones en la función tiroidea, hipertensión, crisis epilépticas, fibromialgia, dolor muscular y migrañas (Tassanakijpanich et al., 2021). En una revisión reciente se apunta como posible causa fisiopatológica de estos trastornos al efecto neurotóxico de la alteración de los niveles de ARN_m de *FMR1* (Cabal-Herrera et al., 2020).

Algunos individuos con SXF presentan un mosaicismo, con algunas células albergando alelos con la mutación completa y otras con la premutación. Otros individuos presentan una metilación del mosaicismo, con algunas células con alelos *FMR1* metilados y otras sin metilar. En ambos tipos de mosaicismo se da alguna producción de FMRP, por lo que estos individuos podrían presentar problemas cognitivos y de conducta menos severos que aquellos individuos que presentan la mutación completa, totalmente metilada, en los que hay una ausencia total de FMRP (Hagerman et al., 2017).

Las manifestaciones del SXF varían en función del sexo, la edad, los antecedentes genéticos, las influencias ambientales y las variaciones moleculares (como el nivel de metilación o la presencia de mosaicismo del tamaño de la repetición o metilación), que generan diferentes niveles de producción de FMRP (Dyer-Friedman et al., 2002; Loesch et al., 2004; Oostra et al., 2002).

Por otro lado, los niveles de FMRP correlacionan con la ratio de activación. La ratio de activación es el porcentaje de células en sangre que contienen el alelo *FMR1* sano o no afectado en el cromosoma X activo (Tassone et al., 1999; Hagerman et al., 2017). En la literatura está descrito que las mujeres presentan unas manifestaciones menos graves que los varones, debido a que el cromosoma X con el gen *FMR1* no afectado puede producir cierta cantidad de FMRP. La afectación clínica más leve se asocia con una falta total de metilación de *FMR1* en los hombres y con una ratio de activación superior a 0,75 en las mujeres (Hagerman et al., 2017). En este sentido, existe una hipótesis que intenta dar explicación a la elevada variabilidad clínica encontrada entre las mujeres con SXF, según la cual esta variabilidad se debería a la ratio de activación a nivel cerebral entre los cromosomas X activos con el gen *FMR1* con mutación completa y aquellos cromosomas X activos con el gen sano o no afectado.

1.3. Características clínicas del Síndrome X Frágil:

Es importante destacar que en función del sexo del individuo afectado de SXF las manifestaciones clínicas pueden variar tanto en tipo como en intensidad (Dyer-Friedman et al., 2002; Loesch et al., 2004; Oostra et al., 2002). A continuación, se describen tanto las características clínicas generales (en varones y en mujeres), como las manifestaciones propias del SXF en mujeres.

1.3.1. Características clínicas generales:

La mayoría de los bebés con SXF presentan dificultades en la succión durante la lactancia materna y pueden experimentar emesis recurrentes debido al reflujo. Un 60% de los pacientes suelen presentar otitis recurrentes durante los primeros años de vida y en algunos casos llegarán a requerir de drenajes transtimpánicos para normalizar la audición. Más del 20% presentan estrabismo.

Es común el retraso en el desarrollo de habilidades motrices y lingüísticas. Después del primer año de vida suele aparecer la defensa táctil (respuestas conductuales y emocionales negativas y desproporcionadas a ciertos estímulos táctiles), los individuos presentan un contacto ocular evitativo y una tendencia a aletear en momentos de excitación emocional. También son frecuentes conductas como morderse las manos o masticar la ropa.

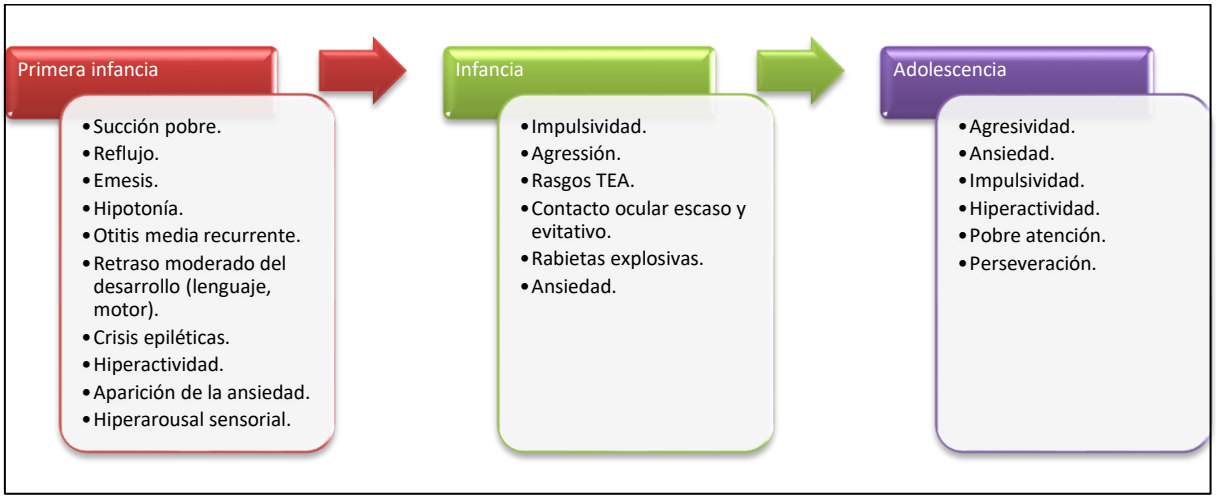
En el segundo año de vida suele aparecer la ansiedad y la hiperactivación sensorial y, una vez que son capaces de caminar, suelen presentar conductas hiperactivas. De hecho, un 80% de los chicos con SXF suele diagnosticarse de un TDAH a los 3 o 4 años, mientras que sólo un 40% de las chicas con SXF

recibe este diagnóstico y suele ser en la edad escolar (Hagerman et al. 2002; Cornish et al., 2013; Cornish et al., 2007).

Las crisis epilépticas se dan en un 8-16% de los chicos y en un 3-7% de las chicas con SXF y suelen presentarse en los primeros 5 años de vida (Berry-Kravis et al., 2010; Kidd et al., 2014; Musumed et al., 1999).

Los síntomas de TEA se pueden desarrollar en la infancia temprana. Un 50-60% de los chicos y un 20% de las chicas con SXF presentan un diagnóstico de TEA comórbido (Hagerman et al., 2017).

Figura 2. Características clínicas del Síndrome X Frágil.



Nota. La figura resume las características del Síndrome X Frágil en la edad pediátrica. Adaptado de "Fragile X Syndrome". (p. 4), por R. Hagerman, 2017. *Nature Reviews. Disease Primers*, Vol 3.

Respecto a los **rasgos físicos** los chicos con SXF suelen presentar cara alargada y estrecha, paladar ojival, orejas prominentes, macroorquidismo (después de la pubertad), hipotonía y pies planos (Garber et al., 2008; Pop et al., 2014; Hagerman et al., 2002; Raspa et al., 2017). Las chicas presentan un fenotipo físico con rasgos mucho más sutiles (Hagerman et al., 1996), siendo las orejas prominentes y la cara alargada los más comunes (Hagerman et al., 1992).

1.3.2.Perfil cognitivo-conductual en SXF.

1.3.2.1. Aspectos generales:

Tanto varones como mujeres presentan un retraso en la comunicación (especialmente en el área de pragmática), la socialización y las habilidades básicas para la vida diaria (Mazzocco et al., 2006).

Los varones con SXF con mutación completa presentan una discapacidad intelectual de leve a moderada. Dentro de su perfil cognitivo destacan como puntos débiles la memoria a corto plazo, la memoria de trabajo, la memoria espacial, el procesamiento secuencial auditivo, el pensamiento abstracto, la función ejecutiva y el razonamiento matemático. En contraposición destacan como puntos fuertes el vocabulario receptivo, la memoria visual, el procesamiento simultaneo, el aprendizaje vivencial y la capacidad de imitación (Raspa et al., 2017). Por su parte, las chicas con SXF con mutación completa, presentan un patrón de puntos fuertes y débiles similar al de los varones, pero con un grado de afectación cognitiva menos grave (Keysor et al., 2002).

Las **comorbilidades psiquiátricas** más frecuentes son:

- Trastorno por Déficit de Atención con Hiperactividad:
    - Aparece en el 84% de los varones y el 67% de las mujeres con mutación completa (Bailey et al., 2008).
    - Los varones suelen presentar síntomas de mayor gravedad que las mujeres, con mayores dificultades en atención, impulsividad y control inhibitorio (Munir et al., 2000; Cornish et al., 2004).
- Trastornos de Ansiedad:
    - El 70% de los varones y el 56% de las mujeres han sido tratados o diagnosticados de ansiedad (Bailey et al., 2008).
    - Los rasgos típicamente asociados a la ansiedad en el SXF son: escaso contacto ocular, mirada evitativa, timidez extrema, aleteo, conductas autolesivas, agresión y síntomas autistas (Raspa et al., 2017).

- Trastorno del Espectro autista:
    - El SXF es la condición genética hereditaria conocida más asociada al TEA. La comorbilidad entre SXF y TEA se encuentra entre un 15%-52% (Bailey et al., 2008; Hernández et al., 2009).
    - Los rasgos TEA más frecuentes en las personas con SXF son: dificultades en la comunicación social, conductas autolesivas, conductas restrictivas o perseverativas, estereotipias motoras y ausencia o retraso del lenguaje (Raspa et al., 2017).
    - Otros problemas de conducta: defensa táctil, rabietas, hipersensibilidad a estímulos sensoriales (Raspa et al., 2017).

1.3.2.2. Perfil cognitivo conductual en niñas y adolescentes con SXF:

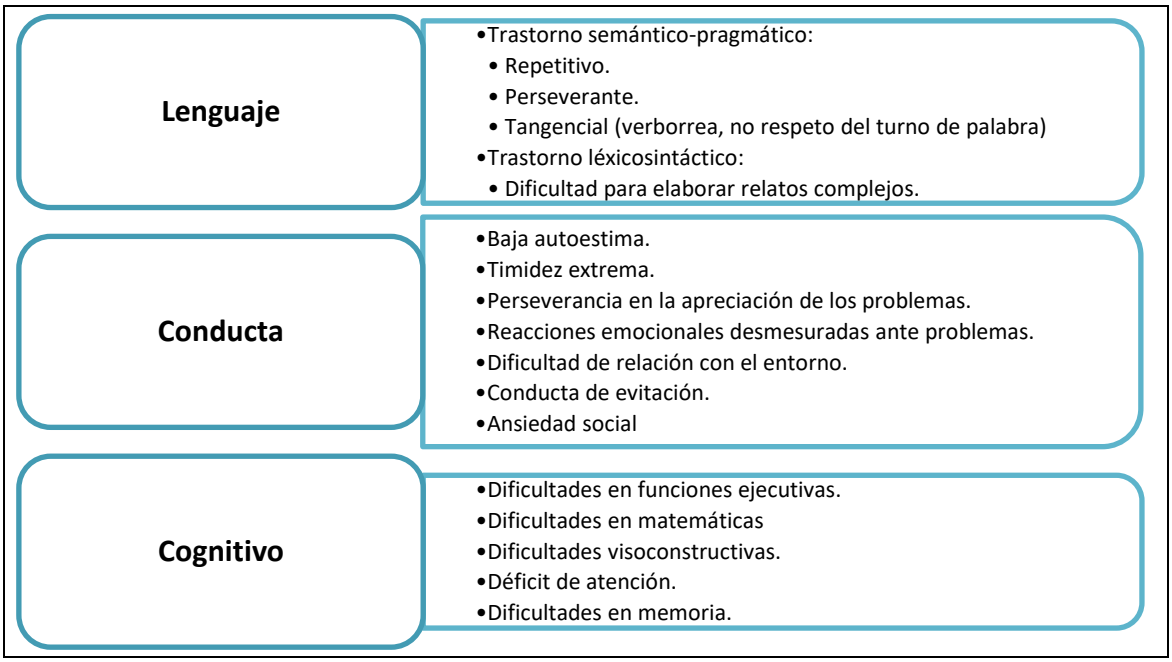
A nivel general, se ha descrito que aproximadamente el 50% de las mujeres con SXF presentan discapacidad intelectual de grado variable (entre leve y moderada) y el otro 50% presentan una capacidad intelectual (CI) en el rango medio o límite (Ferrando et al., 2004; Keysor et al., 2002).

En uno de los primeros estudios realizado en el año 1986, se analizó el perfil cognitivo-conductual de 23 mujeres con SXF. Los resultados de las escalas Wechsler de inteligencia mostraban un patrón caracterizado por una alteración en los subtests de Aritmética, Span de Dígitos y Cubos (Kemper et al.,1986).

En una revisión realizada por Ferrando et al. (2004) destacan como signos de alarma en la primera infancia el presentar un retraso en el desarrollo del lenguaje, problemas en la regulación de las emociones y trastornos de conducta. Más adelante, en la edad escolar se han descrito trastornos de aprendizaje (especialmente en el área de matemáticas), dificultades en el razonamiento abstracto, las funciones ejecutivas, el razonamiento visoespacial y la

interpretación de situaciones sociales. También se puede dar la presencia de rasgos de un trastorno del espectro autista, déficit de atención, hiperactividad e impulsividad, ansiedad, timidez extrema y conductas de evitación.

Figura 3. Fenotipo cognitivo conductual en niñas con Síndrome X Frágil



Nota. La figura resume las características del fenotipo cognitivo conductual del Síndrome X Frágil en niñas. Adaptado de *Aspectos cognitivos en niñas con Síndrome X Frágil* (p. S55) por M. T. Ferrando, 2004, *Revista de Neurología*, 38 (Supl 1), S53-S57

Durante la edad escolar y la adolescencia, Keysor et al. (2002) destacan que las chicas con SXF presentan como puntos fuertes las habilidades verbales y el reconocimiento de caras. Por el contrario, describen como puntos débiles el procesamiento visoespacial de estímulos abstractos, la función ejecutiva, la teoría de la mente, el razonamiento abstracto y la aritmética. Así mismo, a nivel socio-emocional destacan la presencia de: rasgos de un trastorno por déficit de atención con hiperactividad en un tercio de las chicas con mutación completa (especialmente el déficit de atención y la impulsividad); rasgos de un trastorno del espectro autista (dificultades en la comunicación, déficit en la interacción social, estereotipias); síntomas de ansiedad en el 23-50% de los casos (timidez

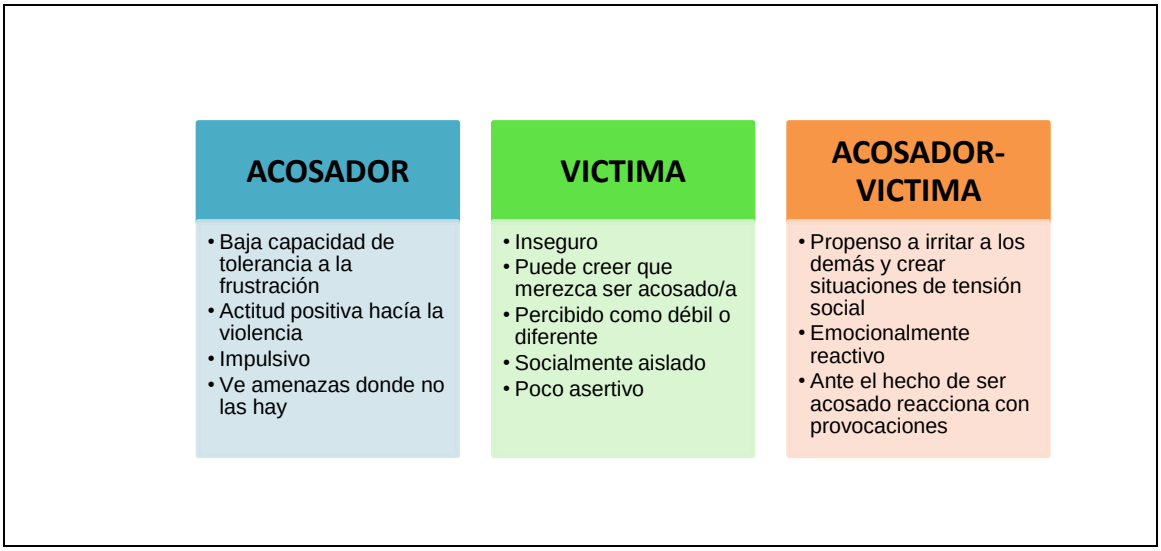
extrema y disconfort en las interacciones sociales, evitación social) y síntomas depresivos en el 38% de los casos.

1.4. Acoso escolar en población con trastornos del neurodesarrollo.

Basándonos en la investigación de Hellström y Beckam (2020) podemos definir el acoso escolar como una serie de conductas agresivas con la intencionalidad de causar daño o dolor en el contexto de una desigualdad de poderes (Olweus, 1996). Estas conductas pueden tomar una forma directa (agresiones físicas y/o verbales) o indirecta (exclusión social, aislar a la persona, mentir, difundir rumores o manipular otras relaciones sociales) (Maïano et al., 2015; Wang et al., 2009).

En las situaciones de acoso escolar se han definido tres roles (Stephens et al., 2018), que se resumen en la figura 4.

Figura 4. Características de los principales roles descritos en situaciones de acoso escolar



Nota. Adaptado de *Chilhood Bullying: Implications for Physicians* (p. 188), por M. M. Stephens, 2018. *American Family Physician,* 97 (3).

En población con discapacidad intelectual Maïano et al. (2016) encontraron que los jóvenes con DI se ven involucrados de forma más frecuente como víctimas (36,3%), pero también pueden ser acosadores (15,1%) o "acosador-víctima" (25,2%). La exclusión social y la falta de apoyo social son la forma de acoso que con mayor frecuencia experimentan los sujetos con diferentes tipos de discapacidades o de necesidades especiales (Maïano et al., 2016; Mayo et al., 2019).

Tabla 2. Frecuencia de acoso escolar en función del diagnóstico

DIAGNOSTICO	FRECUENCIA ACOSO ESCOLAR
Discapacidad intelectual	63,3%
Trastorno del espectro autista	62,5%
Trastorno por déficit de atención con hiperactividad	39,4%
Dificultades de aprendizaje	25%

Nota. Datos extraídos de Prevalence of bullying and perceived happiness in adolescents with learning disability, intellectual disability, ADHD, and autism spectrum disorder: In the Taiwan Birth Cohort Pilot Study (p. 3) por Lung, 2019.

Finalmente, en la revisión realizada por Maïano et al. (2016) destacan los siguientes factores de riesgo para sufrir acoso escolar en población con necesidades especiales: apariencia física (rasgos físicos característicos); bajo rendimiento académico o conductas inapropiadas; relaciones sociales limitadas o amistades poco estables; déficits en las habilidades sociales y de solución de problemas.

1.5. Neuroanatomía:

1.5.1. Neuroimagen estructural.

Los estudios de neuroimagen realizados han mostrado diversas diferencias entre la morfología cerebral de los individuos con SXF en comparación con individuos sanos.

En mujeres con la premutación se ha encontrado una reducción en la difusividad de la sustancia blanca, lo que nos indica que ésta es un área vulnerable para los individuos con premutación de SXF (Shelton et al., 2017; Hagerman et al., 2017).

En individuos con la mutación completa, se han encontrado alteraciones en los **Ganglios Basales** (núcleo caudado, putamen y globo pálido), una región importante en el control de la función ejecutiva (atención y atención alternante) así como en la planificación motora. Se ha observado un ensanchamiento del **núcleo caudado** (Reiss et al., 1995; Hagerman et al., 2017) que es más pronunciado en hombres que en mujeres con SXF (Eliez et al., 2001; Hagerman et al., 2017). Este ensanchamiento del núcleo caudado se presenta de forma temprana en el desarrollo (durante los tres primeros años de vida) y es específico del SXF (Hagerman et al., 2017). El ensanchamiento del caudado correlaciona negativamente con los niveles de FMRP (Gothelf et al., 2008; Hoeft et al., 2008), lo cual sugiere un papel de dicha proteína en la prevención del exceso de crecimiento. Además, el tamaño del núcleo caudado se ha asociado con las conductas repetitivas (Wolff et al., 2013).

Las alteraciones o anormalidades encontradas en individuos con SXF en el **lóbulo temporal** son más variables. Diversos estudios han encontrado un ensanchamiento del hipocampo (implicado en la memoria y el aprendizaje) en edades tempranas, pero no en edades más avanzadas (Hoeft et al., 2008; Reiss et al., 1994; Kates et al., 1997; Jakala et al., 1997; Hagerman et al., 2017), lo cual sugiere un desarrollo atípico. Se ha hipotetizado que este desarrollo atípico

puede estar relacionado con los problemas emocionales y cognitivos de las personas con SXF. Otras alteraciones estructurales del lóbulo temporal son un ensanchamiento del giro fusiforme (involucrado en la cognición) y una reducción de la ínsula (implicada en el procesamiento de las emociones) y la amígdala (implicada en el procesamiento emocional, el miedo y la memoria) (Hoeft et al., 2008; Gothelf et al., 2008; Hazlett et al., 2009; Kates et al., 1997).

Eliez et al. (2001) analizaron mediante pruebas de resonancia magnética estructural un grupo de 37 sujetos con SXF (27 chicas y 10 chicos) de edades comprendidas entre los 4 y los 19 años y lo compararon con un grupo control (GC) de 85 niños con desarrollo normotípico. Los resultados de su investigación se muestran en las tablas 3 y 4:

Tabla 3. Resumen del desarrollo cerebral en personas con SXF

Aspectos del desarrollo cerebral normotípicos en individuos con SXF	Aspectos del desarrollo cerebral atípicos en individuos con SXF
Constancia del volumen cerebral después de los 5 años.	Aumento en el volumen de la SG del núcleo caudado
Reducción de la SG relacionada con la edad y aumento complementario de la SB.	Incremento del volumen de los ventrículos laterales con la edad.
Diferencia de volumen cerebral en función del género (mayor volumen de SG en chicos).	Falta de predominancia del volumen de los ventrículos laterales izquierdos*

Nota. Información extraída de *Brain anatomy, gender and IQ in children and adolescents with fragile X síndrome* (p.1615-1616), por Eliez, 2001. Brain.
SG= Sustancia Gris. SB= Sustancia blanca *Signo de falta de especialización y menor eficiencia neuronal

Tabla 4. Resumen del efecto del género en el volumen cerebral en personas con SXF

Efecto del género en el volumen cerebral en SXF
Volumen cerebral total mayor en chicos vs chicas
Mayor volumen de la SG total y del núcleo caudado en chicos vs chicas
Mayor volumen de SB global en relación al volumen cerebral global

Nota. Información extraída de *Brain anatomy, gender and IQ in children and adolescents with fragile X síndrome* (p. 1615-1616), por Eliez, 2001. Brain.
SG= Sustancia Gris. SB= Sustancia blanca

Las alteraciones encontradas en el grupo con SXF fueron más pronunciadas en los varones.

1.5.2.Neuroimagen funcional.

La ansiedad social es uno de los rasgos clínicos característicos del SXF que suele manifestarse por un contacto ocular escaso y evitativo relacionado con una aversión a la mirada directa. Esta evitación del contacto ocular se ha relacionado con zonas cerebrales involucradas en la ansiedad social (Garret et al., 2004). Watson et al. (2008) encontraron diferencias de género en individuos con SXF, en comparación con sujetos sanos, en los paradigmas del contacto ocular: las mujeres mostraron una activación reducida de la ínsula y el giro fusiforme en respuesta a estímulos faciales, mientras que los hombres mostraron una activación aumentada de la amígdala y la ínsula.

Por otro lado, Holsen et al., (2008) encontraron una activación reducida en las regiones superiores y medial del giro frontal en tareas de memoria de caras, sugiriendo que una pobre cognición social podría impedir la codificación de la información facial.

En lo que refiere a las conexiones fronto-estriatales, que tienen un importante papel en los déficits de las funciones ejecutivas en individuos con SXF, varios estudios han encontrado patrones de activación diferentes en las personas con SXF. Kwon et al. (2001) y Menon et al. (2004) encontraron que los individuos con SXF mostraron un patrón de activación menor en el córtex frontal ante tareas de memoria de trabajo. Por su parte Rivera et al. (2002) y Klabunde et al. (2015) encontraron un patrón de activación aberrante del córtex frontal cuando realizaban operaciones matemáticas.

En regiones orbitofrontales se ha encontrado una reducción de la activación en tareas que implican atención y control de impulsos (Tamm et al., 2002). Se ha observado que mayores niveles de FMRP reflejan un patrón de activación frontoestriatal más normo-típico. Menon et al. (2004) hallaron un patrón de activación anormal del córtex prefrontal en chicas con SXF al realizar tareas de inhibición, encontrándose que la reducción de la activación estaba relacionada con los niveles de expresión de *FMR1.*

2. JUSTIFICACIÓN

2. Justificación.

El SXF es una condición genética ligada a la herencia del cromosoma X. En el caso de los varones, al contar tan solo con un cromosoma X, el hecho de ser portadores de la mutación completa del gen *FMR1* provoca una ausencia total de FMRP mientras que, en el caso de las mujeres, conlleva una disminución parcial de FMRP ya que el cromosoma con el gen *FMR1* sano será capaz de sintetizar cierta cantidad de FMRP. Todo esto implica que la clínica en varones suele expresarse de forma más grave que en las mujeres. Este hecho ha influido en que la gran mayoría de investigación científica se haya centrado en describir el fenotipo neurocognitivo de los varones afectos y que el número de investigaciones realizadas en mujeres sea significativamente inferior.

Por otro lado, la mayoría de estos estudios realizados en población femenina se centran en la edad adulta o cuentan con rangos de edades muy amplios (desde la edad escolar a la edad adulta) y se realizaron con pruebas que hoy en día han quedado desfasadas (Cronister et al., 1991; Grigsby et al., 1990; Hull et al., 1993; Thompson et al., 1994; Lachiewicz et al., 2006; Keysor et al., 2002; Simon et al., 2001). En los últimos años ha habido actualizaciones importantes en los tests de evaluación cognitiva y conductual, y en la actualidad contamos con instrumentos de medida que permiten describir perfiles mucho más amplios y específicos. Un ejemplo de estos avances sería la nueva versión de las escalas Wechsler para evaluar la capacidad intelectual: el WISC-V. En comparación con la versión anterior (WISC-IV), el WISC-V ofrece la posibilidad de analizar el perfil de habilidades que conforman la capacidad intelectual de forma mucho más detallada. En la nueva versión encontramos subtests e índices nuevos que aportan una información muy valiosa en el análisis del perfil neurocognitivo de la persona evaluada. Algunos de ellos se especifican en las tablas 5 y 6.

Tabla 5. Descripción de los nuevos subtest de la escala WISC-V.

SUBTEST	DESCRIPCIÓN
Balanzas	Mide la habilidad para hacer inducciones
Puzles visuales	Mide la capacidad de visoconstrucción no motora Interviene el razonamiento visoespacial y la rotación mental
Span de dibujos	Mide la capacidad de memoria de trabajo visual

Nota. La tabla resume la descripción de las habilidades medidas por los nuevos subtest del WISC-V. Tomado de *Escala de Inteligencia de Wechsler para Niños V*, por W. Wechsler, 2015, Pearson Educación.

Tabla 6. Descripción de los nuevos índices de la escala WISC-V.

ÍNDICE	DESCRIPCIÓN
Razonamiento visoespacial	• Mide la aptitud para evaluar los detalles visuales y entender las relaciones visoespaciales a fin de construir diseños geométricos a partir de un modelo. • Requiere razonamiento visoespacial, integración y síntesis de las relaciones parte-todo, atención a los detalles visuales, formación de conceptos no verbales e integración visomotora.
Memoria de trabajo auditiva	• Indicador de las destrezas de memoria de trabajo auditiva del niño
Índice no verbal	• Medida de la aptitud intelectual general que reduce al mínimo la intervención del lenguaje expresivo.
Índice de competencia cognitiva	• Ofrece una estimación de la eficacia con la que se procesa la información durante el aprendizaje, la resolución de problemas y el razonamiento de nivel superior. • Eficacia para procesar y manipular la información.

Nota. La tabla resume la descripción de las habilidades medidas por los nuevos Índices del WISC-V. Tomado de *Escala de Inteligencia de Wechsler para Niños V*, por W. Wechsler, 2015, Pearson Educación.

Por otro lado, a pesar de que existen diferentes investigaciones en las que se ha estudiado el perfil de ciertas funciones cognitivas en chicas con SXF (el lenguaje o la función ejecutiva), los aspectos conductuales y las habilidades de adaptación funcional de forma independiente, existe una falta de literatura científica patente que estudie la relación de las diferentes variables cognitivas con los problemas conductuales y emocionales así como con el nivel de adaptación funcional de estas pacientes.

Por último, teniendo en cuenta las características de las chicas con SXF descritas anteriormente (timidez extrema, ansiedad social, problemas de aprendizaje, etc.) sería de esperar que éstas se encontrasen ante un mayor riesgo de sufrir acoso escolar, pero en la revisión bibliográfica realizada para la presente tesis no se encontraron publicaciones al respecto.

3. OBJETIVOS E HIPÓTESIS

3. Objetivos e hipótesis de la investigación.

El objetivo principal de la presente tesis es el de describir el perfil neurocognitivo en niñas y adolescentes con el diagnóstico de SXF y su relación con los problemas de conducta, los síntomas emocionales y las habilidades de adaptación funcional.

Objetivos específicos:

1. Definir la asociación entre la capacidad intelectual global y el nivel de adaptación funcional en su día a día.
2. Analizar la relación entre la percepción social y el nivel de adaptación funcional.
3. Valorar la relación entre las funciones lingüísticas y el resto de funciones cognitivas, el nivel de adaptación funcional, los problemas de conducta y los síntomas emocionales.
4. Valorar la relación entre las funciones ejecutivas y el resto de funciones cognitivas, el nivel de adaptación funcional, los problemas de conducta y los síntomas emocionales.
5. Estudiar el riesgo de sufrir acoso escolar y su relación con el nivel de adaptación funcional, los problemas de conducta y los síntomas emocionales.

En relación a los objetivos anteriormente especificados se plantearon las siguientes hipótesis:

1. Hipótesis sobre el cociente intelectual total (CIT), la percepción social y la ansiedad social:
    a. Se hallará una relación positiva entre el desempeño en la prueba de CIT y la conducta adaptativa. Esta relación se manifestará de diferente forma dependiendo de la presencia del diagnóstico de SXF.
    b. Un mejor desempeño en tareas de reconocimiento de emociones y teoría de la mente implicará un mejor desempeño en ciertas áreas de la conducta adaptativa, estilo de socialización y estado emocional. Esta relación se manifestará de diferente forma dependiendo de la presencia del diagnóstico de SXF.
    c. En comparación con el grupo de control, las niñas con SXF presentarán niveles más altos de ansiedad social.

2. Hipótesis sobre las funciones lingüísticas:
    a. Un mejor desempeño en algunas tareas de las funciones lingüísticas implicará un mejor desempeño en determinadas tareas de las funciones ejecutivas y el razonamiento cuantitativo. Esta relación se producirá de forma diferente dependiendo de la presencia del diagnóstico de SXF.
    b. Un mejor desempeño en algunas tareas de las funciones lingüísticas implicará un mejor desempeño en algunas tareas de percepción social y habilidades sociales. Esta relación se producirá de forma diferente dependiendo de la presencia del diagnóstico de SXF.
    c. Un mejor desempeño en algunas tareas de las funciones lingüísticas implicará mejores puntuaciones en algunas subáreas del comportamiento adaptativo. Esta relación se producirá de forma diferente dependiendo de la presencia del diagnóstico de SXF.

3. Hipótesis sobre las funciones ejecutivas (FE):
    a. Un mejor desempeño en algunas tareas de FE implicará un mejor desempeño en ciertas tareas de razonamiento lingüístico y cuantitativo. Esta relación ocurrirá de manera diferente dependiendo de la presencia del diagnóstico de SXF.
    b. Un mejor desempeño en algunas tareas de FE implicará un mejor desempeño en ciertas tareas de percepción social o habilidades sociales. Esta relación ocurrirá de una manera diferente dependiendo de la presencia del diagnóstico de SXF.
    c. Un mejor desempeño en algunas tareas de FE implicará mejores puntajes en algunos aspectos del comportamiento adaptativo. Esta relación ocurrirá de una forma diferente dependiendo de la presencia del diagnóstico de SXF.
4. Hipótesis sobre el riesgo de sufrir acoso escolar:
    a. En la muestra analizada, al menos el 50% de las niñas con diagnóstico de SXF habrán sufrido algún tipo de acoso escolar en el papel de víctima.
    b. Habrá una asociación entre sufrir acoso escolar en el papel de víctima y su conducta adaptativa, estilo de socialización y estado emocional. Estas asociaciones serán diferentes dependiendo de la presencia o no del diagnóstico de SXF.

4. MATERIAL Y MÉTODO

4.MATERIAL Y MÉTODO:

4.1. Participantes:

La muestra total está compuesta por un total de 40 niñas y adolescentes con edades comprendidas entre los 7 y los 16 años. De la muestra total 26 chicas tenían un diagnóstico de SXF confirmado mediante prueba genética y el resto de participantes constituyeron el grupo control (n=14). Se comprobó mediante análisis estadístico que ambos grupos fueran equivalentes en las siguientes variables: CIT, edad, síntomas TDAH y nivel socioeconómico.

A continuación, se describen los criterios de inclusión y exclusión de ambos grupos:

- **Criterios de inclusión:**
    - Grupo SXF: sexo femenino, edad entre 7 y 16 años, confirmación medinate estudio genético del diagnóstico de SXF (> 200 repeticiones; mutación completa).
    - Grupo control: sexo femenino, edad entre 7 y 16 años.
- **Criterios de exclusión:**
    - Grupo SXF: presentar TEA o TDAH comórbidos, ausencia de lenguaje expresivo y trastornos neurológicos adquiridos (epilepsia, traumatismo craneoencefálico).
    - Grupo control: cumplir con los criterios de diagnóstico para el diagnóstico de TEA o TDAH, ausencia de lenguaje expresivo; trastornos neurológicos adquiridos (epilepsia, lesión cerebral traumática) y otros trastornos cognitivo-conductuales genéticamente basados.
    - Todas las chicas del grupo control con DI contaban con un análisis genético que descartaba la presencia del SXF, en el caso de las chicas sin DI no se realizó el estudio genético por motivos éticos. Aun así, se

hizo una evaluación clínica de las participantes sin DI para valorar si presentaban síntomas compatibles con el SXF (rasgos físicos, características cognitivo-conductuales) y se recabaron los antecedentes familiares preguntando de forma específica por la existencia de algún familiar con SXF.

En ambos grupos se incluyeron participantes con rasgos de TDAH y TEA propios del SXF, pero fueron excluidas aquellas que cumplían con todos los criterios diagnósticos de TDAH y TEA según el Manual Diagnóstico y Estadístico de los Trastornos Mentales-5 (DSM-5).

4.2. Diseño y fases del estudio:

La presente investigación se ha realizado con un diseño ex post facto transversal analítico. Se llevó a cabo en el Hospital Parc Taulí de Sabadell que forma parte de la Red de Unidades de Experiencia Clínica en enfermedades minoritarias en Cataluña (Barcelona, España) y contó con la aprobación del Comité de Ética de dicho hospital (referencia 2016595).

Para el reclutamiento de las participantes se solicitó la colaboración a las familias de las pacientes diagnosticadas de SXF atendidas en el propio hospital. Así mismo, se contó con la colaboración de la Federación Española de SXF, diferentes asociaciones de pacientes SXF (Cataluña, País Vasco, Madrid, Valencia) y de pacientes con enfermedades genéticas (D'Genes Murcia). Así mismo se hizo un llamamiento mediante redes sociales profesionales como Linked-In y correo electrónico a los equipos de asesoramiento psicopedagógico de la zona y a los colegios de educación especial.

Las sesiones de exploración de las participantes del área metropolitana de Barcelona se llevaron a cabo en el Hospital Parc Taulí. En el caso de las participantes de otras comunidades autónomas la doctoranda se desplazó a la Comunidad Autónoma correspondiente para realizar las evaluaciones con el objetivo de crear la menor molestia posible tanto a las familias como a las participantes. En primer lugar, se hizo llegar una carta explicativa del proyecto a las asociaciones de pacientes y éstas fueron las encargadas de su difusión. En los casos en los que hubo familias interesadas en participar se organizaron, juntamente con la asociación, unos días en los que la doctoranda se desplazó a la Comunidad Autónoma pertinente para realizar las evaluaciones en las instalaciones proporcionadas por las asociaciones. Las comunidades que finalmente participaron fueron: Cataluña, Madrid, País Vasco, Galicia, Valencia y Murcia. Se obtuvo un consentimiento informado de los tutores legales de todas las participantes.

4.3. Medidas y escalas:

Las evaluaciones se realizaron en 3 sesiones a razón de una hora cada una, para evitar el efecto del cansancio sobre las participantes. El protocolo de evaluación se compuso de un amplio número de tests y cuestionarios:

- Pruebas para valorar el rendimiento cognitivo:
    - WISC-V. Escala de Inteligencia Wechsler para niños-V (Wechsler, 2015).
    - Test de denominación de Boston *(*Kaplan et al., 2005).
    - Peabody. Test de Vocabulario en Imágenes (Lloyd et al., 2006).
    - Test de Clasificación de Tarjetas de Wisconsin (Robert k. et al., 2009).
    - Batería Neuropsicológica Infantil (NEPSY-II): subtests de comprensión de instrucciones, fluidez verbal semántica y fonética, conciencia fonológica, atención auditiva, flexibilidad cognitiva, inhibición,

reconocimiento de emociones, teoría de la mente (Korman et al., 2014).
  - Torre de Londres (Culbertson et al., 2005).

- Cuestionarios y escalas de conducta (versión para padres):
  - Cuestionario de Conducta SENA (Fernández-Pinto et al., 2015).
  - ADHD Rating Scale (DuPaul et al., 1998).
  - BAS-2. Batería de Socialización (Silva et al., 2018).
  - BRIEF-2. Evaluación conductual de la función ejecutiva-2 (Gioia et al., 2017).
  - ABAS-II. Sistema de Evaluación de la Conducta Adaptativa-II (Harrison et al., 2013).

Las puntuaciones directas de todas las pruebas de funcionamiento cognitivo fueron transformadas a puntuaciones estándar con media 100 y desviación típica de 15.

En la tabla 7 se resumen la relación entre la prueba administrada y la variable evaluada.

Tabla 7. Relación entre las escalas de medida y las variables evaluadas.

PRUEBA/TEST	VARIABLE
WISC-V: Semejanzas Matrices Vocabulario Span de Dibujos Dígitos Letras y Número Balanzas Aritmética	Capacidad intelectual total Capacidad de abstracción verbal Capacidad de abstracción visual Vocabulario expresivo Memoria de trabajo visual Memoria de trabajo auditiva Memoria de trabajo auditiva Razonamiento inductivo Razonamiento cuantitativo
Test de denominación de Boston	Denominación
Peabody. Test de Vocabulario en Imágenes	Vocabulario comprensivo
Test de Clasificación de Tarjetas de Wisconsin	Flexibilidad cognitiva
NEPSY-II: Comprensión de Instrucciones Fluidez Procesamiento fonológico Atención Auditiva Flexibilidad Cognitiva Inhibición Reconocimiento de Emociones Teoría de la Mente	Comprensión de instrucciones Fluidez verbal semántica y fonética Conciencia fonológica Atención auditiva Flexibilidad cognitiva Inhibición Reconocimiento de emociones Teoría de la mente
Torre de Londres	Planificación Solución de problemas
Cuestionario SENA	Screening conductual y emocional
ADHD Rating Scale de DuPaul	Síntomas TDAH
Batería de Socialización. BAS-2	Perfil de habilidades sociales Perfil relacional
Evaluación Conductual de la Función Ejecutiva- 2 (BRIEF-2)	Medida ecológica de la función ejecutiva
Sistema de Evaluación de la Conducta Adaptativa-II (ABAS-II)	Conducta adaptativa global Adaptación conceptual Adaptación social Adaptación práctica

4.4. Análisis estadístico:

El análisis estadístico se realizó con el software SPSS Statistics for Windows, versión 25.0. Se descartó una posible distribución diferencial de las variables de control, la edad, CIT, síntomas TDAH y nivel socioeconómico, entre los grupos de control y el grupo SXF, utilizando la prueba t- de Student. La comparación de variables relacionadas con las habilidades cognitivas y el comportamiento entre el grupo de control y el grupo SXF se llevó a cabo utilizando la prueba U de Mann-Whitney debido a una distribución no normal de los datos. Se descartaron comparaciones entre variables cualitativas utilizando la prueba de Chi Cuadrado. La asociación entre las variables de funcionamiento cognitivo y conductual se examinó mediante regresión lineal, controlando el efecto de grupo. Si éste no era significativo, se eliminó del modelo.

Para las variables binarias, se construyeron las correspondientes tablas de contingencia para evaluar el riesgo de sufrir acoso escolar en el grupo FXS en comparación con el grupo de control, y se calculó la Odds Ratio (OR) con sus intervalos de confianza al 95%. Para las variables cuantitativas, el efecto de presentar SXF sobre el estado emocional, la conducta adaptativa y el estilo de socialización se investigaron mediante regresión lineal. modelos que incluían un período de interacción entre el grupo y la presencia de acoso escolar.

5. RESULTADOS

5.1. Artículo 1. “Pilot Study of Socio-emotional factors and Adaptive Behavior in young females with Fragile X Syndrome”.

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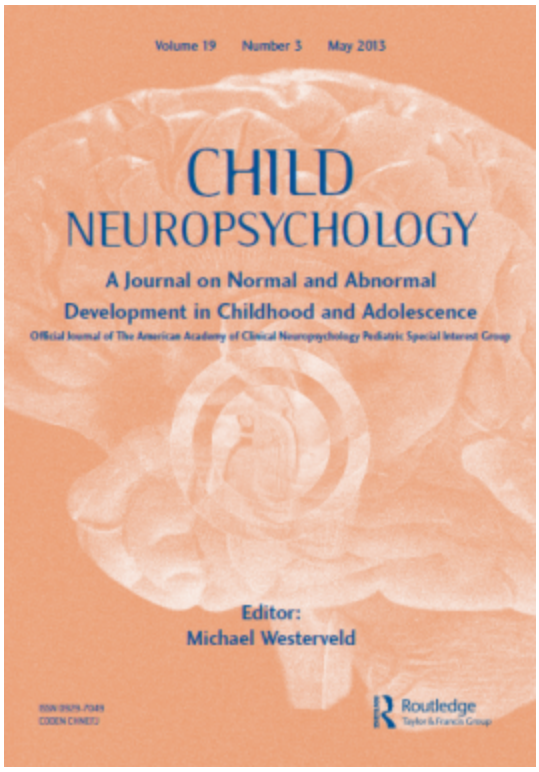

Pilot Study of Socio-emotional factors and Adaptive Behavior in young females with Fragile X Syndrome

Journal:	*Child Neuropsychology*
Manuscript ID	CNY-OA 20-136.R2
Manuscript Type:	Original Article
Keywords:	Social anxiety, Adaptive behavior, Fragile X syndrome, Young females, Emotion recognition, Theory of mind

Pilot Study of Socio-emotional factors and Adaptive Behavior in young females with Fragile X Syndrome.

Abstract: Girls with Fragile-X-Syndrome (FXS) present high levels of social anxiety, social avoidance, extreme shyness, tendency to social isolation, poor eye contact, learning difficulties, and depression. The aims of the present study, which is based on a group of young females with FXS are: 1) to analyze the possible associations between emotion recognition, theory of mind, and social anxiety, and adaptive behavior, and emotional state; 2) to study the relationship between intelligence quotient (IQ) and adaptive behavior; and 3) to assess whether social anxiety is more prevalent in girls with FXS. The study has 40 female participants aged between 7 and 16 years (26 positive full mutation FXS and 14 as a control group). A neuropsychological assessment was conducted using the following tests: WISC-V, NEPSY-II, SENA, ADHD Rating Scale, BAS, and ABAS-II. In comparison with the control group, the group with FXS presented a greater association between IQ and self-direction ability, and between emotion recognition and leadership. The FXS group presented higher levels of social anxiety and shyness. In the group of girls with FXS, IQ may have prognostic value for both self-direction ability and social adaptation level.

Keywords: Social anxiety; Adaptive behavior; Emotion recognition; Theory of mind; Fragile X syndrome; Young females

1. Introduction

Fragile X Syndrome (FXS) caused by an alteration in the "fragile X mental retardation 1" (FMR1) gene [1,2], is the leading cause of hereditary intellectual disability. This alteration causes an expansion of the CGG trinucleotide repeats and generates a deficiency or absence of a protein called "fragile X mental retardation 1 protein" (FMRP). FMRP is an RNA-binding protein which plays an important role in the regulation of many $msRNA_s$ in postsynaptic neurons [3,4,5]. Epidemiological studies report an estimated frequency of FXS of 1.4: 10,000 men and 0.9: 10,000 women [6] with a prevalence of 1 in 2,500 to 7,000 men and 1 in 2,500 to 11,000 women [7].

In the previous scientific literature, we find that most research has focused on describing this phenotype in males, and that few authors have studied in females. Men with FXS full mutation have severe to moderate intellectual disability (IQ <55). Within their cognitive profile, short-term memory, working memory, spatial memory, auditory sequential processing, abstract thinking, executive function, and mathematical reasoning stand out as weaknesses. In contrast, receptive vocabulary, visual memory, simultaneous processing, experiential learning, and the capacity for imitation stand out as strengths [8]. Meanwhile, girls with FXS full mutation present a pattern of strengths and weaknesses like boys, but with a less severe degree of affectation [9]. Both men and women show a delay in communication (especially in pragmatics), socialization and basic skills for daily life [10, 11].

It has been described that approximately 50% of women with FXS have intellectual disability (ID) of variable severity (from mild to moderate) and the other 50% an intelligence quotient (IQ) within the average [9]. Other authors conclude that girls with FXS present high levels of social anxiety, social avoidance, extreme shyness, tendency to social isolation, poor eye contact, features of an autism spectrum disorder (ASD) (deficits

in social interaction and communication, stereotypes), learning difficulties, and depression [7, 12].

A 2004 review of girls with FXS describes warning signs in early childhood to include delays in language development, problems with emotion management and behavior disorders. Later, at school age, learning disabilities (especially in mathematics), difficulties in abstract reasoning, executive functions, visuospatial reasoning, and interpreting social situations have been described. These manifestations can concur with traits of an ASD, attention deficit, hyperactivity and impulsivity, anxiety, extreme shyness, and avoidance behaviors [13]. During school age and adolescence, verbal skills and face recognition stand out as strengths of girls with FXS. Their weaknesses are processing abstract visuospatial stimuli, executive function, theory of mind, abstract reasoning, and arithmetic. Weaknesses on a socio-emotional level that, stand out are attention deficit hyperactivity disorder traits in a third of the girls with full mutation (especially attention deficit and impulsivity); ASD traits (difficulties with communication, deficits in social interaction, stereotypes); anxiety in 23-50% of cases (extreme shyness and discomfort in social interactions, social avoidance), and depressive symptomatology in 38% of cases [9].

Regarding adaptive behavior, we found a study by Glaser et al. [13] which investigates how both biological and environmental influences affect the development of adaptive behavior in children with FXS (80 boys and 40 girls) and their unaffected siblings (58 boys and 62 girls). They found that adaptive behavior was predicted by IQ, age, gender, and home environment for both boys with FXS and their unaffected siblings (58 boys and 62 girls). For girls with fragile X, adaptive behavior was most strongly associated with IQ. Adaptive behavior was not significantly associated with FMRP in boys or girls with fragile X [13]. A study carried out by Hatton et al. [14] based a group

of 70 children with FXS (ages 1 to 12 years) showed how adaptive skills increased steadily and gradually over time, and how the children with less autistic behavior and higher percentages of FMPR expression showed better performance in all areas of adaptive behavior. Children without autistic behavior displayed higher scores and rates of growth in the Daily Living Skills domain, with the lowest scores in Socialization. Comparison to Brief IQs indicate that children with fragile X syndrome display nonverbal IQs superior to their adaptive behavior when they are below age 10 but that these skills seem to converge as they get older [14].

Given that girls with FXS have been described to present traits of an ASD, the present investigation aimed to study the relationship between emotion recognition, theory of mind and social anxiety, and adaptive behavior, socialization style, and emotional state. Furthermore, in our daily clinical experience we find that the intellectual quotient (IQ) of our patients, assessed through standardized tests, often does not reflect the degree of autonomy they achieve in their daily lives. Thus, the second objective was to study the relationship between IQ and adaptive behavior. Last, we set out to assess whether social anxiety is more prevalent in girls with FXS through a comparison with a group of girls without an FXS diagnosis, both groups matched for age and IQ.

Hypotheses:

- A better performance in emotion recognition and theory of mind tasks implies a better performance in certain domains of adaptive behavior, socialization style, and emotional status. This relationship will be stronger in the group of girls with FXS.

- There will be a positive relationship between performance on the IQ test and their adaptive behavior. This relationship will be stronger in the group of girls with FXS.

- Compared to the control group, girls with FXS will present higher levels of social anxiety.

2. Materials and Methods

2.1. Method:

The present research was carried out at Sabadell's Parc Taulí Hospital, which belongs to the Clinical Experience Units Network for minority diseases (Barcelona, Spain) and is also a member of the Fragile X Syndrome Clinical Research Consortium. It follows on from a previous study that assessed the relationship between linguistic functions and executive function using other cognitive and behavioral variables (social perception, quantitative reasoning, and adaptive behavior). It was approved by the Ethics Committee of the same hospital (reference 2016595).

The Spanish FXS Federation and different associations of patients with FXS (Catalonia, the Basque Country and Valencia) or other genetic diseases (D'Genes Murcia) took part in disseminating the project through professional social networks such as LinkedIn and by emailing psychopedagogy professionals and special education colleges in the area. Informed consent was obtained from the participants' legal guardians and participants gave their verbal consent.

The assessment sessions consisted of the administration of an extensive battery of tests to assess the following variables: IQ, emotion recognition, theory of mind, adaptive behavior, and cognitive profile (language, executive function, quantitative reasoning, visuospatial reasoning, and fluent reasoning). They were carried out in three 1-hour sessions to prevent the effect of fatigue on the participants.

2.2. Participants:

The participants were part of a larger study which assessed the relationship between different cognitive and behavioral variables. They were 40 females (n = 40) aged between 7 and 16 years, divided into 2 groups:

1) FXS group: *n* = 26. The participants were recruited through the UEC of the Parc Taulí Hospital and the different patient associations.

2) CG: *n* = 14. The participants were recruited via the control visits of the Neuropediatrics Unit of the Hospital Parc Taulí de Sabadell and in the schools of the area (both ordinary education and special education).

Inclusion criteria:

- FXS group: female sex, age between 7 and 16 years, confirmation by genetic study of the diagnosis of FXS (> 200 repetitions; full mutation). The identification of full mutation status was made by PCR.
- CG: female sex, age between 7 and 16 years. All participants with ID have a genetic study that ruled out the diagnosis of FXS.

Exclusion criteria:

- FXS group: present an ASD or comorbid Attention Deficit Hyperactivity Disorder (ADHD), absence of expressive language, acquired neurological disorders (epilepsy, head trauma).
- CG: meet all diagnostic criteria for ASD, ADHD, absence of expressive language; acquired neurological disorders (epilepsy, traumatic brain injury) and other genetically based cognitive-behavioral disorders. In the case of the participants without ID, the genetic study was not carried out for ethical reasons, but in the initial

interview they were explicitly asked about a family history of FXS and the presence of symptoms compatible with the diagnosis of FXS.

- Given that one of the objectives of the research was to study the relationship between emotion recognition and theory of mind with adaptive behavior and emotional state in both groups, those who met all DSM-5 criteria for the diagnosis of an ASD (participants with a comorbid ASD) were excluded from the sample. Those who only showed some traits of an ASD that are features of the FXS diagnosis were not excluded. The assessment was performed by an expert in pediatric neurology, psychology, or psychiatry.

2.3.Variables:

For the first aim of the study, the independent variable were emotion recognition and theory of mind and the dependent variables were adaptive behavior (conceptual, social, practice, and global), emotional status (depression, anxiety, social anxiety), and socialization style (leadership, joviality, social sensitivity, self-control, aggression, apathy-withdrawal, anxiety, and shyness). Regarding the second objective, the independent variable was IQ, and the dependent variable was adaptive behavior.

The measures and scales used for the assessment of each variable are specified in the following section.

2.4. Measures and scales:

- *Wechsler Intelligence Scale for Children-Fifth Edition (WISC-V). Spanish Version:* measure to assess Intelligence Quotient, Verbal Comprehension, Fluent Reasoning,

Visuospatial Reasoning, Working Memory, Processing Speed, and Quantitative Reasoning ($\bar{x}$ = 100 ±15) [15].

- *Neuropsychological Battery for Children (NEPSY-II):* measure to assess emotion recognition and theory of mind (Subtest: emotion recognition and theory of mind); ($\bar{x}$ = 100 ±15) [16].

- *Child and Adolescent Evaluation System (SENA):* parent version. Evaluation of a wide spectrum of emotional and behavioral problems (depression, anxiety, hyperactivity and impulsivity, challenging behavior, substance use, eating problems, learning problems, etc.), contextual problems (problems with the family, with school, and with peers), areas of vulnerability (problems of emotional regulation, isolation, rigidity, etc.), and psychological resources (self-esteem, integration and social competence, and emotional intelligence, etc.) ($\bar{x}$ = 50 ±10) [17].

- *ADHD Rating Scale DuPaul*: parent version. Assessment of the presence of ADHD symptoms (percentile scores) [18].

- *BAS-2. Battery of socialization:* parent version. Estimation scales in four facilitating dimensions of socialization (Leadership, Joviality, Social sensitivity, and Respect-self-control), three of its disturbing dimensions (Aggression-stubbornness, Apathy-withdrawal and Anxiety-shyness), and a global scale of social adaptation or Criterial -socialization (percentile scores) [19].

- *Adaptative Behavior Assessment System-Second Edition (ABAS-II) Spanish version:* parents' version. A measure to assess adaptive behavior in the conceptual domain (communication, functional, and self-directed academic skills), the social domain (recreation and social), the practical domain (self-care, home life, use of community resources, and health and safety), and the global domain ($\bar{x}$ = 100 ±15) [20].

- The *Hollingshead scale* was used to collect and measure information about socioeconomic status [21].

The direct scores of all the cognitive functioning tests were transformed to standard scores with mean 100 and standard deviation of 15.

2.5. Statistical analysis:

There were no outliers excluded from the study.

A possible different distribution of the control variables (age and IQ) between the control and the FXS groups was ruled out using the Student's t-test for comparison of means. The comparison of the variables related to cognitive and linguistic abilities and those related to behavior between the control group and the FXS group was carried out using the Mann-Whitney U test. The association between the variables of cognitive and behavioral functioning was examined using linear regression, controlling for the group effect. If this was not significant, it was removed from the model.

3. Results

Once the comparison of means was performed using the Student's *t*-test, no statistically significant differences were found between the variables age, IQ, socioeconomic status, and ADHD symptoms (Table 1). The Cronbach's Alfa values are summarized in Table 2.

INSERT TABLE 1 AND 2 AROUND HERE.

In the domain of social emotion recognition, theory of mind and social anxiety, only some relationships at the limit of statistical significance were found between groups in the emotion recognition. In comparison with the CG, the FXS group presented a greater association between the ability of emotion recognition and leadership. In this same sense, a relationship at the limit of statistical significance was found between emotion recognition and joviality, and between emotion recognition and social adaptation. No statistically significant differences were found between the two groups when analyzing the influence of social anxiety on adaptive behavior, and emotional state (Table 3). The lack of statistically significant relationships could be due to the small sample size.

INSERT TABLE 3 AROUND HERE

Regarding IQ and adaptive behavior, when analyzing the results of the two groups together, a relationship was found between IQ and communication, academic skills, social adaptation, leisure, use of community resources, capacity for self-direction, health and safety, conceptual adaptation, and level of global adaptation. Among all these variables, only statistically significant differences between groups were found in self-direction ability. Compared with the CG, the group of girls with FXS presented a greater association between IQ and self-direction ability. In this same sense, a relationship was found at the limit of statistical significance between IQ and the social adaptation domain (Table 4).

INSERT TABLE 4 AROUND HERE

When analyzing the variables used to assess social anxiety, some statistically significant differences between groups were found. The group of girls with FXS presented significantly higher levels of social anxiety ($p = 0.015$). Likewise, it was found that girls with FXS presented higher levels of anxiety and shyness with a value at the limit of statistical significance ($p = 0.067$) (Figures 1 and 2). Where values were found at the limit of statistical significance, this could be due to the lack of power of the test used resulting from the small size of the sample.

INSERT FIGURE 1 AND 2 AROUND HERE

4. Discussion

The aims of the present study were to analyze the possible relationships between emotion recognition, theory of mind and social anxiety, and adaptive behavior, cognitive functions, socialization style, and emotional state; to study the relationship between intelligence quotient and adaptive behavior; and to assess whether social anxiety is more prevalent in girls with FXS.

The first aim was to analyze the possible association between emotion recognition, theory of mind and social anxiety, and adaptive behavior, socialization style, and emotional state. Regarding emotion recognition, we found differences between the two groups, with the group of girls with FXS showing a greater relationship between emotion recognition and leadership ability, level of joviality, and social adaptation. A better ability to recognize emotions in others is essential to be able to know how they feel, and to be able to act accordingly and adapt our behavior to their needs. A person who possesses these skills is more likely to be perceived as a leader and consequently to have a better social adaptation and a higher level of joviality. These results are in line with Hatton's

research, which found that participants with fewer ASD traits performed better in all areas of adaptive behavior [14].

Regarding IQ and adaptive behavior, we found that when studying the total sample, IQ has a positive relationship with communication skills, academic skills, leisure, use of community resources, self-direction, health and safety, social life, conceptual adaptation, and global adaptation. When analyzing the differences between the CG and the group of girls with FXS, we found that the group of girls with FXS showed the greatest association between IQ and some of the skills of adaptive behavior, such as the abilities of self-direction and social adaptation. These results are consistent with the findings of Glaser et al., according to which IQ is strongly associated with adaptive behavior in girls with FXS [13]. To this effect, we observed that in the group of girls with FXS, a higher IQ is more closely related to better self-direction and a better level of social adaptation. According to the American Psychological Association, intelligence refers to the ability to understand information, to adapt to the environment, and to learn from experience. In this regard, it is logical to find that the better the IQ of the participants, the better their level of functional adaptation. The fact that in the group of girls with FXS there is a stronger relationship between IQ and self-direction ability and social adaptation than in the CG could be of prognostic value for these two areas of adaptive behavior.

The last objective was to assess whether social anxiety is more prevalent in girls with FXS than in girls in the CG. Our findings show that the group of girls with FXS presented a higher level of social anxiety and shyness than the control group, as described in the literature. Given that social anxiety and shyness are a widely described characteristic feature of girls with FXS [7,12], both should be considered as one of the main objectives when designing a therapeutic program for girls with FXS.

STRENGTHS AND LIMITATIONS:

One of the limitations of this study is the relatively small sample size. Even though only 26 girls with FXS were able to participate, it is still the largest sample of the female population of child and adolescent age collected to date in Spain and one of the largest worldwide. Over a period of 4 years, the person responsible for conducting the evaluations travelled to different parts of Spain to be able to incorporate as many participants as possible. Another limitation was the great difficulty we encountered in getting a larger number of girls for the CG. Despite this, there are no significant differences between the groups in the control variables of age, IQ, socio economic status, and ADHD symptoms.

Given that one of the objectives of the research was to study the relationship between emotion recognition and theory of mind with adaptive behavior and emotional state in both groups, those who met all DSM-5 criteria for the diagnosis of an ASD (participants with a comorbid ASD) were excluded from the sample. Rejecting those participants with comorbid ASD implies that the results of the present investigation can only be applied to the subgroup of females with FXS who do not have a comorbid diagnosis of ASD, but to those with some features of ASD.

Furthermore, while all the CG girls with ID had a genetic analysis that ruled out FXS, in the case of the girls without ID the genetic study was not carried out for ethical reasons. However, a clinical evaluation of the participants was carried out to assess whether they had symptoms compatible with FXS (physical features, cognitive-behavioral characteristics), and family history was also collected, specifically asking about the existence of a family member with FXS. Last, for future research it would be interesting

to study whether the relationship found between IQ and adaptive behavior in the group of FXS girls remains constant or varies throughout their life cycles.

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Table 1. Descriptive measures and distribution of age, IQ, ADHD Symptoms, and socioeconomic status.

Variables	FXS Group *n* = 26	Control Group *n* = 14	Significance
Age			
M (SD)	10.58 (3.384)	10.50 (2.345)	0.940
IQ			
M (SD)	71.50 (14.795)	76.36 (16.80)	0.351
ADHD symptoms			
M (SD)	81.54 (4.341)	68.29 (6.984)	0.104
Socioeconomic status			
Low	3.8%	16.7%	0.211
Medium	88.5%	75%	
High	7.7%	8.3%	

FXS = Fragile X Syndrome. IQ = Intelligence Quotient. ADHD = Attention Deficit Hyperactivity Disorder. M=mean. SD = Standard Deviation. M= Mean.

Table 2. Adaptive Behavior Assessment System- Second Edition (ABAS-II) Cronbach's Alfa.

	Cronbach's Alfa	
	Control Group	**Fragile X Syndrome**
Social adaptation	0.778	0.691
Conceptual Adaptation	0.755	0.832
Practical Adaptation	0.842	0.903

Table 3. Results of linear regression of cognitive profile, emotional state, and adaptive behavior (dependent variables) vs group and emotion recognition (independent variables).

	Emotion Recognition	Group	adjusted R^2
Joviality	$p = 0.051$ $\beta = 0.364$	$p = 0.064$ $\beta = -12.421$	$r^2 = 0.160$
Leadership	$p = 0.012$ $\beta = 0.305$	$p = 0.059$ $\beta = -8.059$	$r^2 = 0.223$
Conceptual adaptation	$p = 0.001$ $\beta = 0.447$	$p = 0.268$ $\beta = -5.231$	$r^2 = 0.255$
Social adaptation	$p = 0.002$ $\beta = 0.431$	$p = 0.065$ $\beta = -9.004$	$r^2 = 0.283$
Practical adaptation	$p = 0.044$ $\beta = 0.355$	$p = 0.752$ $\beta = -1.946$	$r^2 = 0.07$
Global adaptation	$p = 0.005$ $\beta = 0.426$	$p = 0.301$ $\beta = -5.374$	$r^2 = 0.199$

Table 4. Results of linear regression of adaptive behavior (dependent variable) vs group and Intelligence Quotient (independent variables).

	Intelligence quotient	Group	adjusted R^2
Communication	$p = 0.011$ $\beta = 0.546$	$p = 0.750$ $\beta = -2.115$	$r^2 = 0.130$
Academic skills	$p < 0.001$ $\beta = 0.708$	$p = 0.599$ $\beta = -2.648$	$r^2 = 0.351$
Leisure	$p = 0.019$ $\beta = 0.405$	$p = 0.237$ $\beta = -6.368$	$r^2 = 0.150$
Social	$p = 0.233$ $\beta = 0.258$	$p = 0.071$ $\beta = -12.740$	$r^2 = 0.091$
Use of community resources	$p = 0.010$ $\beta = 0.515$	$p = 0.563$ $\beta = -3.570$	$r^2 = 0.145$
Home life	$p = 0.737$ $\beta = 0.059$	$p = 0.929$ $\beta = 0.506$	$r^2 = -0.052$
Self-direction	$p = 0.037$ $\beta = 0.401$	$p = 0.037$ $\beta = 12.905$	$r^2 = 0.195$
Health and security	$p = 0.028$ $\beta = 0.455$	$p = 0.425$ $\beta = -5.182$	$r^2 = 0.109$
Conceptual adaptation	$p = 0.001$ $\beta = 0.536$	$p = 0.229$ $\beta = -5.598$	$r^2 = 0.292$
Social adaptation	$p = 0.044$ $\beta = 0.327$	$p = 0,079$ $\beta = -9.093$	$r^2 = 0.157$
Practical adaptation	$p = 0.093$ $\beta = 0.332$	$p = 0.639$ $\beta = -2.938$	$r^2 = 0.039$
Global adaptation	$p = 0.013$ $\beta = 0.421$	$p = 0.261$ $\beta = -5.954$	$r^2 = 0.161$

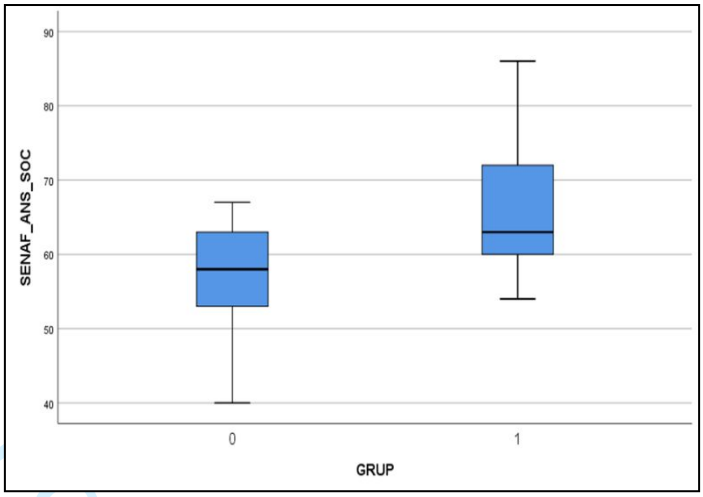


Figure 1. Presence of social anxiety according to group. Group 0 = Control Group. Group 1 = Fragile X Syndrome. SENAF_ANS_SOC=social anxiety (Child and Adolescent Evaluation System. SENA).

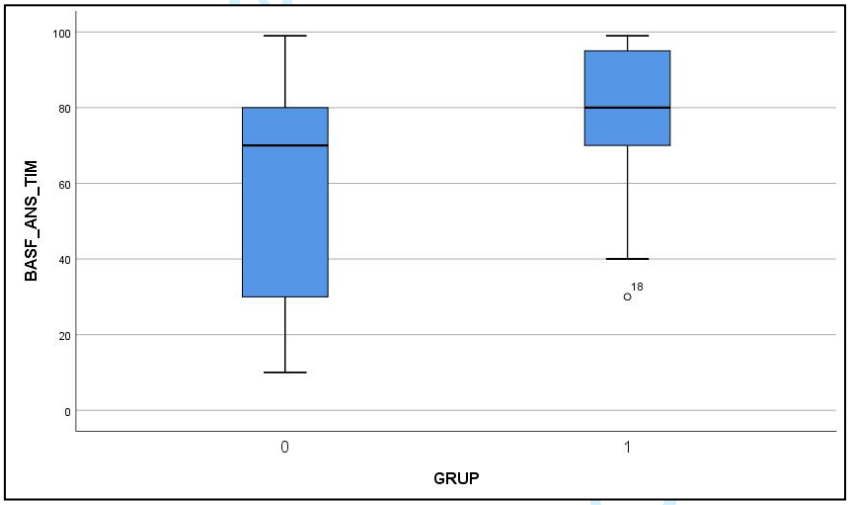
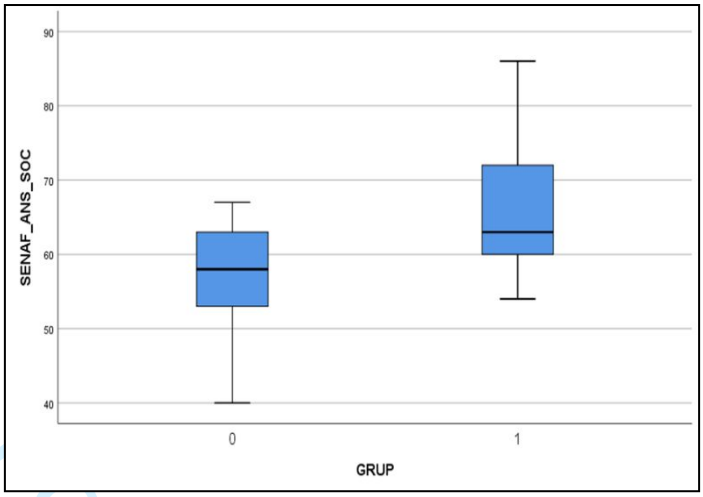


Figure 2. Presence of anxiety and shyness according to the group. Group 0 = Control Group. Group 1 = Fragile X Syndrome. BASF_ANS_TIM=anxiety and shyness (BAS-2. Battery of socialization).



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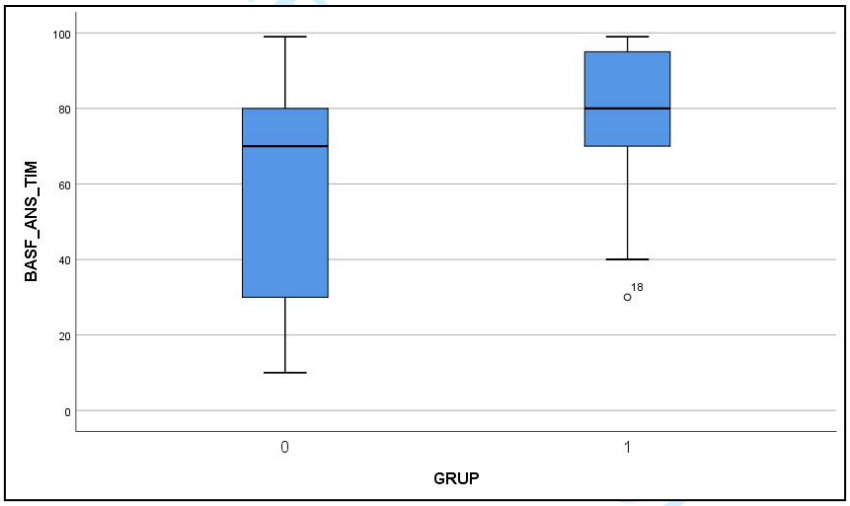

Figure 2. Presence of anxiety and shyness according to the group. Group 0 = Control Group. Group 1 =Fragile X Syndrome. BASF_ANS_TIM=anxiety and shyness(BAS-2. Battery of socialization).

5.2. Artículo 2. “Language in young females with Fragile-X-Syndrome: Influence on the Neurocognitive Profile and Adaptive Behavior”.

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Language in young females with fragile X syndrome: Influence on the neurocognitive profile and adaptive behavior

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Abstract

Fragile X syndrome (FXS) is the leading cause of inherited intellectual disability. The objective of this research is to analyze the relationship between linguistic functions and performance of the following neuropsychological functions: executive, quantitative reasoning, social perception, behavior, social skills, and adaptive behavior. A neuropsychological and behavioral evaluations were carried out with a group of 26 girls with FXS, and 14 girls without FXS as a control group, using standardized tests. The two groups were homogeneous in age and IQ. Significant differences were found between groups in the relationship between some language processes: inhibition, auditory working memory, cognitive flexibility, level of social adaptation, self-direction, conceptual adaptation, academic skills, leadership ability, theory of mind, and arithmetic. In the group of girls with FXS, it was found that different aspects of language influence some of the executive functions evaluated, in addition to some specific aspects of social perception, adaptive behavior, and quantitative reasoning, in different ways. Future research should incorporate the study of the influence of other cognitive variables such as visual perception and executive function on behavioral, social, and adaptive aspects to know the real influence of all the cognitive variables on the behavior of girls with FXS.

KEYWORDS
behavior, cognition, females, fragile-X syndrome, language

1 | INTRODUCTION

Fragile X syndrome (FXS) is the leading cause of inherited intellectual disability. It is associated with an alteration in the "fragile X mental retardation 1"*(FMR1)* gene located in Xq27.3 (Bennetto et al., 2001; Tassone et al., 2014). It is generally attributed to a trinucleotide CGG repeat expansion in the untranslated promoter region of the gene (Lozano et al., 2014; Reches, 2019), although there are also cases of mutation in the gene itself.

Depending on the number of repetitions, subjects can be classified into three categories: unaffected individuals (6–54 repetitions), premutation carriers (55–200 repetitions), and persons with a complete mutation (>200 repetitions) (Reches, 2019). Subjects with 45–54 repetitions are in the gray zone. Epidemiological studies report an estimated incidence of FXS of 1.4 males and 0.9 females per 10,000 population (Jorge et al., 2018), with a prevalence of 1 in 2500 to 7000 males and 1 in 2500 to 11,000 females (Bartholomay et al., 2019).

Given that it is a genetic condition linked to X chromosome inheritance, most of the previous scientific research has focused on describing the neurocognitive phenotype of affected males, and there are few studies on this phenotype in females. Most of these studies focus on adulthood or include very broad age ranges (from school age

[Corrections added after online publication, 25 February 2021: The affiliations of Dr. Joga-Elvira & Dr. Jacas-Escarcelle were incorrect in the initial publication. It has been updated and other affiliations were reordered to match journal style.]

to adulthood) and were conducted in the 1980s and 1990s (Cronister, Hagerman, et al., 1991; Cronister, Schreiner, et al., 1991; Doco-fenzy et al., 2006; Grigsby et al., 1990; Hull & Hagerman, 1993; Keysor & Mazzocco, 2002; Simon et al., 2001; Thompson et al., 1994); since then, there have been huge advances in cognitive and behavioral evaluation tools, enabling us to measure and describe cognitive-behavioral profiles much more specifically nowadays.

In one of the first studies conducted, Hagerman et al. analyzed the profile of 23 women with FXS. The results of the Wechsler Intelligence Scales showed a pattern characterized by an alteration in the arithmetic, digit span, and block design subtests (Kemper et al., 1986). It has also been described that approximately 50% of women with FXS have an intellectual disability (ID) of varying degrees (between limit and moderate), while the other 50% have a general cognitive ability in the midrange (Keysor & Mazzocco, 2002).

Many of the studies that have focused on girls with FXS describe language as a skill that stands out from the rest, with a profile characterized by an initial delay in language development, followed by a subsequent normalization of phonetic, phonological, and syntactic aspects, and impaired pragmatic features (Ferrando et al., 2004). In a study conducted by Raspa it was found that girls with FXS performed better in receptive vocabulary tasks as compared with their non-verbal intellectual ability, and that pragmatic function was impaired. Difficulties were noted with respecting turn taking and they produced fewer clarifying questions compared with the control group (CG) (Raspa et al., 2017). In an ongoing longitudinal study of 55 children with FXS (11 girls) and their mothers, the findings indicated that, while language proficiency continues to be very delayed for most participants, positive slopes were detected for vocabulary measured by standardized test. Rates of number of different words grew steadily for most participants until age of 10 years and then decreased somewhat (Brady et al., 2020).

A review made by Bartholomay (Bartholomay et al., 2019) conclude that women with FXS have a profile of impairments associated with socio-emotional difficulties, learning disorders, and mental health problems. While women with FXS have greater potential to achieve a higher level of autonomy than males with FXS, the delay in receiving specific treatments often means that the difference in this autonomy between males and females is smaller than expected. Many women with FXS meet the DSM-5 diagnostic criteria for: generalized anxiety disorder, social anxiety disorder, dyscalculia, intellectual disability (ID), autism spectrum disorder (ASD), and attention deficit hyperactivity disorder (ADHD). The cognitive phenotype varies widely across subjects, with intellectual capacities ranging from moderate ID to scores in the midrange (Bartholomay et al., 2019). Among the affected skills, executive functioning and visuo-spatial reasoning can be highlighted. In contrast, verbal skills stand out as a relatively preserved function. At the social–emotional level, these subjects are more likely to suffer from social anxiety, social and behavioral avoidance, and depressive disorder. Regarding adaptative behavior and level of independence, the Intelligence Quotient (IQ) test appears to be a predictor of achievements in adaptive behavior (Bartholomay et al., 2019). Although girls with FXS obtain higher scores in adaptive behavior than boys, these scores appear to worsen over time with the greatest decline in the area of communication (verbal and written). This fact seems to be related more to a slower pace of development than to a loss of functions. The most powerful predictor described for level of autonomy in women with FXS seems to be the ability to interact appropriately in social environments, an especially difficult area for these subjects. Despite having the required functional skills, less than half of women with FXS achieve high levels of autonomy (Bartholomay et al., 2019). These same authors analyzed a sample of girls aged between 6 and 14 years diagnosed with FXS, finding that they obtained higher scores for verbal skills than for non-verbal skills and overall score. They also scored higher in reading compared with arithmetic. Regarding the association between cognitive ability and adaptive behavior, these authors found significantly positive correlations between non-verbal reasoning and communication skills, daily life, and overall adaptive behavior. In contrast, they found no significant correlation between verbal reasoning ability and any subdomain of the Vineland-III scale that assesses degree of functional autonomy. Last, they found a negative correlation between the aberrant social skills scale and adaptive behavior (Bartholomay et al., 2019).

Another study conducted by Sterling and Abbeduto (Sterling & Abbeduto, 2013) examines receptive vocabulary and expressive syntax in 21 girls with FXS ranging in age from 7 to 15 years. Their results show a good level of receptive vocabulary in relation to these subjects' IQ. Regarding expressive syntax, they found a wide range of variability with a lower-than-expected overall score relative to participants' chronological age (10% of the sample obtained a score corresponding to preschool age). Regarding the syntactic ability of girls with FXS, there is a recent publication aiming to establish the extent of delay, and the effects of context, on the use of complex syntactic structures in spontaneous language in females with FXS; as well as to identify predictors of individual variability in syntactic complexity (Kover & Abbeduto, 2019). The results show that the spoken language of females with FXS was comprised of utterances significantly shorter than would be expected for their age. It was observed that phonological memory and verbal working memory correlated with syntactic ability in narration, in terms of mean length of C-unit (MLCU), proportion of complex utterances produced, and average level of syntactic complexity (Kover & Abbeduto, 2019). It was also found that females with better phonological memory and verbal working memory skills were more likely to be affected by social anxiety provoked by the demands of a reciprocal conversation, decreasing the syntactic complexity produced in that context (Kover & Abbeduto, 2019).

Mazzocco (Mazzocco et al., 2006) compare the start of social interactions in role-play situations in three groups of women: FXS (n = 20; ages 7 to 22 years), Turner syndrome (n = 27; ages 7 to 22 years), and a CG with normal development (n = 28; ages 6 to 20 years). The results showed a lower number of "*continuation questions*" for the FXS group in comparison to the CG. In a study that focused on assessing pragmatic difficulties for the purpose of highlighting the lack of understanding of an unclear oral message, Martin (Martin et al., 2017) found no significant differences between the FXS group of subjects and the CG. Differences were only found where there was comorbid presentation of FXS and ASD, with this group having greater difficulty in understanding the message

correctly. The results of another investigation with the aim of studying the relationship between expressive language sampling and clinical measures in FXS and typical development, showed that all Expressive Language Sampling Narrative (ELS-N) variables differentiated the FXS group from de TD group, with unintelligibility of speech, syntactic complexity, and lexical diversity providing the most pronounced differences (Shaffer et al., 2020). Also, greater intellectual functioning standard scores were associated with greater lexical diversity, syntactic complexity, and intelligibility for the FXS group. In addition, verbal knowledge and nonverbal fluid reasoning were positively related to syntactic complexity and negatively related to unintelligibility. When correlations were completed for FXS males and females separately, the relationship between Abbreviate IQ and ELS-N variables was primarily driven by the males in the group (Shaffer et al., 2020). Stronger adaptive skills and daily living skills standard scores were related to more intelligible speech. When males and females were analyzed separately, the relationship between ELS-N and Vineland Expressive Communication and daily living skills standard scores appeared to be primarily driven by females in the sample (Shaffer et al., 2020).

Given that the literature has described language as a relatively preserved skill in women with FXS, the present study was undertaken with the aim of describing the relationship between linguistic functions (such as expressive vocabulary, comprehensive vocabulary, comprehension of instructions, semantic verbal fluency, naming, and phonological processing), and the level of performance in the following areas of neurocognitive functioning: executive function, quantitative reasoning, social perception, social skills, and adaptive behavior in FXS females. To achieve this objective, a group of FXS females was compared with a control group matched by age and IQ.
Three basic hypotheses were formulated:

1. Better performance in some language function tasks implies better performance in certain executive function and quantitative reasoning tasks. This relationship will occur in a different way depending on the presence of the FXS diagnosis.
2. Better performance in certain language function tasks implies better performance in some social perception and social skills tasks. This relationship will occur in a different way depending on the presence of the FXS diagnosis.
3. Better performance in some language function tasks implies better scores in some sub-areas of adaptive behavior. This relationship will occur in a different way depending on the presence of the FXS diagnosis.

2 | METHOD

The present research was carried out at the Parc Taulí Hospital in Sabadell as part of the Network of Clinical Experience Units (CEU) for rare diseases (Barcelona, Spain) and was approved by the hospital's Ethics Committee (reference 2,016,595). This hospital is also a member of the Clinical Research Consortium for FXS (CRCFXS). The Spanish FXS Federation, different FXS associations (Catalonia, The Basque Country, Madrid, Valencia) and patients with genetic diseases (D'Genes Murcia) collaborated with recruiting the participants. An appeal for participation was also made through professional social networks such as Linked-In, and an email about the study was sent to the teams of psychopedagogy specialists in the area and to special education schools. Informed consent was obtained from the legal guardians of all the participants.

2.1 | Participants

It has been described that girls with FXS present a great variability in terms of IQ: approximately 50% of women with FXS have ID to varying degrees (between limit and moderate), while the other 50% have a general cognitive ability that sits within the midrange (Keysor & Mazzocco, 2002). This is a fact that we find in our daily clinical practice, and hence the sample features participants with IQ ranging from intellectual disability to within midrange, which is a realistic representation of the way FXS manifest in girls. To avoid any potential confounding, a statistical analysis was performed to ensure that there were no significant differences between both groups in terms of IQ, age, socio economic status (SES), and ADHD symptoms. The means comparison was made using the Student's *t* test, and no statistically significant differences were found between groups in these variables (Table 2).

The participants were part of a larger study that aimed to assess the relationship between different cognitive and behavioral variables (Ethics Committee reference 2,016,595). The sample group was made up of 40 female participants (n = 40) aged between 7 and 16 years, who were divided into two groups:

1. FXS group: n = 26. Participants were recruited through the CEU of Parc Taulí Hospital and the different patient associations.
2. CG: n = 14. Participants were recruited through appointments at the Neuropediatrics Unit of Parc Taulí Hospital in Sabadell and in the schools in the area (both standard education and special education schools).

The inclusion criteria for the FXS group were the following: female, aged between 7 and 16 years, and FXS diagnosis confirmed by genetic study (>200 repetitions). For the CG they were female, aged between 7 and 16 years. The exclusion criteria for the FXS group were presenting comorbid ASD, comorbid ADHD, absence of expressive language, and acquired neurological disorders (epilepsy, head injury). Some individuals with FXS meet diagnostics criteria for ASD, and those with ASD have been reported to have poorer language outcomes (Haebig et al., 2020), and tend to have more impaired cognition (Haebig et al., 2020). Sometimes it can be difficult to determine if language outcomes are more affected by IQ or autism status (Brady et al., 2020). One aim of the present investigations is to assess the influence of language on social perception and executive functions in girls with FXS. Since ADHD is characterized by an executive dysfunction and ASD is characterized by an alteration in communication and

social interaction, participants with FXS and ADHD and/or ASD comorbid were excluded from the sample to avoid any possible effect of these diagnoses on variables of social perception and executive function.

Additionally, candidates were excluded from the CG if they met the diagnostic criteria for ASD, ADHD, absence of expressive language, acquired neurological disorders (epilepsy, head injury, and so forth), or other genetically based cognitive-behavioral disorders. As for non-ID, participants were excluded from the sample if they had a family history of FXS and presented symptoms clinically compatible with FXS diagnosis. In both groups, ASD and/or ADHD diagnoses were ruled out by an expert neurologist on neurodevelopmental disorders based on the DMS-5 criteria.

2.2 | Measures and procedure

Participants from the Barcelona metropolitan area were examined at the Parc Taulí Hospital, and the principal investigator traveled to the autonomous regions where the rest of the participants lived to carry out their assessment, thus ensuring minimum discomfort for them and their families. First, a letter explaining about the project was forwarded to the patients' associations, who disseminated the information and organized the principal investigator's visit to conduct the assessments of willing participants in the facilities provided by the associations. The participating autonomous regions were Catalonia, Madrid, the Basque Country, Galicia, Valencia, and Murcia.

The assessments were carried out by an expert neuropsychologist in their native language (Spanish language), and in three separate one-hour sessions to ensure that participants did not become overtired. The assessor was not blind to subjects' characteristics.

2.3 | Variables and scales

The following aspects of language were used as independent variables: expressive vocabulary, comprehensive vocabulary, comprehension of instructions, semantic verbal fluency, phonological processing, and naming. The instruments used for the assessment of these variables were Vocabulary Subtest (WISC-V, Wechsler, 2015), Peabody Picture Vocabulary Test (Dunn & Dunn, 2006), Comprehension Instructions subtest Neuropsychological Battery for Children (NEPSY-II, Korkman et al., 2014), Fluency subtest (NEPSY-II, Korkman et al., 2014), Phonological Processing subtest (NEPSY-II, Korkman et al., 2014), and Boston naming test (Kaplan et al., 2005), respectively.

Dependent variables include aspects of cognitive and behavioral functioning described below. For the cognitive variables, the Wechsler Intelligence Scale for Children-V (Wechsler, 2015) was used to assess General Cognitive Ability, Visual Working Memory (Picture Span subtest), Auditory Working Memory (Digits and Letters and Numbers subtest), and Quantitative Reasoning (Figure Weights and Arithmetic subtest). Some of the NEPSY-II subtest were used to assess Hearing Attention (Auditory Attention subtest, total correct), Cognitive Flexibility (Cognitive Flexibility subtest, total correct), Inhibition (Inhibition subtest, total correct), Emotion Recognition (Emotion Recognition subtest), and Theory of Mind (Theory of Mind subtest: verbal theory of mind and total theory of mind) (NEPSY-II, Korkman et al., 2014). The Wisconsin Card Sorting Test (WCST) (Heaton et al., 2009) was used to assess Cognitive Flexibility (Learning to learn) and the Tower of London children version for Problem Solving (Total Correct), Problem Solving Efficiency (Total Move), and Breaking Rules (Total Rule Violation) (Culbertson & Zillmer, 2005).

The following questionnaires and scales were used to assess the behavioral variables: Child and Adolescent Evaluation System (SENA), parents' version, for the assessment of a wide range of emotional and behavioral problems, contextual problems, areas of vulnerability, and psychological resources (Fernández-Pinto et al., 2015); ADHD Rating Scale (parents' version) to assess the ADHD Symptomatology for the exclusion criteria (Paul et al., 1998); Battery of socialization (BAS-2), parents' version, to asses four domains facilitating socialization (leadership, joviality, social sensitiveness, and respect-self-control), three domains that disrupt socialization (aggressiveness-obstinacy, apathy-withdrawnness, and anxiety-shyness), and a global social adaptation or criterial-socialization scale (Silva & Martorell, 2018); Behavioral assessment of executive function-2 (BRIEF-2), parents' version, as an ecological measure of executive function (Gioia et al., 2017); and Adaptative Behavior Assessment System- Second Edition Spanish version (ABAS-II), parents' version, as a measure of Adaptive Behavior (Harrison & Oakland, 2013).

The Hollingshead index was used to collect and measure information about socioeconomic status (Hollingshead, 1975).

The direct scores for all the cognitive functioning tests and for the ABAS-II were converted into standard scores with a mean of 100 and SD of 15. The direct scores for the SENA and BRIEF-2 were converted into standard scores with a mean of 50 and SD of 10, and the direct scores for the ADHD Rating Scale were converted into percentile scores.

2.4 | Statistical analysis

Statistical analysis was performed with the SPSS Statistics for Windows software, Version 25.0. A possible differential distribution of the control variables, age, and Intellectual Quotient (IQ), between the control groups and the FXS group was ruled out using the Students' *t* test. The comparison of variables relating to cognitive and linguistic skills and behavior between the control group and the FXS group was carried out using the Mann–Whitney *U* test because of a non-normal distribution of the data (Table 1). Comparisons between qualitative variables were ruled out using the chi-square test. The association between the cognitive and behavioral functioning variables was examined using linear regression, controlling for group effect. If this was not significant, it was removed from the model.

TABLE 1 Kurtosis and skewness index of cognitive variables

Variables	FXS group *n* = 26	Control group *n* = 14
General cognitive ability (WISC-V)		
Skewness (SD)	0.647 (0.456)	0.296 (0.597)
Kurtosis (SD)	0.486 (0.887)	−1.208 (1.154)
Expressive vocabulary (WISC-V)		
Skewness (SD)	1.319 (0.456)	−0.191 (0.597)
Kurtosis (SD)	3.411 (0.887)	−0.845 (1.154)
Comprehension instructions (NEPSY-II)		
Skewness (SD)	0.284 (0.456)	0.669 (0.597)
Kurtosis (SD)	−1.459 (0.887)	−0.744 (1.154)
Semantic verbal fluency (NEPSY-II)		
Skewness (SD)	−0.270 (0.456)	0.994 (0.597)
Kurtosis (SD)	−0.093 (0.887)	1.138 (1.154)
Comprehensive vocabulary (PEABODY)		
Skewness (SD)	0.427 (0.456)	0.243 (0.597)
Kurtosis (SD)	−0.600 (0.887)	−1.824 (1.154)
Naming (BNT)		
Skewness (SD)	0.449 (0.456)	−0.324 (0.597)
Kurtosis (SD)	0.601 (0.887)	−1.257 (1.154)
Phonological awareness (NEPSY-II)		
Skewness (SD)	0.431 (0.456)	0.250 (0.597)
Kurtosis (SD)	−0.656 (0.887)	−1.189 (1.154)
Auditory working memory (NEPSY-II)		
Skewness (SD)	0.464 (0.456)	0.059 (0.597)
Kurtosis (SD)	−0.686 (0.887)	−1.667 (1.154)
Cognitive flexibility (NEPSY-II)		
Skewness (SD)	1.147 (0.456)	−0.027 (0.597)
Kurtosis (SD)	0.825 (0.887)	−1.642 (1.154)
Inhibition (NEPSY-II)		
Skewness (SD)	1.435 (0.464)	0.520 (0.597)
Kurtosis (SD)	1.284 (0.902)	−1.630 (1.154)
Processing speed (WISC-V)		
Skewness (SD)	0.500 (0.456)	0.197 (0.597)
Kurtosis (SD)	0.276 (0.887)	0.831 (1.154)
Auditory attention (NEPSY-II)		
Skewness (SD)	0.382 (0.456)	−0.008 (0.597)
Kurtosis (SD)	−0.577 (0.887)	−1.415 (1.154)
Problem solving (TOL)		
Skewness (SD)	0.363 (0.464)	0.984 (0.597)
Kurtosis (SD)	−0.755 (0.902)	0.067 (1.154)
Phonetic verbal fluency (NEPSY-II)		
Skewness (SD)	0.257 (0.464)	0.264 (0.616)
Kurtosis (SD)	−0.474 (0.902)	−1.540 (1.191)
Emotion recognition (NEPSY-II)		
Skewness (SD)	0.167 (0.464)	−0.051 (0.597)
Kurtosis (SD)	−0.353 (0.902)	−1.109 (1.154)

(Continues)

TABLE 1 (Continued)

Variables	FXS group *n* = 26	Control group *n* = 14
Verbal Theory of mind (NEPSY-II)		
Skewness (SD)	2.771 (0.456)	1.187 (0.597)
Kurtosis (SD)	9.852 (0.887)	0.289 (1.154)
Global Theory of mind (NEPSY-II)		
Skewness (SD)	3.242 (0.456)	1.365 (0.597)
Kurtosis (SD)	12.139 (0.887)	0.608 (1.154)
Figure Weights (WISC-V)		
Skewness (SD)	0.384 (0.456)	1.137 (0.597)
Kurtosis (SD)	−1.054 (0.887)	1.541 (1.154)
Arithmetic (WISC-V)		
Skewness (SD)	0.887 (0.456)	−0.210 (0.597)
Kurtosis (SD)	0.558 (0.887)	−0.670 (1.154)

Abbreviations: BNT, Boston Naming Test; BRIEF-2, Ecological measure of executive function: Behavioral assessment of executive function-2; NEPSY-II, Neuropsychological Battery for Children-II; TOL, Tower of London; WISC-V, Wechsler Intelligence Scale for Children-V.

TABLE 2 Descriptive measures and distribution of age, IQ, ADHD symptoms, and socioeconomical status

Variables	FXS group *n* = 26	Control group *n* = 14	Significance
Age, M (SD)	10.58 (3.384)	10.50 (2.345)	0.940[a]
IQ, M (SD)	71.50 (14.795)	76.36 (16.80)	0.351[a]
ADHD symptoms, Md (Pc 25–75)	90.50 (75.25–95.75)	75.00 (38.75–90.75)	0.104[b]
Socioeconomical status			0.211[c]
Low	3.8%	16.7%	
Medium	88.5%	75%	
High	7.7%	8.3%	

Abbreviations: ADHD, Attention Deficit Hyperactivity Disorder; FXS, Fragile X syndrome; IQ, intelligence quotient; M, mean; Md, Median; Pc, Percentile.
[a]*t* test.
[b]U Mann–Whitney.
[c]Chi Square test.

3 | RESULTS

On comparing the means using the Student's *t* test and the Mann–Whitney *U* test no statistically significant differences were found between the control variables age, IQ, and ADHD symptoms (Table 2). Significant differences were found between groups in the relationship between some of the variables in the areas assessed.

Regarding intellectual ability, in the group of girls with FXS 3.84% of the participants obtained IQ scores in the range of moderate ID (IQ 35–40 to 50–55), 46.15% in the range of mild ID (IQ 50 to 70), 38.46% in the borderline range (IQ 70–85), and 11.53% within the average range (IQ > 85).

Statistically significant differences were found between groups in the executive function domain. Compared to the CG, the group of girls with FXS presented a greater influence of some of the verbal skills on certain executive functions: expressive vocabulary and auditory working memory (AWM) (p = 0.009); expressive vocabulary and cognitive flexibility (p = 0.001); expressive vocabulary and inhibition (p < 0.001); expressive vocabulary and Processing Speed (p = 0.018); comprehension of instructions and AWM (p = 0.007); comprehension of instructions and inhibition (p < 0.001); comprehension of instructions and cognitive flexibility (p = 0.003); comprehension of instructions and processing speed (p = 0.007); semantic verbal fluency and inhibition (p = 0.005); semantic verbal fluency and auditory attention (p = 0.009); phonological processing and inhibition (p = 0.010); phonological processing and cognitive flexibility (p = 0.01); naming and AWM (p < 0.01); phonetic naming and fluency (p < 0.01); comprehensive vocabulary and inhibition (p = 0.001); and comprehensive vocabulary and AWM (p = 0.009) (Table 3).

In the area of Social Perception, it was found that the capacity for verbal abstraction was related to the theory of mind in both the verbal theory of mind variable (p < 0.001) and the total theory of mind variable (p < 0.001) of NEPSY-II. To this effect, statistically significant differences were found between groups: the FXS group presented a greater influence of verbal abstraction capacity on verbal and total theory of mind than the CG. The same type of relationship was found

TABLE 3 Results of linear regression of executive function as dependent variable vs. group and language as independent variables

	Expressive vocabulary	Comprehension instructions	Semantic verbal fluency	Comprehensive vocabulary	Naming	Phonological awareness
Auditory Working Memory (WISC-V)	r^2 0.643 p = 0.009** β =0.849	r^2 0.637 p = 0.007** β = 0.784	r^2 0.415 p = 0.246 β 0.686	r^2 0.531 p = 0.009** β 0.600	r^2 0.383 p < 0.001*** β 0.351	r^2 0.720 p = 0.828 β 0.801
Visual Working memory (WISC-V)	r^2 0.484 p = 0.167 β 0.753	r^2 0.409 p = 0.166 β 0.646	r^2 0.330 p = 0.700 β 0.639	r^2 0.353 p = 0.137 β 0.507	r^2 0.252 p = 0.011* β 0.302	r^2 0.455 p = 0.752 β 0.652
Cognitive flexibility (NEPSY-II)	r^2 0.366 p = 0.001*** β 0.529	r^2 0.365 p < 0.001** β 0.491	r^2 0.266 p = 0.003** β 0.235	r^2 0.249 p = 0.001*** β 0.233	r^2 0.215 p 0.001*** β 0.100	r^2 0.492 p = 0.01** β 0.620
Inhibition (NEPSY-II)	r^2 0.446 p < 0.001*** β 0.618	r^2 0.475 p < 0.001*** β 0.605	r^2 0.335 p = 0.005** β 0.471	r^2 0.307 p = 0.001*** β 0.330	r^2 0.271 p < 0.001*** β 0.189	r^2 0.449 p = 0.010*** β 0.554
Processing speed (WISC-V)	r^2 0.321 p = 0.018* β 0.627	r^2 0.449 p = 0.007** β 0.711	r^2 0.243 p = 0.090 β 0.533	r^2 0.176 p = 0.023** β 0.326	r^2 0.190 p 0.004** β 0.239	r^2 0.407 p = 0.237 β 0.644
Auditory attention (NEPSY-II)	r^2 0.154 p = 0.043* β 0.401	r^2 0.219 p = 0.032* β 0.472	r^2 0.316 p = 0.009** β 0.349	r^2 0.117 p = 0.039* β 0.252	r^2 0.114 p 0.014* β 0.172	r^2 0.139 p = 0.165 β 0.332
Problem solving (TOL)	r^2 0.216 p = 0.242 β 0.508	r^2 0.388 p = 0.160 β 0.616	r^2 0.181 p = 0.621 β 0.477	r^2 0.168 p = 0.188 β 0.359	r^2 0.163 p = 0.028* β 0.245	r^2 0.220 p = 0.858 β 0.457
Problem solving efficiency (TOL)	r^2 0.175 p = 0.287 β 0.576	r^2 0.351 p = 0.202 β 0.728	r^2 0.212 p = 0.706 β 0.635	r^2 0.078 p = 0.258 β 0.330	r^2 0.172 p = 0.029* β 0.312	r^2 0.265 p = 0.988 β 0.616
Breaking rules (TOL)	r^2 0.296 p = 0.289 β 0.553	r^2 0.037 p = 0.359 β 0.238	r^2 0.075 p = 0.641 β 0.323	r^2 0.130 p = 0.267 β 0.308	r^2 0.041 p = 0.128 β 0.145	r^2 0.198 p = 0.970 β 0.413
Phonetic verbal fluency (NEPSY-II)	r^2 0.293 p = 0.029* β 0.517	r^2 0.417 p = 0.022* β 0.578	r^2 0.365 p = 0.178 β 0.575	r^2 0.272 p = 0.038* β 0.383	r^2 0.518 p < 0.001*** β 0.378	r^2 0.508 p = 0.434 β 0.611
Self-supervision (BRIEF-2)	r^2 0.013 p = 0.541 β –0.239	r^2 0.177 p = 0.493 β –0.374	r^2 0.090 p = 0.851 β –0.373	r^2 0.027 p = 0.482 β –0.208	r^2 0.006 p = 0.258 β –0.121	r^2 -0.030 p = 0.705 β –0.104
Emotional control (BRIEF-2)	r^2 0.049 p = 0.684 β 0.021	r^2 0.026 p = 0.689 β –0.204	r^2 0.021 p = 0.470 β –0.215	r^2 -0.038 p = 0.707 β –0.065	r^2 0.044 p = 0.855 β –0.031	r^2 -0.045 p = 0.613 β –0.048
Initiative (BRIEF-2)	r^2 0.295 p = 0.089 β –0.482	r^2 0.348 p = 0.067 β –0.486	r^2 0.107 p = 0.261 β –0.289	r^2 0.163 p = 0.088 β –0.277	r^2 0.170 p = 0.012* β –0.197	r^2 0.240 p = 0.525 β –0.386
Working memory (BRIEF-2)	r^2 0.096 p = 0.680 β –0.319	r^2 0.344 p = 0.577 β –0.487	r^2 0.043 p = 0.966 β –0.258	r^2 0.116 p = 0.575 β –0.265	r^2 0.081 p = 0.176 β –0.164	r^2 0.148 p = 0.669 β –0.331
Organization planning (BRIEF-2)	r^2 0.170 p = 0.592 β –0.355	r^2 0.232 p = 0.536 β –0.374	r^2 -0.015 p = 0.777 β –0.138	r^2 0.110 p = 0.510 β –0.236	r^2 0.203 p = 0.054 β –0.207	r^2 0.152 p = 0.742 β –0.303
Task supervision (BRIEF-2)	r^2 0.210 p = 0.125 β –0.419	r^2 0.354 p = 0.079 β –0.505	r^2 0.134 p = 0.313 β –0.340	r^2 0.239 p = 0.083 β-0.349	r^2 0.156 p = 0.016* β –0.196	r^2 0.235 p = 0.581 β –0.395
Organization of materials (BRIEF-2)	r^2 - 0.029 p = 0.471 β –0.087	r^2 0.023 p = 0.446 β –0.199	r^2 -0.029 p = 0.552 β –0.088	r^2 -0.034 p = 0.459 β –0.046	r^2 -0.02 p = 0.315 β –0.064	r^2 -0.028 p = 0.610 β –0.081
Behavioral regulation (BRIEF-2)	r^2 0.029 p = 0.525 β –0.233	r^2 0.059 p = 0.497 β –0.258	r^2 0.034 p = 0.758 β –0.244	r^2 0.096 p = 0.432 β –0.252	r^2 -0.12 p = 0.308 β –0.082	r^2 -0.024 p = 0.716 β –0.106

(Continues)

TABLE 3 (Continued)

	Expressive vocabulary	Comprehension instructions	Semantic verbal fluency	Comprehensive vocabulary	Naming	Phonological awareness
Emotional regulation (BRIEF-2)	r^2 -0.026 p = 0.882 β –0.151	r^2 0.077 p = 0.903 β –0.307	r^2 -0.005 p = 0.691 β –0.204	r^2 0.031 p = 0.955 β –0.207	r^2–0.04 p = 0.866 β –0.057	r^2 -0.047 p = 0.781 β –0.067
Cognitive regulation (BRIEF-2)	r^2 0.183 p = 0.165 β –0.367	r^2 0.281 p = 0.124 β –0.418	r^2 0.039 p = 0.309 β –0.186	r^2 0.225 p = 0.110 β –0.316	r^2 0.145 p = 0.022* β –0.178	r^2 0.138 p = 0.550 β –0.285
Global Executive Function (BRIEF-2)	r^2 0.098 p = 0.652 β –0.347	r^2 0.163 p = 0.604 β –0.388	r^2 0.035 p = 0.922 β –0.266	r^2 0.189 p = 0.514 β –0.345	r^2 0.058 p = 0.202 β –0.161	r^2 0.057 p = 0.876 β –0.263
Inhibition (BRIEF-2)	r^2 0.000 p = 0.911 β –0.180	r^2 0.032 p = 0.933 β –0.211	r^2 0.029 p = 0.659 β –0.226	r^2 -0.008 p = 0.969 β –0.129	r^2–0.037 p = 0.810 β –0.054	r^2 0.006 p = 0.596 β –0.168
Flexibility (BRIEF-2)	r^2 0.089 p = 0.713 β –0.347	r^2 0.239 p = 0.821 β –0.461	r^2 0.012 p = 0.540 β –0.240	r^2 0.042 p = 0.785 β –0.224	r^2 -0.017 p = 0.841 β –0.096	r^2 -0.001 p = 0.469 β –0.192

Note: All values of r^2 are r^2 adjusted. $p \leq 0.05$*; $p \leq 0.01$**; $p \leq 0.001$***.
Abbreviations: BRIEF-2, Ecological measure of executive function: Behavioral assessment of executive function-2; NEPSY-II, Neuropsychological Battery for Children-II; TOL, Tower of London; WISC-V, Wechsler Intelligence Scale for Children-V.

TABLE 4 Results of linear regression of social perception as dependent variable vs. group and language as independent variables

	Expressive vocabulary	Comprehension instructions	Semantic verbal fluency	Comprehensive vocabulary	Naming	Verbal abstraction	Phonological awareness
Emotion recognition (NEPSY-II)	r^2 0.261 p = 0.276 β 0.622	r^2 0.129 p = 0.300 β 0.428	r^2 0.265 p = 0.783 β 0.636	r^2 0.180 p = 0.221 β 0.418	r^2 0.236 p = 0.015* β 0.325	r^2 0.414 p = 0.088 β 0.905	r^2 0.490 p = 0.656 β 0.740
Theory of mind (NEPSY-II)	r^2 0.422 p = 0.049* β 0.472	r^2 0.240 p = 0.074 β 0.327	r^2 0.212 p = 0.260 β 0.335	r^2 0.287 p = 0.048* β 0.302	r^2 0.231 p = 0.005** β 0.187	r^2 0.30 p = 0.03* β 0.469	r^2 0.519 p = 0.730 β 0.467
Global Theory of mind (NEPSY-II)	r^2 = 0.416 p = 0.044* β 0.470	r^2 = 0.200 p = 0.075 β 0.296	r^2 = 0.212 p = 0.240 β 0.334	r^2 = 0.265 p = 0.047* β 0.290	r^2 = 0.215 p = 0.005** β 0.180	r^2 = 0.311 p = 0.026* β 0.478	r^2 = 0.542 p = 0.706 β 0.480

Note: All values of r^2 are r^2 adjusted. $p \leq 0.05$*; $p \leq 0.01$**; $p \leq 0.001$***.
Abbreviation: NEPSY-II, Neuropsychological Battery for Children-II.

TABLE 5 Results of linear regression of quantitative reasoning as dependent variable vs. group and language as independent variables

	Expressive vocabulary	Comprehension instructions	Semantic verbal fluency	Comprehensive vocabulary	Naming	Verbal abstraction	Phonological awareness
Figure Weights (WISC-V)	r^2 0.393 p = 0.515 β 0.464	r^2 0.459 p = 0.430 β 0.462	r^2 0.128 p = 0.972 β 0.297	r^2 0.285 p = 0.407 β 0.315	r^2 0.231 p = 0.039* β 0.200	r^2 0.409 p = 0.230 β 0.560	r^2 0.319 p = 0.501 β 0.377
Arithmetic (WISC-V)	r^2 0.582 p = 0.031* β 0.692	r^2 0.477 p = 0.042* β 0.581	r^2 0.315 p = 0.343 β 0.515	r^2 0.283 p = 0.061 β 0.375	r^2 0.262 p = 0.004** β 0.250	r^2 0.412 p = 0.021* β 0.688	r^2 0.562 p = 0.892 β 0.605

Note: All values of r^2 are r^2 adjusted. $p \leq 0.05$*; $p \leq 0.01$**; $p \leq 0.001$***.
Abbreviation: WISC-V, Wechsler Intelligence Scale for Children-V.

between expressive vocabulary and verbal and total theory of mind (Table 4).

Regarding the possible influence of language on the area of quantitative reasoning, significant relationships were found between the verbal abstraction ability and arithmetic ($p < 0.001$), expressive vocabulary and arithmetic ($p < 0.001$), and comprehension of instructions and arithmetic ($p < 0.001$), with significant differences between groups. The group of girls with FXS presented a significantly greater influence of verbal abstraction, expressive vocabulary, and comprehension of instructions on arithmetic ability (Table 5).

TABLE 6 Results of linear regression of adaptive behavior as dependent variable vs. group and language as independent variables

	Expressive vocabulary	Comprehension instructions	Semantic verbal fluency	Comprehensive vocabulary	Naming	Phonological awareness
Social adaptation (ABAS-II)	r^2 0.159 p = 0.040* β 0.347	r^2 0.140 p = 0.038* β 0.290	r^2 0.199 p = 0.102 β 0.412	r^2 0.331 p = 0.014* β 0.439	r^2 0.198 p = 0.004** β 0.220	r^2 0.148 p = 0.141 β 0.291
Conceptual adaptation (ABAS-II)	r^2 0.238 p = 0.093 β 0.506	r^2 0.359 p = 0.057 β 0.579	r^2 0.189 p = 0.260 β 0.452	r^2 0.419 p = 0.031* β 0.528	r^2 0.266 p = 0.003** β 0.290	r^2 0.325 p = 0.512 β 0.528
Practical (ABAS-II)	r^2 0.014 p = 0.474 β 0.288	r^2 0.059 p = 0.442 β 0.360	r^2 0.025 p = 0.667 β 0.319	r^2 0.206 p = 0.337 β 0.478	r^2 0.066 p = 0.127 β 0.219	r^2 0.069 p = 0.875 β 0.363
General Adaptive Behavior (ABAS-II)	r^2 0.125 p = 0.141 β 0.390	r^2 0.191 p = 0.113 β 0.448	r^2 0.132 p = 0.293 β 0.404	r^2 0.361 p = 0.053 β 0.519	r^2 0.191 p = 0.011* β 0.261	r^2 0.191 p = 0.473 β 0.428
Communication (ABAS-II)	r^2 0.085 p = 0.489 β 0.492	r^2 0.110 p = 0.450 β 0.497	r^2 0.043 p = 0.723 β 0.407	r^2 0.218 p = 0.352 β 0.548	r^2 0.100 p = 0.099 β 0.282	r^2 0.123 p = 0.992 β 0.497
Academic skills (ABAS-II)	r^2 0.267 p = 0.264 β 0.657	r^2 0.400 p = 0.183 β 0.732	r^2 0.323 p = 0.705 β 0.723	r^2 0.364 p = 0.146 β 0.589	r^2 0.334 p = 0.005** β 0.394	r^2 0.493 p = 0.745 β 0.774
Self-Direction (ABAS-II)	r^2 0.197 p = 0.017* β 0.425	r^2 0.312 p = 0.009** β 0.565	r^2 0.137 p = 0.039* β 0.285	r^2 0.35 p = 0.005** β 0.515	r^2 0.194 p = 0.003** β 0.227	r^2 0.194 p = 0.075 β 0.371
Leisure (ABAS-II)	r^2 0.120 p = 0.129 β 0.379	r^2 0.098 p = 0.122 β 0.314	r^2 0.199 p = 0.298 β 0.498	r^2 0.300 p = 0.06 β 0.473	r^2 0.168 p = 0.013* β 0.244	r^2 0.122 p = 0.367 β 0.338
Social (ABAS-II)	r^2 0.096 p = 0.047* β 0.290	r^2 0.095 p = 0.44* β 0.263	r^2 0.091 p = 0.080 β 0.275	r^2 0.234 p = 0.022* β 0.466	r^2 0.119 p = 0.013* β 0.195	r^2 0,094 p = 0.110 β 0.251
Utilization of community resources (ABAS-II)	r^2 0.060 p = 0.349 β 0.388	r^2 0.223 p = 0.278 β 0.602	r^2 0.090 p = 0.585 β 0.454	r^2 0.255 p = 0.216 β 0.537	r^2 0.123 p = 0.054 β 0.274	r^2 0.160 p = 0.850 β 0.501
Home life (ABAS-II)	r^2–0.050 p = 0.965 β 0.078	r^2–0.049 p = 0.974 β 0.081	r^2–0.012 p = 0.780 β 0.228	r^2 0.020 p = 0.974 β 0.230	r^2–0.028 p = 0.704 β 0.096	r^2 -0.044 p = 0.832 β 0.103
Health and security (ABAS-II)	r^2 0.117 p = 0.257 β 0.493	r^2 0.125 p = 0.233 β 0.468	r^2 0.036 p = 0.409 β 0.320	r^2 0.307 p = 0.137 β 0.592	r^2 0.092 p = 0.057 β 0.241	r^2 0.126 p = 0.650 β 0.451
Self-care (ABAS-II)	r^2–0.021 p = 0.419 β 0.176	r^2 0.004 p = 0.402 β 0.267	r^2–0.015 p = 0.522 β 0.213	r^2 0.097 p = 0.334 β 0.412	r^2 = 0.037 p = 0.148 β 0.212	r^2 0.015 p = 0.673 β 0.290

Note: All values of r^2 are r^2 adjusted. $p \leq 0.05$*; $p \leq 0.01$**; $p \leq 0.001$***.
Abbreviation: ABAS-II, Adaptive Behavior: Adaptive Behavior Assessment System-II.

Regarding socialization style, it was found that only the variables naming, and receptive vocabulary showed a statistically significant relationship with leadership ability ($p < 0.001$ in both cases). The group of girls with FXS presented a significantly greater influence of naming on leadership ability ($r^2 = 0.398$; $p = 0.001$), and receptive vocabulary on leadership ability ($r^2 = 0.377$; $p = 0.007$).

In the area of adaptive behavior, a relationship was found between the variables receptive vocabulary and social adaptation ($p < 0.001$); receptive vocabulary and self-directed ability ($p = 0.001$); receptive vocabulary and conceptual adaptation ($p < 0.001$); comprehension of instructions and self-direction ($p = 0.002$); and naming and academic skills ($p < 0.001$). The group of girls with FXS presented a significantly greater influence of receptive vocabulary on social adaptation, self-direction, and conceptual adaptation. The same type of relationship was found between comprehension of instructions and self-direction, and naming and academic skills (Table 6).

Variables of interest, including central tendency and variability, are summarized in Table 7.

4 | DISCUSSION

The objective of the present research was to study the relationship between language functions, described in the literature as relatively

TABLE 7 Variables: Central tendency and variability

Variables	FXS group md	FXS group pc 25 - pc 75	Control group md	Control group pc 25 - pc 75	Significance
Intelligent Quotient (WISC-V)	69.00	60.75–81.25	73.00	63.00–92.00	0.361
Expressive Vocabulary (WISC-V)	78.00	70.00–90.00	77.50	70.00–91.25	0.747
Comprehension instructions (NEPSY-II)	70.00	58.75–90.00	70.00	60.00–86.25	0.944
Semantic verbal fluency (NEPSY-II)	85.00	76.00–95.	91.50	80.00–95.00	0.408
Comprehensive vocabulary (PEABODY)	81.00	55.00–86.25	72.00	55.00–95.00	0.834
Naming (BNT)	92.00	80.00–103.00	79.00	34.00–94.00	0.048
Phonological awareness (NEPSY-II)	70.00	60.00–80.00	78.00	60.00–100.00	0.210
Auditory Working Memory (WISC-V)	61.50	47.25–73.50	71.50	51.00–90.25	0.104
Cognitive flexibility (NEPSY-II)	69.00	60.00–78.50	90.00	69.75–111.25	0.002
Inhibition (NEPSY-II)	55.00	55.00–77.00	76.50	69.00–105.00	0.002
Processing speed (WISC-V)	75.00	62.50–90.00	90.00	82.50–97.50	0.039
Auditory attention (NEPSY-II)	79.00	66.75–90.00	90.00	75.75–105.00	0.076
Problem solving (TOL)	78.00	68.00–88.00	78.00	72.00–93.50	0.361
Phonetic verbal fluency (NEPSY-II)	80.00	70.00–90.00	95.00	70.00–107.50	0.210
Emotion recognition (NEPSY-II)	85.00	75.00–95.00	92.50	75.00–105.00	0.426
Verbal Theory of mind (NEPSY-II)	72.00	69.00–78.00	75.00	69.00–87.50	0.210
Global Theory of mind (NEPSY-II)	69.00	69.00–72.75	72.00	69.00–87.50	0.098
Figure Weights (WISC-V)	80.00	76.00–95.00	85.00	78.75–95.00	0.705
Arithmetic (WISC-V)	70.00	60.00–81.25	75.50	70.00–90.00	0.104
ADHD Symptoms (Rating Scale)	90.50	75.25–95.75	75.00	38.75–90.75	0.104
Self-supervision (BRIEF-2)	54.50	44.00–71.00	56.50	41.00–61.00	0.254
Emotional control (BRIEF-2)	53.50	43.25–62.00	56.50	43.00–63.50	0.624
Initiative (BRIEF-2)	65.00	60.00–77.50	60.00	50.50–74.25	0.171
Working memory (BRIEF-2)	68.50	57.25–74.25	63.50	55.00–74.00	0.685
Organization planning (BRIEF-2)	63.00	54.00–70.00	61.00	52.50–73.00	0.812
Task supervision (BRIEF-2)	65.50	55.00–77.00	62.00	45.75–72.00	0.664
Organization of materials (BRIEF-2)	59.00	48.00–69.00	50.50	43.50–69.25	0.332
Behavioral regulation (BRIEF-2)	58.50	50.00–70.50	54.00	44.50–68.00	0.528
Emotional regulation (BRIEF-2)	59.50	50.50–73.00	57.50	52.75–74.25	0.967
Cognitive regulation (BRIEF-2)	72.00	56.50–78.00	64.50	52.25–73.25	0.243
Global Executive Function (BRIEF-2)	66.00	58.50–77.25	66.50	50.75–76.50	0.747
Inhibition (BRIEF-2)	55.0	46.00–64.00	55.50	45.00–65.25	0.989
Flexibility (BRIEF-2)	65.00	56.00–76.25	69.00	56.00–74.50	0.780
Leadership (BAS-2)	7.00	1.00–7.00	7.00	4.75–7.00	0.185
Social adaptation (ABAS-II)	75.00	69.50–87.00	89.00	76.00–97.25	0.024
Conceptual adaptation (ABAS-II)	74.00	57.00–85.50	82.00	70.00–100.25	0.133
Practical (ABAS-II)	79.00	67.00–91.50	82.50	72.25–104.25	0.331
General Adaptive Behavior (ABAS-II)	75.00	65.50–85.00	80.50	74.25–102.50	0.141
Communication (ABAS-II)	80.00	57.50–92.50	82.50	58.75–105.00	0.534
Academic skills (ABAS-II)	65.00	55.00–82.50	75.00	58.75–100.00	0.303
Self-Direction (ABAS-II)	80.00	62.50–90.00	100.00	78.75–106.25	0.20
Leisure (ABAS-II)	80.00	70.00–90.00	92.50	77.50–96.25	0.105
Social (ABAS-II)	70.00	60.00–95.00	95.00	75.00–107.50	0.054
Home life (ABAS-II)	95.00	85.00–105.00	100.00	80.00–106.25	0.828

TABLE 7 (Continued)

Variables	FXS group md	FXS group pc 25 - pc 75	Control group md	Control group pc 25 - pc 75	Significance
Health and security (ABAS-II)	85.00	75.00–102.50	97.50	82.25–111.25	0.216

Abbreviations: ABAS-II, Adaptive Behavior: Adaptive Behavior Assessment System-II; BNT, Boston Naming Test; BRIEF-2, Ecological measure of executive function: Behavioral assessment of executive function-2; FXS, Fragile X syndrome; Md, Median; NEPSY-II, Neuropsychological Battery for Children-II; Pc, Percentile; TOL = Tower of London; WISC-V, Wechsler Intelligence Scale for Children-V.

preserved skills within the neurocognitive profile of girls with FXS, and performance in the neurocognitive domains of executive function, quantitative reasoning, social perception, behavioral profile, adaptive behavior, and socialization style. In line with Mazzocco et al. (2002), in the sample analyzed it was found that half the girls with a diagnosis of FXS had an IQ > 85 and the other half had an IQ < 70.

The results obtained in our research suggest that language plays a fundamental role in many of the variables studied. First, the measure of expressive language, expressive vocabulary, and verbal abstraction were the only variables found to be related to verbal and total theory of mind in the social perception domain. This may be because in the Verbal Theory of Mind task the subjects had to make inferences about the situation described using verbal abstraction, given that the linguistic information provided about each situation had to be analyzed. To this effect, the results obtained agree with Raspa (Raspa et al., 2017), who describe expressive vocabulary as a relatively preserved skill of the profile of girls with FXS.

The results of this research also highlight the importance of the receptive language in the adaptive behavior domain. To this effect, in the FXS group an influence of the receptive vocabulary variable was found on the domains of social adaptation, conceptual adaptation and self-directed ability, and of the variable comprehension of instructions on the ability to self-direct. Regarding the adaptive behavior domain, which evaluates the degree of independence the person achieves in their daily life, the results show that a greater ability to understand instructions correlates with better independent self-management by not having to rely on the external guidance of a third person to perform daily tasks. While previous studies such as those carried out by Sterling and Abbeduto (2012) point to receptive vocabulary being a preserved skill in girls with FXS, they did not assess the possible relationship between this aspect and their level of autonomy to perform everyday tasks. Last, the only association found in the expressive language domain was between naming and academic skills. These results are in line with those of the study carried out by Shaffer, according to which, better adaptive skills and daily living skills are related to more intelligible speech (Shaffer et al., 2020).

Since the studies conducted by Hagerman (Kemper et al., 1986), which describe a pattern of difficulties in the arithmetic, digit span and block design subtests on the Wechsler Scales, several authors have described executive and visuo-spatial functions as affected domains in the cognitive profile of girls with FXS (Bartholomay et al., 2019), and it is accepted that impairments in mathematical processes are due to difficulties in visual function. However, in this study, an influence of the receptive and expressive processes of language was found on executive function, socialization style, and quantitative reasoning. Within the area of executive function, an influence of expressive vocabulary on auditory working memory, cognitive flexibility, inhibition, and processing speed was found, and an influence of comprehension of instructions was found on auditory working memory, cognitive flexibility, inhibition, and processing speed. From a developmental point of view, language is considered as a useful and indispensable tool for subjects' self-regulation (Stuss & Benson, 1986; Vygotsky, 1962). To this effect, it is logical to think that a better level of expressive vocabulary and comprehension of instructions helps the person to self-manage more effectively and be more skilled at regulating inhibition and cognitive flexibility using linguistic strategies, since a better ability to perceive, process, and execute oral instructions is helpful to better understand the instructions of any given task, thus allowing them to perform it better.

Regarding socialization style, a link was found between naming and leadership ability, and between receptive vocabulary and leadership ability. At the most basic level, children's language skills contribute to their ability to understand instructions for cognitive tasks (Fletchet, 2011). Lexicon is a domain of language (Hoover et al., 2011), so greater facility to access lexicon and a better understanding of vocabulary are factors that favor communicative exchange between people.

With respect to quantitative reasoning verbal abstraction, expressive vocabulary, and comprehension of instructions were all related to arithmetic skills. It was previously considered that impairments in mathematical reasoning, as described by other authors in girls with FXS, were due to greater difficulties at the level of visuo-spatial functions (Bartholomay et al., 2019; Raspa et al., 2017). Contrarily, the present study found an important influence of verbal abstraction and comprehension of instructions on the arithmetic component of the domain of quantitative reasoning. A possible explanation for this finding is that to correctly carry out the required mathematical calculation, the description of the problem must first be deciphered and correctly understood. No differences were found between groups in the Figure weights subtest of the quantitative reasoning area, which measures the reasoning process that can be expressed mathematically based on inductive or deductive logic. It is important to note that linguistic processes are given less weight in the Figure weights subtest, given that the information is presented visually, and the subject must simply select the correct answer from the several options given. Thus, contrary to the above, the results obtained lead us to think that the worse performance of the girls in the FXS group in the arithmetic task may be due to an impairment in the processing of linguistic information, rather than being solely an impairment in inductive-deductive mathematical reasoning. In short, the results obtained indicate that in

the FXS group, linguistic functions have a greater influence than expected on executive functions, quantitative reasoning, social perception, adaptive behavior, and style of socialization.

5 | LIMITATIONS

One of the limitations of this study is the relatively small sample size which made impossible to perform a control for multiple comparisons in the data analysis. However, and while only 26 girls with FXS participated, this is still the largest female child/youth sample to date in Spain and one of the largest in the world. Another limitation was the small number of participants in the control group. Nonetheless, no significant differences were found between the control variables IQ, age, ADHD symptoms, and SES in either group. Furthermore, while FXS in all the girls in the CG with an ID was ruled out by genetic analysis, there were no ethically justified grounds to carry out a genetic study on the girls without an intellectual disability. However, a clinical evaluation of the participants was made to assess whether they had symptoms compatible with the FXS (physical traits, cognitive behavioral characteristics) and the family history was collected, asking specifically for the existence of a family member with FXS. Participants' family history was collected by asking specifically about whether any family member had an FXS diagnosis. For the CG, the ID was idiopathic.

Last, given the results obtained, in future research it would be interesting to extend the present study to assess how other cognitive functions (visuo-spatial functions or executive functions) may influence adaptive behavior, social skills, and quantitative reasoning. A greater understanding of this relationship would allow us to identify which variables in the neurocognitive profile are most relevant in the degree of autonomy of girls with FXS in terms of their daily lives, providing the information needed to develop specific programs to train these skills thus promoting a higher level of autonomy.

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CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

Lorena Joga-Elvira: Conceptualization, methodology, formal analysis, validation, investigation, resources, data curation, writing, original draft preparation, writing—review and editing, visualization, funding acquisition, and project administration. Ana Roche-Martínez: Conceptualization, methodology, writing—review and editing. María-Luisa Joga: Conceptualization, methodology, writing—review and editing. Carlos Jacas-Escarcelle: Conceptualization, methodology, writing—review and editing. Carme Brun-Gasca.: Conceptualization, methodology, writing—review and editing.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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5.3. Artículo 3. "Fragile X Syndrome in Young Females: Influence of Executive Functions on the Neurocognitive Profile and Adaptive Behavior".

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Fragile X syndrome in young females: Influence of executive function on the neurocognitive profile and adaptive behavior

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ABSTRACT

Introduction: The aim of this study is to describe the relationship between executive function (EF) and performance in different areas of the neurocognitive profile in young girls with Fragile-X-Syndrome (FXS).
Method: A neuropsychological assessment was carried out to 40 female participants aged 7–16 years (26 FXS, 14 control group).
Results: Regarding intellectual ability, in the group of girls with FXS 3.84 % of the participants obtained IQ scores in the range of moderate ID (IQ 35–40 to 49), 46.15 % in the range of mild ID (IQ 50–70), 38.46 % in the borderline range (IQ 70–85), and 11.53 % within the average range (IQ > 85). EF was found to have a greater influence on adaptive behavior, arithmetic ability, theory of mind, leadership, social integration, social competence, and anxiety/shyness in the group with FXS.
Conclusions: In girls with FXS, EF showed a greater influence on adaptive behavior, arithmetic ability, and social domain.

What this paper adds?

This paper is one of the largest samples studied so far in our country (Spain) in girls with Fragile X Syndrome (FXS). The sample was collected all around the country to make it as representative as possible. It is one of the few researches that studies the relationship between executive function and adaptive behavior with girls with fragile X syndrome (FXS). The use of updated tests and questionnaires has allowed us to assess new aspects of the neurocognitive profile that had not been assessed until now, obtaining innovative results in relation to what has been described so far.

1. Introduction

Fragile-X-Syndrome (FXS) is a genetic condition associated with an alteration in the *FMR1* ("fragile X mental retardation 1") gene

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located in Xq27.3 (Bennetto, Pennington, Porter, Taylor, & Hagerman, 2001; Tassone, González-Teshima, Forero-Forero, Ayala-Zapata, & Hagerman, 2014). This alteration causes an expansion in the CGG trinucleotide repeats in the non-transcribed promoter region of the gene (Bunney, Zink, Holm, Billington, & Kotz, 2017; Bunney, Zink, Holm, Billington, & Kotz, 2017; Reches, 2019; Lozano, Rosero, & Hagerman, 2014), although cases of mutation in the gene itself have also occurred. It is the most common inherited cause of intellectual disability.

Depending on the number of repetitions there can be normal level (6–44 repetitions), grey zone level (45–54 repetitions), individuals carrying the premutation (55–200 repetitions), and individuals with the full mutation (>200 repetitions) (Reches, 2019).

Epidemiological studies report an estimated prevalence of FXS (full mutation) 1 in every 2,500 to 7,000 men and 1 in every 2,500 to 11,000 women (Bartholomay, Lee, Bruno, Lightbody, & Reiss, 2019). The premutation status of the *FMR1* gene prevalence estimates ranging between 1 in 148 and 1 in 204 for females and between 1 in 290 and 1 in 468 for males (Wheeler, Raspa, Hagerman, Mailick, & Riley, 2017).

Since FXS is a genetic condition linked to inheritance of the X chromosome, women tend to have a lower level of involvement and many of the investigations have focused on describing the cognitive-behavioral phenotype of affected men, leading to a lack of research in the study of this phenotype in females. In the vast majority of studies conducted on women, the samples collected focus on adulthood or have too wide age ranges, and were carried out in the 1990s and early 2000s (Cronister, Hagerman, Wittenberger, & Amiri, 1991; Cronister, Schreiner et al., 1991; Doco-fenzy et al., 2006; Grigsby, Kemper, Hagerman, & Myers, 1990; Hull & Hagerman, 1993; Keysor & Mazzocco, 2002; Simon, Keenan, Pennington, Taylor, & Hagerman, 2001; Thompson et al., 1994). Since then there have been advances and updates in cognitive and behavioral evaluation tools, enabling us to measure and describe cognitive-behavioral profiles much more specifically nowadays.

Regarding intellectual capacity, it has been described that approximately 50 % of females with FXS have an intellectual disability (ID) of varying degrees (between mild and moderate) and the other 50 % have an intellectual ability in the middle range (Keysor & Mazzocco, 2002). In one of the first studies conducted, the cognitive-behavioral profile of 23 women with FXS was analyzed and the results of the Wechsler Intelligence Scales showed a pattern characterized by an alteration in the subtests of Arithmetic, Span of Digits, and Block Design (Kemper, Hagerman, Ahmad, & Mariner, 1986).

In much of the research carried out to date, executive function (EF) is described as a domain of cognitive weakness in girls with FXS. EF is a construct that encompasses a set of skills needed to carry out a goal directed behavior. Among these skills there are Working Memory (skill required for the temporary storage of information for immediate use, often requiring the manipulation of this information); Inhibitory Control (ability to suppress an automatic response, and includes the control of interference, directed forgetting, and emotional control); Cognitive Flexibility (ability to adapt and change behavior based on the demands of the context); Attention (ability to fix, maintain or change the focus of attention and to divide selective attention between tasks); and Planning (ability to organize in advance and approach a task in a structured and efficient way) (Martin, Quintin, Hall, & Reiss, 2016; Schmitt, Shaffer, Hessl, & Erickson, 2019).

In another investigation (Mazzocco, Hagerman, Cronister-Silverman, & Pennintong, 1992), the neurocognitive phenotypes of 30 women (10 diagnosed with FXS, 10 carriers of the premutation, and 10 negative FXS) were studied and an executive dysfunction profile was described in the group of women with FXS characterized by perseverative thinking and difficulties in maintaining attitude, formation of abstract concepts, and planning.

Borghgraef, Umans, Steyaert, Legius, and Fryns (1996) studied a sample of 9 girls aged between 7 and 15 years (5 FXS full mutation, 1 with premutation, and 3 FXS negative). The results confirmed lower intellectual quotient (IQ) scores in girls with FXS (three of them obtained an IQ < 80) and an alteration in attention skills, visual memory, and analysis capacity. In contrast, the psychiatric evaluation did not detect a higher incidence of behavioral problems compared to the control group (CG). These results should be interpreted with caution due to the small sample size.

In another study carried out at the beginning of the 21 st century (Keenan & Simon, 2004), a sample of 50 women aged between 18 and 58 years old was studied (16 negative FXS, 12 with FXS full mutation, and 22 with premutation) finding that women with FXS obtained significantly lower IQ scores. Likewise, the results obtained suggest a deficit in verbal working memory in the group of women with FXS. Along similar lines, in an extensive review it was found that perseverative errors are the most consistent alteration in the profile of women with FXS (Schmitt et al., 2019).

Other authors have studied the cognitive profile of 8-year-old girls with FXS (n = 12) and Turner Syndrome (n = 20), describing a characteristic profile in girls with FXS that consists in an alteration in cognitive flexibility and working memory (WM) not attributable to their IQ (Kirk, Mazzocco, & Kover, 2005).

In the only research found on the role of EF in skills for independent living in adolescents and young adults females with FXS (n = 18) and Turner Syndrome (n = 16), no significant differences were found between the two groups, and the conclusion drawn that worst performance in the tasks used to assess EF is attributable to their IQ and not to the fact of presenting the FXS condition. Despite not finding significant differences between the groups, it was concluded that EF (and specifically phonetic verbal fluency), are related to the basic skills for daily life (Martin et al., 2016).

Given that in the reviewed literature numerous authors agree to point to EF as a domain of relative weakness in the profile of women with FXS, the current study was undertaken with the aim of describing the relationship between EF and level of performance in the following areas of the neurocognitive profile: linguistic functions, quantitative reasoning, social perception, social skills profile, and adaptive behavior.

The work was designed based on three hypotheses:

1) Better performance in some EF tasks implies better performance in certain linguistic and quantitative reasoning tasks. This relationship will occur in a different way depending on the presence of the FXS diagnosis.
2) Better performance in some EF tasks implies better performance in certain social perception or social skills tasks. This relationship will occur in a different way depending on the presence of the FXS diagnosis.
3) Better performance in some EF tasks implies better scores in some aspects of adaptive behavior. This relationship will occur in a different way depending on the presence of the FXS diagnosis.

2. Method

The current research is the continuation of a previous investigation in which the relationship between linguistic functions and social perception, quantitative reasoning, and adaptive behavior was investigated. It had the approval of the Parc Tauli Hospital's Ethics Committee (reference 2016595).

The Parc Taulí Hospital, Spanish FXS Federation, different associations of patients with FXS (Catalonia, Basque Country, Madrid, and Valencia), and patients with genetic diseases (D'Genes Murcia) collaborated in the dissemination of the project to facilitate the recruitment of participants. Likewise, a call was made via professional social networks such as Linked-In and emails sent to the psychopedagogical advisory teams in the area and to the special education colleges.

Informed consent was obtained from the legal guardians of all the participants. The tests to be performed on the young girls and adolescents were also explained. If they had refused to perform the tests, the evaluation would not have been carried out. All of them verbally agreed to perform the tests.

2.1. Participants

A total of 40 females participated in the study (n = 40). The inclusion and exclusion criteria are summarized in Table 1. Participants were aged between 7 and 16, and were divided into 2 groups (Table 2):

1) FXS Group: n = 26.
2) Control group (CG): n = 14.

2.2. Procedure

The sessions to evaluate the participants from the metropolitan area of Barcelona were held at the Parc Taulí Hospital. Regarding the participants from other Autonomous Communities, the principal investigator travelled to their hometowns to carry out the assessment in order to create as little inconvenience for them and their families as possible. The participating communities were Catalonia, Madrid, the Basque Country, Galicia, Valencia, and Murcia.

First, an explanatory document about the project was drafted, and sent to the associations of affected patients who were responsible for their dissemination among families. Where there were families interested in collaborating, a few days were organized when the principal investigator traveled to the Autonomous Community to carry out the evaluations in the facilities provided by the associations. The assessments were carried out in three separate one-hour sessions to ensure that participants did not become overtired.

2.3. Measures and scales

The following aspects of executive function were used as independent variables: Visual Working Memory (WISC-V. Picture Span subtest), Auditory Working Memory (WISC-V. Digits and Letters and Numbers subtest) (Wechsler, 2015); Auditory Attention (NEPSY-II. Auditory Attention subtest), Cognitive Flexibility (NEPSY-II. Cognitive Flexibility subtest, total correct), Inhibition (NEPSY-II. Inhibition subtest, total correct), (Korkman, Kirk, & Kemp, 2014); Cognitive Flexibility (Wisconsin Card Storing Test. Learning to learn) (Heaton, Chelune, Talley, Kay, & Curtiss, 2009); Problem Solving (Tower of London. Total Correct), Problem Solving Efficiency (Tower of London. Total Move), and Breaking Rules (Tower of London. Total Rule Violation) (Culbertson & Zillmer, 2005). Behavioral assessment of executive function-2 (BRIEF-2), parents' version, was used as an ecological measure of executive function (Gioia, Isquith, Guy, & Kenworthy, 2017).

For the cognitive variables, the Wechsler Intelligence Scale for Children-V (Wechsler, 2015) was used to assess General Cognitive Ability, Expressive Vocabulary (Vocabulary Subtest), and Quantitative Reasoning (Figure Weights and Arithmetic subtest). Some of the NEPSY-II subtest were used to Semantic Verbal Fluency (Fluency subtest), Phonological Processing (Phonological Processing subtest), Comprehension of Instructions (Comprehension Instructions subtest), Emotion Recognition (Emotion Recognition subtest), and Theory of Mind (Theory of Mind subtest) (NEPSY-II, Korkman et al., 2014). Comprehensive Vocabulary, and naming were assess using the Peabody Picture Vocabulary Test (Dunn & Dunn, 2006), and the Boston Naming Test (Kaplan, Goodglass, & Weintraub, 2005) respectively.

The following questionnaires and scales were used to assess the behavioral variables: Child and Adolescent Evaluation System (SENA), parents' version, for the assessment of emotional and behavioral problems, contextual problems, areas of vulnerability, and psychological resources (Fernández-Pinto, Santamaría, Sánchez-Sánchez, Carrasco, & del Barrio, 2015); ADHD Rating Scale (parents' version) to assess the ADHD Symptomatology (DuPaul et al., 1998); Battery of socialization (BAS-2), parents' version, to asses four domains facilitating socialization (leadership, joviality, social sensitiveness, and respect-self-control), three domains that disrupt

Table 1
Inclusion and exclusion criteria for the FXS and CG.

	INCLUSION CRITERIA	EXCLUSION CRITERIA
FXS GROUP	Female Age between 7 and 16 years old FXS diagnosis confirmed by genetic study (> 200 repetitions).	Comorbidity of an autism spectrum disorder or attention deficit with hyperactivity disorder Absence of expressive language Acquired neurological disorders (epilepsy, head trauma)
CG	Female Age between 7 and 16 years old Matched in age and IQ with FXS group	Meet diagnostic criteria for an autism spectrum disorder or attention deficit hyperactivity disorder Absence of expressive language Acquired neurological disorders (epilepsy, head trauma) In the case of participants without intellectual disability: have a family history of FXS and presenting symptoms clinically compatible with a FXS diagnosis.

FXS = Fragile X Syndrome. CG = control group. IQ = intelligence quotient.

Table 2
Descriptive measures and distribution of age, IQ, ADHD Symptoms, and socioeconomical status.

Variables	FXS Group n = 26	Control Group n = 14	Significance
Age			
M (SD)	10.58 (3.384)	10.50 (2.345)	0.940
IQ			
M (SD)	71.50 (14.795)	76.36 (16.80)	0.351
ADHD symptoms			
M (SD)	81.54 (4.341)	68.29 (6.984)	0.104
Socioeconomical status			0.211
Low	3.8 %	16.7 %	
Medium	88.5 %	75 %	
High	7.7 %	8.3 %	

FXS = Fragile X Syndrome. IQ = intelligence quotient. ADHD = Attention Deficit Hyperactivity Disorder. M = mean. SD = standard deviation.

socialization (aggressiveness-obstinacy, apathy-withdrawnness, and anxiety-shyness), and a global social adaptation or criterial-socialization scale (Silva & Martorell, 2018); and Adaptative Behavior Assessment System- Second Edition Spanish version (ABAS-II), parents' version, as a measure of Adaptive Behavior (Harrison & Oakland, 2013).

The direct scores for all the cognitive functioning tests and for the ABAS-II were converted into standard scores with a mean of 100 and standard deviation of 15. The direct scores for the SENA and BRIEF-2 were converted into standard scores with a mean of 50 and standard deviation of 10, and the direct scores for the ADHD Rating Scale were converted into percentile scores.

2.4. Statistical analysis

A statistical analysis was performed with the SPSS Statistics for Windows software, Version 25.0. The Students *t*-test was used to compare the variables of the control groups, age and IQ. The comparison of the variables related to cognitive and linguistic skills and those related to behavior between the control group and the FXS group was performed using the Mann-Whitney *U* test because of a non-normal distribution of the data. The association between the cognitive and behavioral functioning variables was examined using Pearson linear regression, controlling for group effect. If this was not significant, it was removed from the model.

Table 3
Results of linear regression of social domain as dependent variable vs group and executive function as independent variables.

	Verbal Theory of mind	Total theory of mind	Leadership	Social sensitivity	Anxiety shyness	Social anxiety	Social competence integration
Verbal abstraction	$r^2 = 0.30$ p = 0.03* β -0.947	$r^2 = 0.311$ p = 0.026* β -7.169	$r^2 = 0.250$ p = 0.009** β -10.897	$r^2 = 0.159$ p = 0.011* β -22.539	$r^2 = 0.095$ p = 0.048* β 16.106	$r^2 = 0.217$ p = 0.006** β 7.842	$r^2 = 0.062$ p = 0.052 β -8.978
Self-supervision	$r^2 = 0.012$ p = 0.124 β -5.758	$r^2 = 0.019$ p = 0.107 β -6.067	$r^2 = 0.116$ p = 0.043* β -9.045	$r^2 = 0.217$ p = 0.025* β -18.977	$r^2 = 0.071$ p = 0.045* β 16.574	$r^2 = 0.207$ p = 0.006** β 7.885	$r^2 = 0.142$ p = 0.057 β-8.399
Working memory	$r^2 = 0.185$ p = 0.130 β -5.135	$r^2 = 0.163$ p = 0.121 β -5.373	$r^2 = 0.348$ p = 0.023* β -8.761	$r^2 = 0.095$ p = 0.02* β -21.236	$r^2 = 0.222$ p = 0.036* β 15.795	$r^2 = 0.184$ p = 0.006** β 8.104	$r^2 = 0.120$ p = 0.05* β -8.755
Planning	$r^2 = 0.209$ p = 0.140 β -4.936	$r^2 = 0.168$ p = 0.131 β -5.233	$r^2 = 0.229$ p = 0.038* β -8.633	$r^2 = 0.093$ p = 0.022* β -20.953	$r^2 = 0.111$ p = 0.047* β 16.008	$r^2 = 0.150$ p = 0.006** β 8.273	$r^2 = 0.062$ p = 0.051 β -9.019
Materials organization	$r^2 = 0.013$ p = 0.133 β -5.637	$r^2 = 0.016$ p = 0.116 β -5.937	$r^2 = 0.084$ p = 0.043* β -9.225	$r^2 = 0.153$ p = 0.029* β -19.217	$r^2 = 0.133$ p = 0.056 β 15.278	$r^2 = 0.247$ p = 0.007** β 7.638	$r^2 = 0.165$ p = 0.063 β -8.111
Behavioral Regulation	$r^2 = 0.012$ p = 0.128 β -5.710	$r^2 = 0.017$ p = 0.111 β -6.011	$r^2 = 0.148$ p = 0.044* β -8.825	$r^2 = 0.244$ p = 0.025* β -18.686	$r^2 = 0.111$ p = 0.05* β 15.846	$r^2 = 0.17$ p = 0.006** β 8.054	$r^2 = 0.245$ p = 0.055 β -7.964
Cognitive flexibility	$r^2 = 0.056$ p = 0.073 β -6.792	$r^2 = 0.038$ p = 0.077 β -6.826	$r^2 = 0.145$ p = 0.018* β -10.782	$r^2 = 0.082$ p = 0.027* β -20.800	$r^2 = 0.273$ p = 0.046* β 13.735	$r^2 = 0.139$ p = 0.011* β 7.447	$r^2 = 0.134$ p = 0.042* β -9.293
Violation rule	$r^2 = 0.392$ p = 0.237 β -3.523	$r^2 = 0.366$ p = 0.212 β -3.833	$r^2 = 0.362$ p = 0.049* β -7.625	$r^2 = 0.086$ p = 0.026* β -20.781	$r^2 = 0.071$ p = 0.051 β 16.478	$r^2 = 0.181$ p = 0.007** β 8.138	$r^2 = 0.09$ p = 0.049* β -9.154
Attitude maintenance	$r^2 = 0.012$ p = 0.132 β -5.728	$r^2 = 0.016$ p = 0.121 β -5.940	$r^2 = 0.100$ p = 0.021* β -10.587	$r^2 = 0.106$ p = 0.016* β -22.281	$r^2 = 0.112$ p = 0.020* β 19.150	$r^2 = 0.164$ p = 0.004** β 8.798	$r^2 = 0.231$ p = 0.008** β -11.643

$p \leq 0.05$*; $p \leq 0.01$**; $p \leq 0.001$***.

Table 4
Results of linear regression of adaptive behavior as dependent variable vs group and executive function as independent variables.

	Self -Direction	Social Adaptation	Conceptual adaptation
	$r^2 = 0.361$	$r^2 = 0.30$	$r^2 = 0.175$
Inhibitory control	$p = 0.006^{**}$	$p = 0.021^{*}$	$p = 0.088$
	β -15.278	β -11.015	β -8.555
	$r^2 = 0.322$	$r^2 = 0.357$	$r^2 = 0.245$
Self-supervision	$p = 0.022^{*}$	$p = 0.05^{*}$	$p = 0.162$
	β -12.945	β -8.863	β -6.696
	$r^2 = 0.41$	$r^2 = 0.212$	$r^2 = 0.149$
Emotional Control	$p = 0.002^{**}$	$p = 0.021^{*}$	$p = 0.073$
	β -16.453	β -11.637	β -9.155
	$r^2 = 0.354$	$r^2 = 0.216$	$r^2 = 0.363$
Working Memory	$p = 0.013^{*}$	$p = 0.046^{*}$	$p = 0.104$
	β -13.700	β -9.955	β -7.157
	$r^2 = 0.293$	$r^2 = 0.134$	$r^2 = 0.366$
Planning	$p = 0.022^{*}$	$p = 0.058$	$p = 0.136$
	β -13.292	β -9.904	β -6.540
	$r^2 = 0.347$	$r^2 = 0.252$	$r^2 = 0.275$
Organization of materials	$p = 0.027^{*}$	$p = 0.07$	$p = 0.192$
	β -12.278	β -8.823	β -6.124
	$r^2 = 0.354$	$r^2 = 0.249$	$r^2 = 0.24$
Cognitive flexibility	$p = 0.006^{**}$	$p = 0.019^{*}$	$p = 0.043^{*}$
	β -16.117	β -11.951	β -10.098

$p \leq 0.05^{*}$; $p \leq 0.01^{**}$; $p \leq 0.001^{***}$.

Table 5
Variables: central tendency and variability.

Variables	FXS Group M (SD)	FXS Group CI 95 %	Control Group M (SD)	Control Group CI 95 %
Intelligent Quotient (WISC-V)	71.50 (14.795)	(65.52–77.48)	76.36 (16.80)	(66.66–86.06)
Auditory Working Memory (WISC-V)	61.46 (2.797)	(55.70–67.22)	70.36 (4.891)	(59.79–80.92)
Cognitive flexibility (NEPSY-II)	72.08 (3.105)	(65.68–78.47)	91.29 (5.059)	(80.36–102.22)
Inhibition (NEPSY-II)	66.36 (3.218)	(59.72–73.00)	84.71 (4.534)	(74.92–94.51)
Auditory attention (NEPSY-II)	78.65 (3.515)	(71.41–85.89)	90.43 (4.613)	(80.46–100.40)
Problem solving (TOL)	78.92 (2.902)	(72.93–84.91)	84.29 (4.659)	(74.22–94.35)
Verbal Theory of mind (NEPSY-II)	74.69 (1.734)	(71.12–78.26)	80.43 (3.719)	(72.39–88.46)
Total Theory of mind (NEPSY-II)	73.42 (1.726)	(69.87–76.98)	79.36 (3.772)	(72.21–87.51)
Arithmetic (WISC-V)	71.27 (2.799)	(65.51–77.03)	77.93 (3.128)	(71.17–84.69)
ADHD Symptoms (Rating Scale)	81.54 (4.341)	(72.60–90.48)	68.29 (6.984)	(53.20–83.37)
Self-supervision (BRIEF-2)	58.23 (3.142)	(51.76–64.70)	55.14 (3.596)	(47.37–62.91)
Emotional control (BRIEF-2)	54.19 (2.393)	(49.26–59.12)	55.86 (3.167)	(49.01–62.70)
Initiative (BRIEF-2)	68.00 (2.418)	(63.02–72.98)	61.43 (3.937)	(52.92–69.93)
Working memory (BRIEF-2)	66.04 (2.285)	(61.33–70.74)	64.36 (3.860)	(56.02–72.70)
Organization planning (BRIEF-2)	62.27 (2.028)	(58.09–66.45)	60.36 (3.632)	(52.51–68.20)
Task supervision (BRIEF-2)	65.81 (2.632)	(60.39–71.23)	59.43 (3.664)	(51.51–67.34)
Organization of materials (BRIEF-2)	58.31 (2.330)	(53.51–63.11)	55.14 (3.964)	(46.58–63.71)
Behavioral regulation (BRIEF-2)	59.62 (2.524)	(54.42–64.81)	56.86 (3.630)	(49.02–64.70)
Emotional regulation (BRIEF-2)	61.12 (2.885)	(55.17–67.06)	67.79 (3.248)	(54.77–68.80)
Cognitive regulation (BRIEF-2)	67.65 (2.322)	(62.87–72.44)	62.29 (3.605)	(54.50–70.07)
Global Executive Function (BRIEF-2)	66.35 (2.510)	(61.18–71.52)	64.36 (4.123)	(55.45–73.26)
Inhibition (BRIEF-2)	56.23 (2.209)	(51.68–60.78)	56.64 (3.393)	(49.31–63.97)
Flexibility (BRIEF-2)	64.62 (2.897)	(58.65–70.58)	66.00 (3.497)	(58.38–73.62)
Leadership (BAS-2)	7.76 (1.476)	(4.71–10.81)	17.43 (5.194)	(6.21–28.65)
Social Sensitivity (BAS-2)	25.60 (25.536)	(15.06–36.14)	46.64 (25.925)	(31.67–61.61)
Anxiety-Shyness (BAS-2)	76.96 (19.584)	(68.88–85.04)	59.93 (29.379)	(42.97–76.89)
Social Anxiety (SENA)	65.62 (8.476)	(62.19–69.04)	57.29 (8.1)	(52.61–61.96)
Social Competence Integration (SENA)	31.42 (10.47)	(27.19–35.65)	40.64 (17.522)	(30.53–50.76)
Social adaptation (ABAS-II)	77.08 (3.028)	(70.83–83.33)	87.86 (4.359)	(78.44–97.27)
Conceptual adaptation (ABAS-II)	73.64 (3.152)	(67.14–80.14)	82.00 (4.217)	(72.89–91.11)
General Adaptive Behavior (ABAS-II)	76.16 (3.260)	(69.43–82.89)	84.29 (4.565)	(74.42–94.15)
Self-Direction (ABAS-II)	78.60 (3.691)	(70.98–86.22)	93.57 (4.929)	(82.92–104.22)

FXS = Fragile X Syndrome. CI = Confidence Interval. M = mean. SD = standard deviation. WISC-V = Wechsler Intelligence Scale for Children-V. NEPSY-II = Neuropsychological Battery for Children-II. TOL = Tower of London. BRIEF-2 = Ecological measure of executive function: Behavioral assessment of executive function-2. ABAS-II: Adaptive Behavior: Adaptive Behavior Assessment System-II. BNT = Boston Naming Test.

3. Results

Regarding intellectual ability, in the group of girls with FXS 3.84 % of the participants obtained IQ scores in the range of moderate ID (IQ 35–40 to 49), 46.15 % in the range of mild ID (IQ 50–70), 38.46 % in the borderline range (IQ 70–85), and 11.53 % within the average range (IQ > 85).

Once the comparison of means was performed using the Student's *t*-test, no statistically significant differences were found between the control variables, age, IQ, ADHD symptoms and socioeconomical status (Table 2). There were significant differences between groups in the relationship between some of the variables of the domains evaluated.

Statistically significant differences were found between groups in the social domain (Social Perception and Social Skills). Compared to the CG, the FXS group presented a greater influence of some EF on certain social skills: verbal abstraction ability and verbal theory of mind ($p = 0.03$; $r^2 = 0.30$), ability of verbal abstraction and total theory of mind ($p = 0.026$; $r^2 = 0.311$), ability of verbal abstraction and leadership ($p = 0.009$; $r^2 = 0.25$); capacity for self-supervision and social sensitivity ($p = 0.025$; $r^2 = 0.217$); WM and leadership ($p = 0.023$; $r^2 = 0.348$), WM and anxiety/shyness ($p = 0.036$; $r^2 = 0.222$); planning/organization and leadership ($p = 0.038$; $r2 = 0.229$); materials organization and social anxiety ($p = 0.007$; $r^2 = 0.247$); emotional regulation and social integration/competence ($p = 0.023$; $r^2 = 0.244$); emotional regulation and anxiety/shyness ($p = 0.022$; $r^2 = 0.232$); behavioral regulation and social sensitivity ($p = 0.025$; $r^2 = 0.244$); cognitive flexibility and anxiety/shyness ($p = 0.046$; $r^2 = 0.273$); follow the rules and leadership ($p = 0.049$; $r^2 = 0.362$); attitude maintenance and social integration/competence ($p = 0.008$; $r^2 = 0.231$) (Table 3).

Regarding the adaptive behavior domain, statistically significant differences were found between groups, and the group of girls with FXS was the one that presented a greater influence of some of the EF on the following adaptive behavior skills: inhibitory control and self-direction skills ($p = 0.006$; $r^2 = 0.361$) and social adaptation ($p = 0.02$; $r^2 = 0.30$); self-supervision ability and self-direction skills ($p = 0.022$; $r^2 = 0.322$) and social adaptation ($p = 0.05$; $r^2 = 0.357$); emotional control ability and self-direction skills ($p = 0.002$; $r^2 = 0.41$) and social adaptation ($p = 0.02$; $r^2 = 0.212$); WM and self-direction skills ($p = 0.013$; $r^2 = 0.354$) and social adaptation ($p = 0.046$; $r^2 = 0.216$); planning/organization capacity and self-direction ability ($p = 0.022$; $r^2 = 0.293$); capacity materials organization and self-direction ability ($p = 0.027$; $r^2 = 0.347$); emotional regulation and social adaptation ($p = 0.023$; $r^2 = 0.277$); behavioral regulation and social adaptation ($p = 0.043$; $r^2 = 0.442$); cognitive flexibility and self-direction ($p = 0.006$; $r^2 = 0.354$); cognitive flexibility and social adaptation ($p = 0.019$; $r^2 = 0.249$) and cognitive flexibility; and conceptual adaptation ($p = 0.043$; $r^2 = 0.24$) (Table 4).

Likewise, in the quantitative reasoning domain the group of girls with FXS presented a significantly greater influence of the ability of verbal abstraction on arithmetic ability ($p = 0.021$; $r^2 = 0.412$; β -8.436). Last, no statistically significant differences were found between the groups when analyzing the influence of EF on language skills.

Variables of interest, including central tendency and variability, are summarized in Table 5.

4. Discussion

The aim of our research was to study the relationship between EF and performance in the domains of language, social perception, quantitative reasoning, behavioral profile, and adaptive behavior. The results obtained indicate that the ability of verbal abstraction, follow the rules, WM, planning/organization, self-supervision, behavioral and emotional regulation, cognitive flexibility, material organization, and inhibition are the EF that play an important role in some of the variables studied. This relationship is more relevant in the group of girls with FXS.

First, we found a relationship between the ability of verbal abstraction and theory of mind (verbal and total) of the social perception domain, and this influence was greater in the FXS group. In the case of verbal theory of mind, this relationship may be due to the fact that in the task presented, inferences had to be made about the suggested scenario through the use of the capacity of verbal abstraction, given that the information needed to analyze each situation was provided verbally. On the other hand, in the Total Theory of Mind subtest, the stimuli were presented verbally and visually. However, when calculating a standardized score, the scales only allowed us to obtain a total score that encompasses verbal and visual items. If, despite including visual stimuli in the Total Theory of Mind task, an influence of the ability of verbal abstraction were to continue, it would follow that the verbal component has an important weight. To this effect, the author of this paper agrees with previous research that described language as a preserved skill in the cognitive profile of girls with FXS (Raspa, Wheeler, & Riley, 2017).

In the previous scientific literature, the alterations in mathematical reasoning typically described in girls with FXS were considered to be secondary to the visual-spatial alterations (Bunney et al., 2017a, 2017b; Bartholomay et al., 2019; Kemper et al., 1986). In the group of girls with FXS, in this investigation a strong association between the ability of verbal abstraction and the arithmetic variable of the Quantitative Reasoning domain was found. No differences were found between groups when analyzing the relationship between the ability of visual abstraction (subtest Matrix Reasoning) and the ability to perform mathematical reasoning based on inductive or deductive logic (subtest Figure Weights) and arithmetic (arithmetic subtest). Once other cognitive processes involved in the arithmetic test, such as WM, had been ruled out, a strong influence of the ability of verbal abstraction on arithmetic ability was found. An explanation could be that, to do the required arithmetic calculation correctly, it is necessary to be able to analyze and abstract the information of the statement presented orally. Thus, the results obtained lead us to state that the worse execution in the arithmetic task of the girls in the group with FXS may be due to an alteration in the capacity for verbal abstraction, rather than a pure alteration of mathematical reasoning.

Regarding the behavioral domain and style of socialization, differences between the groups were found, with the group of girls with FXS showing a greater influence of some of the EF on certain behavioral variables. A better capacity for verbal abstraction and

following the rules was observed to be related to greater leadership ability. Similarly, was found that a worse skill in WM and in planning/organization has a negative impact on leadership capacity. It is logical to think that girls with a better ability to process information in a more abstract way and with a good performance in WM can present a greater facility to understand verbal communication, keeping this information in their mind for the time required to be able to process it and understand it correctly. Likewise, if they can follow the established rules and have a good ability to plan, they can become a role model among their partners. These factors may make it easier for them to be considered as a role model by their peers. Along the same lines, we observe that a low ability of self-supervision and regulating one's own behavior is related to a low level of social sensitivity. The ability to self-supervision is essential to be aware of mistakes and correct them. This difficulty in detecting mistakes can lead to the mismanagement of behavioral regulation, which could be interpreted as a lack of social sensitivity, due to the inability to adapt one's behavior to social demands.

It was also found that worse emotional regulation and cognitive flexibility leads to higher levels of anxiety and shyness and that worse performance in WM is related to lower levels of anxiety and shyness. Both cognitive flexibility and emotional regulation are important to achieve a good level of social acceptance given that they allow us to adapt to the demands of the environment. Presenting difficulties in these skills can lead to conflicts in social situations, which could trigger a higher level of anxiety in response to a situation of stress and a subsequent tendency to shyness as a defense mechanism to try not to expose oneself to a stressful, conflictive situation. Contrarily, a low capacity for WM entails greater difficulty in identifying the mistakes made and therefore a lower awareness of these errors. This lack of awareness of the mistakes made means a lower level of anxiety and shyness. In an earlier study it was found that women with FXS need a greater number of trials for memory consolidation (Keysor & Mazzocco, 2002). WM is essential for the generation of medium and long-term memories. An explanatory hypothesis would be that a low ability in WM makes it difficult to consolidate information and generate memories. Thus, the subject would be less aware of their difficulties with social interaction and, therefore, a lower anticipatory anxiety response generated, which in turn would lead to a less intense defense mechanism and a lower degree of shyness. Given the novelty of these findings and the lack of prior literature in this regard, new research is needed on the possible relationship between WM and anxiety in girls with FXS.

Another noteworthy aspect is that a worse ability to organize materials is related to higher levels of social anxiety, and that a good ability to maintain one's attitude and good emotional regulation positively influence social skills and the ability to be socially integrated. Girls with a greater ability to regulate their emotions, maintain their attitude, and be constant in what they are doing have a higher level of social acceptance given that these skills improve their social competence and therefore their ability to integrate.

Regarding adaptive behavior, it was found that a better ability of verbal abstraction has a positive impact on the domain of conceptual adaptation. This domain is composed of academic, communication, and self-management skills. A better performance in verbal abstract reasoning is essential to organize thinking through language, which results in an improvement in self-direction. Likewise, being able to process verbal information in a more abstract way favors communication since it helps with interpreting double meanings and irony. Along the same lines, a good capacity for verbal abstraction is essential to identify the important information in a text, understand statements, mathematical reasoning, metaphors, and so on, which are all aspects closely linked to academic performance. Similarly, a better capacity for inhibition, self-supervision, emotional control and WM has a positive impact on the degree of social adaptation and the capacity for self-direction. Both the ability to suppress an automatic response and environmental distractions, and emotional control and self-criticism (self-supervision) are skills that help us adapt to the demands of the environment. Consequently, the more able a subject is to adapt to these demands, the greater the level of adaptation they will achieve.

Furthermore, girls with better organizational skills (planning/organization and materials organization) showed a greater capacity for self-direction given that they had less need to depend on another person to help them manage and plan their objectives, making them more autonomous in their daily lives. It was also observed that a higher level of emotional and behavioral regulation leads to a better social adaptation. The more a subject is able to regulate their emotions and the more skillful their behaviors, the better they will be adapted to social demands and show greater autonomy at the social level. Similarly, greater cognitive flexibility improves the capacity for self-direction, social adaptation, and conceptual adaptation. The ability to switch between mental states, operations or tasks is one of the most important EF to adapt to the changing environment.

It should be noted that, within the extensive exploration carried out, the tests administered in-office were not very sensitive by themselves when predicting the social development or the degree of autonomy of the participants. Of all the assessment carried out, the only relations found were with the subtest of Similarities of the WISC-V, the rule violation of the Tower of London, and the maintenance of attitude of the WCST (parameters that measure basic skills for functional adaptation). In contrast, BRIEF-2 has proven to be the most sensitive test for predicting girls' social development and degree of autonomy, reinforcing the fact that it is the most ecologically valid test for assessing EF. Thus, it is essential to make a summary of the information extracted from the developmental history, tests and behavioral questionnaires to make a thorough cognitive behavioral assessment.

4.1. Strengths and limitations

One of the limitations of this study is the relatively small sample size. While only 26 girls with FXS participated, this is still the largest sample of young females collected to date in Spain, and one of the largest worldwide. The person responsible for conducting the cognitive assessments spent 4 years traveling to different parts of Spain to recruit as many participants as possible.

Another limitation is the small number of participants in the control group. Nonetheless, no significant differences were found between the IQ control variables and age in either group. While all the girls in the CG with an intellectual disability had a genetic analysis that ruled out the FXS, in the case of the girls without an intellectual disability the genetic study was not carried out for ethical reasons. However, a clinical evaluation of the participants was made to assess whether they had symptoms compatible with FXS (physical traits, cognitive-behavioral characteristics) and the family history was collected asking specifically if they had a family

member with FXS.

Last, given the results obtained, in future research it would be interesting to assess the influence of other cognitive functions such as visospatiality / visoconstruction on adaptive behavior, social skills and quantitative reasoning, and also to assess the relationship found between WM and the level of anxiety and the shyness in females with FXS in greater depth.

Data availability statement

Data Availability Statement The data that support the findings of this study are available on request from the corresponding author. The data are not public available due to privacy or ethical restrictions.

CRediT authorship contribution statement

Lorena Joga-Elvira: Conceptualization, Methodology, Formal analysis, Validation, Investigation, Resources, Data curation, Writing - original draft, Writing - review & editing, Visualization, Funding acquisition, Project administration. **Carlos Jacas:** Conceptualization, Methodology, Writing - review & editing. **María Luisa Joga:** Conceptualization, Methodology, Writing - review & editing. **Ana Roche-Martínez:** Conceptualization, Methodology, Writing - review & editing. **Carme Brun-Gasca:** Conceptualization, Methodology, Writing - review & editing.

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5.4. Artículo 4. "Bullying Victimization in Young Females with FragileX-Syndrome".

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Article

Bullying Victimization in Young Females with Fragile-X-Syndrome

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Abstract: The aim of this study is to investigate the risk associated with girls with fragile X syndrome (FXS) suffering bullying in the role of a victim and its effects on their adaptive behavior, socialization style, and emotional state. A neuropsychological assessment was carried out on a sample of 40 participants (26 FXS positive and 14 control group) using the following instruments: WISC-V, SENA, BAS-2, ABAS-II. The results show that the group of girls with FXS presented higher ratios of lack of social support and isolation from classmates. This finding suggests that problems with social interaction and communication in the group of girls with FXS could lead to difficulties in interpreting social signals and identifying situations of bullying correctly, placing them in a very vulnerable situation.

Keywords: fragile X syndrome; young females; bullying; behavior

1. Introduction

Different definitions of bullying can be found in the scientific literature. In a recent study by Hellström and Beckman [1], bullying was defined as repetitive aggressive behaviors with harmful or hurtful intent and including some form of power imbalance between those involved [2]. It can take the form of direct verbal or physical aggression, relational aggression such as rumor spreading, or gossiping, either online or offline [3]. Bullying can be either direct or indirect. Direct bullying consists of physical and verbal forms of intentional negative behaviors. Indirect or relational bullying comprises exclusion or social isolation, lying, talking behind ones' back, spreading rumors, or manipulating relationships [4].

Three main roles with the following characteristics have been defined within bullying: bully or perpetrator (easily frustrated, has positive attitude toward violence, impulsive, sees threats where none exist); victim (insecure, may believe that he or she deserves to be teased/taunted and harassed, perceived as weak or different, socially isolated, unassertive); and bully-victim (prone to irritating others and creating tension socially, quick tempered and emotionally reactive, reacts to being bullied with provocation, fighting back, and then may claim self-defense) [5].

The 2019 UNESCO report [6] warns that school violence and bullying are serious global problems among the general population. It is estimated that 15.4% of school children in Spain have suffered

bullying. The Save the Children in Spain report finds that 39.65% of children have been involved in a situation of bullying during their childhood. Of these, 27.43% have experienced bullying between one and three times. Regarding the consequences of having been involved in bullying, numerous studies have reported that it can have a significant impact on mental health (anxiety and depression symptomatology, risk of suicide, suicide ideation), quality of life (sleeping problems), risky behavior, and reduced academic performance and chance of future employment [7–10].

Regarding the population with intellectual disabilities (ID), Maïano et al. [4] found that youths with ID are involved in bullying more frequently not only as victims (36.3%) but also as perpetrators (15.1%) and perpetrator-victims (25.2%). The study reported that this victimization can take different forms: verbal (50.2%), physical (33.3%), relational (37.4%), or cyber (38.3%). Their results showed that the perpetrator prevalence ratio in subjects with ID is the same as that of children with normal development. However, the victim and perpetrator-victim ratios were higher in the group with ID than in the group with normal development. Social exclusion and a lack of social support are the most frequent forms of bullying suffered by subjects with different types of disabilities or special needs [4,11]. Children with disabilities are more victimized by their peers than their classmates without disabilities and they are slower in developing social skills, which can increase their vulnerability to bullying [12].

Another study exploring the relationship between a psychiatric diagnosis and the fact of suffering bullying in patients aged 12 revealed that 25.4% of the sample group had reported having suffered from bullying. The frequencies of bullying found depending on the diagnosis were: 63.3% ID, 62.5% Autism Spectrum Disorder (ASD), 39.4% attention deficit hyperactivity disorder (ADHD), and 25% learning disabilities. Higher ratios of bullying are reported in subjects with a diagnosis of ID or ASD irrespective of their gender [13].

Fragile X syndrome (FXS) is a genetic condition associated with an alteration of the *FMR1* gene (fragile X mental retardation 1), which leads to the total absence or partial reduction of the FMRP protein. One of the main areas of expression of the *FMR1* gene is the brain. FMRP plays an important role in synaptic plasticity, axonal-dentritic development and learning and memory processes [14]. Epidemiological studies show an estimated frequency of 1.4:10.000 males and 0.9:10.000 females [15] and a prevalence of 1 per 2.500 to 7.000 males and 1 per 2.500 to 11.000 females [16].

FXS is the leading cause of hereditary ID. In females, it has been described that 50% of subjects present a variable degree of ID (between mild and moderate) and the remaining 50% present an intelligence quotient (IQ) in the medium range [17]. Girls with FXS present higher levels of social anxiety, social avoidance, and shyness, and they tend to isolate socially, have poor eye contact, and show difficulties in establishing an adequate rapport with others, ASD traits (social interaction and communication deficits, stereotypical movements), learning difficulties and depression [18].

The review by Maïano et al. [4] identified the following risk factors of suffering bullying in the population with special needs: physical appearance (characteristic physical traits); poor academic performance and inappropriate behavior; limited social relations and unstable friendships; deficits in social skills and problem solving. Considering the previously described characteristics of girls with FXS, this group would be expected to be at higher risk of suffering bullying during school years, but as far as the authors of this paper know there are no publications to this effect. Hence, the aim of the present work is to study the risk of girls with FXS suffering bullying in the role of victim and its effect on their capacity of adaptation, style of socialization, and emotional state compared with the control group (CG) of a similar age and IQ.

The study was designed based on two hypotheses:

(1) In our sample, at least 50% of girls with an FXS diagnosis have suffered some type of bullying in the role of victim.

(2) There will be an association between suffering bullying in the role of victim and their adaptive behavior, style of socialization, and emotional state. These associations will be different depending on the presence of FXS diagnosis.

2. Materials and Methods

The present research was carried out at Sabadell's Parc Taulí Hospital, which belongs to the Clinical Experience Units Network for minority diseases (Barcelona, Spain) and is also a member of the Fragile X Syndrome Clinical Research Consortium. It follows on from a previous study in which the relationship between linguistic functions and executive function was assessed using other cognitive and behavioral variables (social perception, quantitative reasoning, and adaptive behavior). It was approved by the Ethics Committee of the same hospital (reference 2016595).

The Spanish FXS Federation, and different associations of patients with FXS (Catalonia, the Basque Country and Valencia) or other genetic diseases (D'Genes Murcia) took part in disseminating the project through professional social networks such as LinkedIn and by emailing psychopedagogy consultants and special education colleges in the area.

Informed consent was obtained from the participants' legal guardians and participants gave their verbal consent.

2.1. Participants

It has been described that girls with FXS present a great variability in terms of IQ: approximately 50% of women with FXS have some kind of intellectual disability (ID) to varying degrees (between limit and moderate), while the other 50% have a general cognitive ability that sits within the midrange [17]. This is a fact that we find in our daily clinical practice, and hence the sample features participants with IQ ranging from intellectual disability to within midrange, which is a realistic representation of the way FXS manifest in girls. To avoid any potential confounding, a statistical analysis was performed to ensure that there were no significant differences between both groups in terms of IQ, age, socio economic status (SES), and ADHD symptoms. The means comparison was made using the Student's *t*-test, and no statistically significant differences were found between groups in these variables (Table 1).

Table 1. Descriptive measures and distribution of age, IQ, ADHD Symptoms, and socioeconomical status.

Variables	FXS Group $n = 26$	Control Group $n = 14$	Significance
Age M (SD)	10.58 (3.384)	10.50 (2.345)	0.940
IQ M (SD)	71.50 (14.795)	76.36 (16.80)	0.351
ADHD symptoms M (SD)	81.54 (4.341)	68.29 (6.984)	0.104
Socioeconomical status			
Low	3.8%	16.7%	0.211
Medium	88.5%	75%	
High	7.7%	8.3%	

FXS = Fragile X Syndrome. IQ = intelligence quotient. ADHD = Attention Deficit Hyperactivity Disorder. M = mean. SD = standard deviation. M = mean.

A total of 40 girls aged between 7 and 16 took part in the study. They were divided into the following two groups:

(1) FXS group: $n = 26$. Participants recruited through the Parc Taulí Hospital and the different patient associations.
(2) Control group (CG): $n = 14$. Participants were recruited through outpatients' appointments at the Neuropediatrics Unit of Sabadell's Parc Taulí Hospital and standard and special education schools in the area.

The inclusion and exclusion criteria were as follows:

- Inclusion criteria:

- FXS group: female, aged between 7 and 16 years, FXS confirmed by genetic study (>200 repetitions).
- Control Group: female, aged between 7 and 16 years.

- Exclusion criteria:

- FXS criteria: presence of comorbid ASD or ADHD, absence of expressive language, acquired neurological disorders (epilepsy, head injury).
- Control Group: meeting the diagnostic criteria for ASD or ADHD, absence of expressive language, acquired neurological disorders (epilepsy, head injury) and other cognitive-behavioral disorders. Participants without ID did not undergo a genetic study for ethical reasons, but subjects were questioned explicitly about their family history of FXS and the presence of clinical symptoms compatible with an FXS diagnosis.
- In both groups, participants who meet all DSM-5 criteria for the diagnosis of ASD and ADHD were excluded from the sample. Participants who only showed some symptoms were not excluded. The assessment was performed by an expert in pediatric neurology, psychology, or psychiatry.

2.2. Measures and Procedure

The assessment sessions for the participants from the Barcelona Metropolitan Area took place in Sabadell's Parc Taulí Hospital. The lead investigator travelled to the autonomous regions where the rest of the participants lived to carry out the assessments, thus ensuring as little inconvenience as possible for the participants and their families. The participating autonomous communities were Catalonia, Madrid, the Basque Country, Galicia, Valencia, and Murcia.

First, a document explaining the project was produced and sent to the patient associations for dissemination among the families. When families showed interest in taking part in the study, the lead investigator would travel to the pertinent autonomous region on previously agreed days to carry out the assessments in the facilities provided by the associations. The assessment was divided into three separate one-hour sessions to ensure that participants did not become overtired. Last, parents were asked to complete the corresponding questionnaires. Due to the general and reading comprehension difficulties shown by most of the subjects, administration of self-reported questionnaires was not possible.

2.2.1. Measures and Scales

- Wechsler Intelligence Scale for Children-Fifth Edition (WISC-V) Spanish version: a measure to assess participants' IQ ($\overline{x}$ = 100 ± 15) [19].
- Adaptative Behavior Assessment System-Second Edition (ABAS-II) Spanish version: parents' version. A measure to assess adaptive behavior in the conceptual domain (communication, functional, and self-directed academic skills), the social domain (recreation and social), the practical domain (self-care, home life, use of community resources, and health and safety), and the global domain ($\overline{x}$ = 100 ± 15) [20].
- Child and Adolescent Evaluation System (SENA): parents' version. An assessment of a wide range of emotional and behavioral problems (depression, anxiety, hyperactivity and impulsivity, defiant behavior, substance abuse, eating disorders, learning difficulties, among others), contextual problems (problems with the family, at school, and with peers), areas of vulnerability (problems regulating emotions, isolation, rigidity, and so on), and psychological resources (self-esteem, social competence and integration, emotional intelligence, and so on). For these behavioral measures, standard scores were obtained ($\overline{x}$ = 50 ± 10). The critical items "Risk of school bullying", "Lack of social support", "Isolated by classmates", "Insult by classmates" and "Afraid of a classmate" were used to establish the presence or absence of bullying. For critical items, the outcomes are binary variables (presence vs. absence) [21].

- BAS-2. Battery of socialization: parents' version. Estimation scales in four domains facilitating socialization (leadership, joviality, social sensitiveness, and respect-self-control), three domains that disrupt socialization (aggressiveness-obstinacy, apathy-withdrawnness, and anxiety-shyness), and a global social adaptation or criterial-socialization scale (percentile scores) [22].

2.2.2. Statistical Analysis

The statistical analysis was carried out using the SPSS Statistics for Windows Version 25.0 software. The Student's *t*-test was used to compare the control variables age and IQ for the two groups.

For the binary variables, corresponding contingency tables were built to assess the risk of suffering bullying in the FXS group compared with the control group, and the Odds Ratio (OR) was calculated with its confidence intervals at 95%. For the quantitative variables, the effect of presenting FXS on emotional state, adaptive behavior, and socialization style was investigated using linear regression models that included an interaction period between the group and the presence of bullying.

3. Results

In our sample, regarding IQ, 50% of the participants in the FXS group scored in the range of mild/moderate ID, while the remaining 50% scored in the medium/medium-low range. Of the latter, 69.2% obtained scores corresponding to the borderline range and 30.7% to the medium range. On comparing the means using the Student's *t*-test, no statistically significant differences were found between the control variables age and IQ (Table 1). The Cronbach's Alfa values are summarized in Table 2.

Table 2. Adaptative Behavior Assessment System- Second Edition (ABAS-II) Cronbach's Alfa.

	Cronbach's	**Alfa**
	Control Group	**Fragile X Syndrome**
Social adaptation	0.778	0.691
Conceptual Adaptation	0.755	0.832
Practical Adaptation	0.842	0.903

Taken as a whole, it was found that 50% of the girls in the FXS group presented the condition "Risk of school bullying" versus 42.9% of the CG; 42.3% of the FXS group presented "Lack of social support" versus 28.6% of the CG; 38.5% of the girls with FXS presented "Isolated by classmates" versus 28.6% of the CG; 23.1% of the FXS group presented "Afraid of a classmate" versus 14.3% of the CG; and 26.9% of the girls with FXS were "Insulted by their classmates" versus 35.7% of the CG. The results show that the girls with FXS presented a higher ratio of lack of social support and isolation by their classmates than the girls in the CG (13.7% and 9.9% more, respectively). Conversely, the girls with CG presented a higher ratio of insulted by their classmates than the girls with FXS (8.8% more). Despite the trend found, the differences between groups were not statistically significant. (Table 3).

Table 3. Odds ratio of bullying depending on the group.

	FXS	**CG**	**Odds Ratio**	**Significance**	**95% Confidence Interval**	
					Inferior	**Superior**
Risk of school bullying	50%	42.9%	1.333	0.666	0.360	4.933
Lack of social support	42.3%	28.6%	1.833	0.392	0.454	7.408
Insult by classmates	26.9%	35.7%	0.663	0.563	0.164	2.676
Afraid of a classmate	23.1%	14.3%	1.8	0.507	0.312	10.39
Isolated by classmates	38.5%	28.6%	1.563	0.532	0.384	6.356

FXS = Fragile X Syndrome. CG = control group.

Regarding the multivariant analysis of the effect of FXS on joviality, social competence and integration, depression, personal resources, and self-care with respect to the control group, it was observed that there was a statistically significant interaction between some of the components of Bullying ("Risk of school bullying", "Lack of social support", "Isolated by classmates", "Insulted by classmates" and "Afraid of a classmate") and the presence of the syndrome.

On analyzing the data on the presence of "Risk of school bullying", a significantly different effect was observed depending on the group on joviality ($p = 0.012$), social competence and integration ($p = 0.001$), depression ($p = 0.035$), and personal resources ($p = 0.004$). To this effect, the girls in the CG whose parents' scores had indicated "Risk of school bullying" presented significant worsened average scores in the variables joviality (absence $\overline{x} = 42.38 \pm 28.75$ versus presence $\overline{x} = 6.34 \pm 7.53$ $p = 0.009$), social competence and integration absence $\overline{x} = 52.13 \pm 7.68$ versus presence $\overline{x} = 25.34 \pm 14.95$ $p = 0.005$), personal resources (absence $\overline{x} = 52.5 \pm 5.66$ versus presence $\overline{x} = 29.83 \pm 12.19$ $p = 0.004$), and depression (absence $\overline{x} = 52.75 \pm 9.98$ versus presence $\overline{x} = 75.00 \pm 18.29$ $p = 0.03$), compared with their classmates whose scores did not reflect "Risk of School Bullying". Conversely, in the group of girls with FXS, no significant differences were observed in the means of those who presented "Risk of school bullying" and those who did not in the variables joviality (absence $\overline{x} = 16.59 \pm 15.46$ versus presence $\overline{x} = 10.70 \pm 10.66$ $p = 0.285$), social competence and integration (absence $\overline{x} = 31.85 \pm 11.52$ versus presence $\overline{x} = 31.01 \pm 9.75$ $p = 0.842$), personal resources (absence $\overline{x} = 33.69 \pm 10.09$ versus presence $\overline{x} = 33.31 \pm 13.24$ $p = 0.934$), and depression (absence $\overline{x} = 51.69 \pm 12.83$ versus presence $\overline{x} = 55.46 \pm 10.86$ $p = 0.427$). On comparing the two groups, it was found that in the absence of "Risk of school bullying", the participants with FXS started with a lower score in all the variables (joviality, social competence and integration, and personal resources), except in the case of depression, in which the two groups start with similar scores (Figure 1 and Table 4).

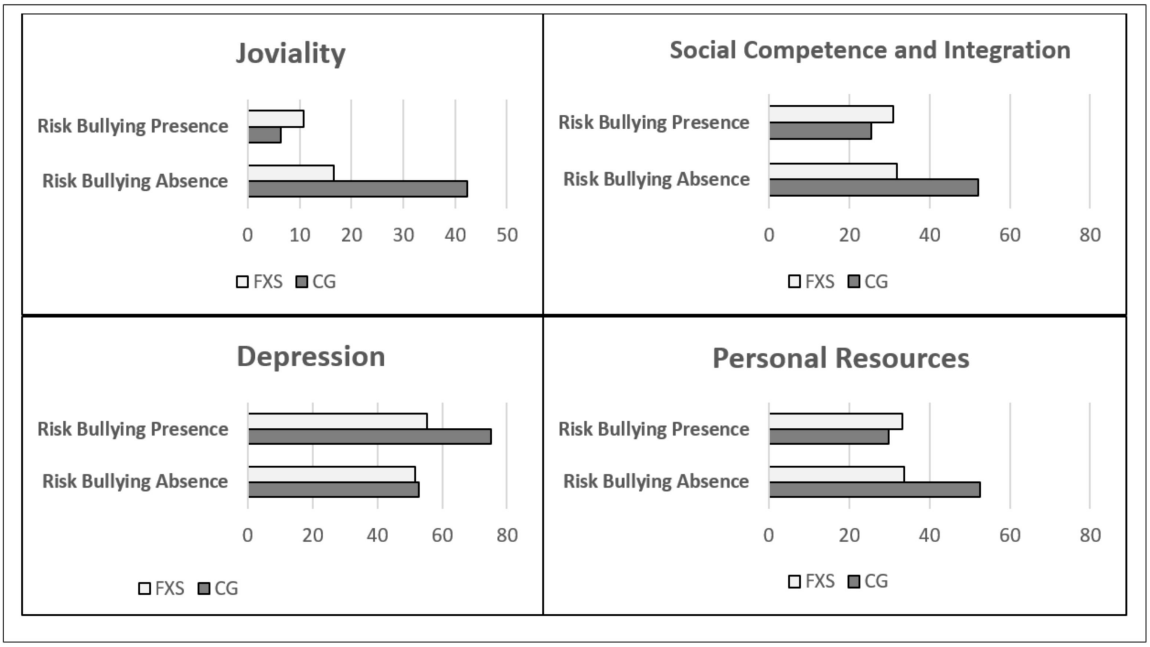

Figure 1. Interaction of "Risk of bullying" with Group on Joviality, Social Competence and Integration, Depression, and Personal Resources. FXS = Fragile X Syndrome. CG = control group.

Regarding "Lack of social support", the effect on joviality ($p = 0.03$), social competence and integration ($p = 0.001$), and personal resources ($p = 0.021$) was found to differ depending on the group. As in the previous case, compared with their peers who did not suffer a "Lack of social support", the CG participants whose parents' scores indicated a "Lack of social support" presented significantly worsened average scores in the variables joviality (absence $\overline{x} = 37.10 \pm 27.69$ versus

presence $\overline{x}$ = 1.5 ± 0.577 p = 0.003), social competence and integration (absence $\overline{x}$ = 49.50 ± 9.19 versus presence $\overline{x}$ = 18.50 ± 12.71 p = 0.01), and personal resources (absence $\overline{x}$ = 49.50 ± 8.22 versus presence $\overline{x}$ = 26.00 ± 13.44 p = 0.032). Conversely, in the group of girls with FXS, no significant differences were observed in the means of the variables joviality (absence $\overline{x}$ = 16.71 ± 14.20 versus presence $\overline{x}$ = 9.45 ± 11.23 p = 0.167), social competence and integration (absence $\overline{x}$ = 32.53 ± 11.51 versus presence $\overline{x}$ = 29.91 ± 9.17 p = 0.524), and personal resources (absence $\overline{x}$ = 35.47 ± 10.41 versus presence $\overline{x}$ = 30.82 ± 12.93 p = 0.339). On comparing the two groups, it was found that in the absence of "Lack of social support" the participants with FXS started with a lower score in joviality, social competence and integration, and personal resources. The same relational pattern, bordering on statistical significance, was found with the variables, leadership ability (p = 0.069), health and Safety (p = 0.077), use of community resources (p = 0.081), and social adaptation (p = 0.088) (Table 5). The lack of significance in the interaction between these variables could be due to a lack of strength in the test given the small size of the sample (Figure 2 and Tables 5 and 6).

Table 4. Interaction of "Risk of bullying" with Group on Joviality, Social Competence and Integration, Depression, and Personal Resources (central tendency and variability).

Variables	β	Confidence Interval 95%		Significance
		Inferior	Superior	
Joviality				
Risk of Bullying	−36.042	−54.630	−17.453	<0.001
Group	−25.792	−41.502	−10.081	0.002
Interaction	30.151	7.012	53.289	0.012
Social Competence and Integration				
Risk of Bullying	−26.792	−38.715	−14.869	<0.001
Group	−20.279	−30.199	−10.358	<0.001
Interaction	25.946	11.210	40.681	0.001
Depression				
Risk of Bullying	22.250	8.396	36.104	0.002
Group	−1.058	−12.585	10.469	0.853
Interaction	−18.481	−35.603	−1.359	0.035
Personal Resources				
Risk of Bullying	−22.667	−34.627	−10.707	<0.001
Group	−18.808	−28.759	−8.856	<0.001
Interaction	22.282	7.501	37.036	0.004

Table 5. Linear regression model with Interaction of "Lack of Social Support" with Group on "leadership", "Health and security", "Use of community resources", "Social adaptation".

	CG "Lack of Social Support"		*Significance*	FXS "Lack of Social Support"		*Significance*
	Absence	Presence		Absence	Presence	
Leadership	$\overline{x}$ = 23.10 ± 20.44	$\overline{x}$ = 3.25 ± 2.87	0.014	$\overline{x}$ = 9.43 ± 7.18	$\overline{x}$ = 5.64 ± 7.39	0.211
Health and safety	$\overline{x}$ = 100.50 ± 15.54	$\overline{x}$ = 77.5 ± 18.48	0.03	$\overline{x}$ = 85.36 ± 23.57	$\overline{x}$ =87.37 ± 16.94	0.773
Social adaptation	$\overline{x}$ = 95.10 ± 11.0	$\overline{x}$ = 69.75 ± 13.20	0.021	$\overline{x}$ = 81.57 ± 14.89	$\overline{x}$ = 71.6 ± 14.06	0.093
Use of community resources	$\overline{x}$ = 96.50 ± 15.46	$\overline{x}$ = 61.25 ± 7.50	0.001	$\overline{x}$ = 86.43 ± 19.36	$\overline{x}$ = 72.27 ± 14.89	0.05

FXS = Fragile X Syndrome. CG = control group.

Table 6. Interaction of "Lack of Social Support" with Group on Joviality, Integration and Social Competence, Personal Resources, Leadership, Health and security, Social Life, and Social Adaptation. FXS = Fragile X Syndrome. CG = control group (central tendency and variability).

Variables	β	Confidence Interval 95%		Significance
		Inferior	Superior	
Joviality				
Lack of Social Support	−35.600	−56.683	−14.517	0.002
Group	−20.386	−35.141	−5.630	0.008
Interaction	28.340	2.832	53.849	0.03
Social Competence and Integration				
Lack of Social Support	−31.000	−43.556	−18.444	<0.001
Group	−16.967	−25.631	−8.302	<0.001
Interaction	28.376	13.256	43.496	0.001
Personal Resources				
Lack of Social Support	−23.500	−36.674	−10.326	0.001
Group	−14.033	−23.124	−4.943	0.003
Interaction	18.852	2.987	34.716	0.021
Leadership				
Lack of Social Support	−19.850	−34.207	−5.493	0.008
Group	−13.671	−23.719	−3.623	0.009
Interaction	16.058	−1.313	33.429	0.069
Health and Safety				
Lack of Social Support	−23.000	−46.403	0.403	0.054
Group	−15.143	−31.521	1.236	0.069
Interaction	25.370	−2.944	53.685	0.077
Use Community Resources				
Lack of Social Support	−35.250	−54.944	−15.944	0.001
Group	−10.071	−23.854	3.711	0.147
Interaction	21.094	−2.733	44.922	0.081
Social Adaptation				
Lack of Social Support	−25.350	−41.694	−9.006	0.003
Group	−13.529	−24.967	−2.090	0.022
Interaction	15.142	−4.632	34.917	0.088

Regarding the variable "Isolated by classmates", just one significantly different effect was found depending on the group, social competence and integration ($p = 0.049$), and another on the borderline of significance, joviality ($p = 0.063$). Like in the previous cases, in the presence of being isolated by classmates the subjects in the CG had worse means compared with their peers who were not isolated by their classmates in social competence and integration (absence $\overline{x} = 46.50 \pm 16.87$ versus presence $\overline{x} = 26.00 \pm 8.76$ $p = 0.013$) and joviality (absence $\overline{x} = 35.50 \pm 29.39$ versus presence $\overline{x} = 5.50 \pm 7.68$ $p = 0.012$). Among the subjects in the FXS group, no significant difference was found in the means of the variables social competence and integration (absence $\overline{x} = 32.38 \pm 11.08$ versus presence $\overline{x} = 29.90 \pm 9.78$ $p = 0.557$) and "joviality" (absence $\overline{x} = 15.27 \pm 14.35$ versus presence $\overline{x} = 10.90 \pm 11.60$ $p = 0.411$). Comparing the two groups, it was found that in the absence of being isolated by classmates the participants with FXS started with a lower score in "social competence and integration" and "joviality" (Figure 3 and Table 7).

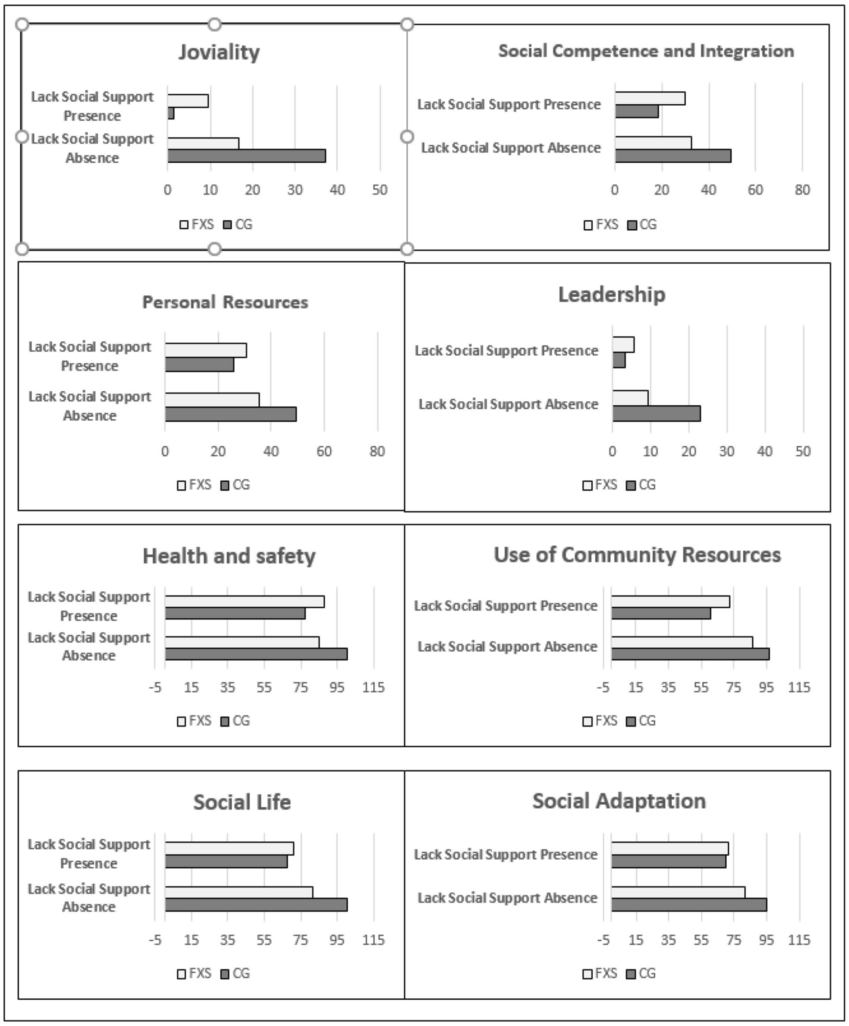

Figure 2. Interaction of "Lack of Social Support" with Group on Joviality, Integration and Social Competence, Personal Resources, Leadership, Health and security, Social Life, and Social Adaptation. FXS = Fragile X Syndrome. CG = control group.

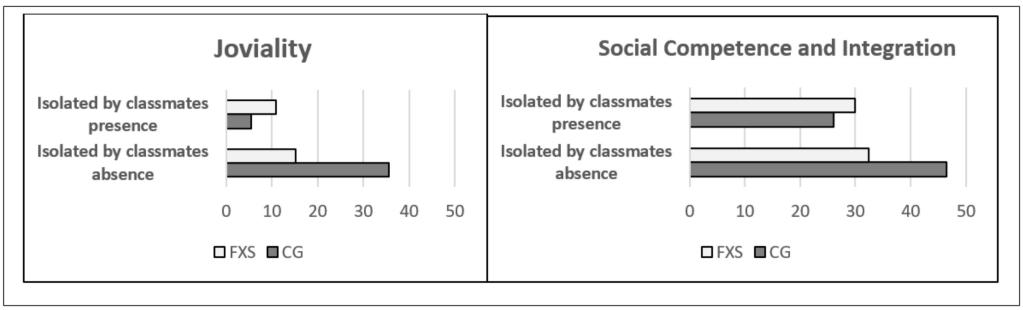

Figure 3. Interaction of "Isolated by classmates" with Group on Social Competence and Integration, and Joviality. FXS = Fragile X Syndrome. CG = control group.

Table 7. Interaction of "Isolated by classmates" with Group on Social Competence and Integration, and Joviality. FXS= Fragile X Syndrome. CG = control group (central tendency and variability).

Variables	β	Confidence Interval 95%		Significance
		Inferior	Superior	
Joviality				
Isolated by Classmates	−30.000	−52.281	−7.719	0.010
Group	−20.233	−35.608	−4.858	0.011
Interaction	25.633	−1.437	52.704	0.063
Social Competence and Integration				
Isolated by Classmates	−20.500	−35.321	−5.679	0.008
Group	−14.125	−24.224	−4.026	0.007
Interaction	18.025	0.090	35.960	0.049

Regarding the variable "Insulted by classmates", significantly different interactions were found depending on the group in social competence and integration (p = 0.001), depression (p = 0.006), and personal resources (p = 0.002), and borderline significant interactions in joviality (p = 0.072) were found. In the presence of being insulted by classmates, the subjects in the CG had worse means compared with their peers who were not insulted by their classmates in social competence and integration (absence $\overline{x}$ = 50.11 ± 9.39 versus presence $\overline{x}$ = 23.60 ± 16.02 p = 0.016), depression (absence $\overline{x}$ = 52.78 ± 9.34 versus presence $\overline{x}$ = 79.40 ± 16.52 p = 0.018), personal resources (absence $\overline{x}$ = 51.22 ± 6.53 versus presence $\overline{x}$ = 27.60 ± 12.18 p = 0.009), and joviality (absence $\overline{x}$ = 37.89 ± 30.07 versus presence $\overline{x}$ = 7.20 ± 8.07 p = 0.017). Among the subjects in the FXS group, no significant difference was found in the means of the variables social competence and integration (absence $\overline{x}$ = 30.89 ± 11.11 versus presence $\overline{x}$ = 32.86 ± 9.10 p = 0.654), depression (absence $\overline{x}$ = 53.16 ± 12.47 versus presence $\overline{x}$ = 54.71 ± 10.56 p = 0.757), personal resources (absence $\overline{x}$ = 32.89 ± 10.37 versus presence $\overline{x}$ = 35.14 ± 15.08 p = 0.725), and joviality (absence $\overline{x}$ = 15.39 ± 14.44 versus presence $\overline{x}$ = 8.71 ± 8.54 p = 0.171). In the absence of being insulted by classmates, the girls in the FXS groups started with a lower score in social competence and integration, personal resources and joviality, but in the case of depression both groups started with a similar score (Figure 4 and Table 8).

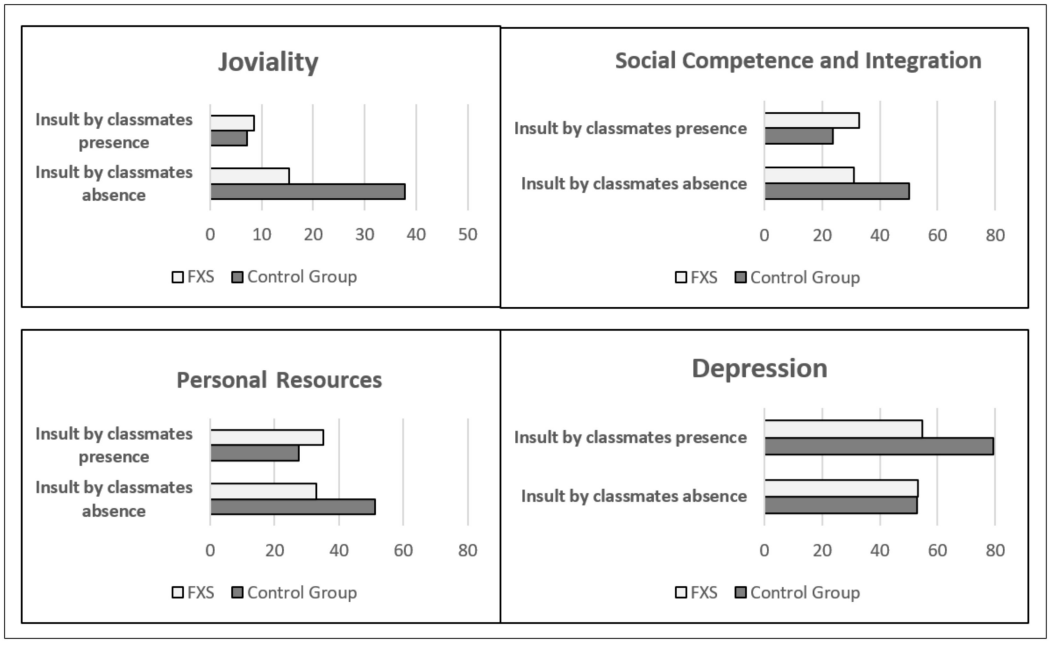

Figure 4. Interaction of "Insult by Classmates" with Group on Joviality, Social Competence and Integration, Personal Resources, and Depression. FXS = Fragile X Syndrome. CG = control group.

Table 8. Interaction of "Insult by Classmates" with Group on Joviality, Social Competence and Integration, Personal Resources, and Depression. FXS= Fragile X Syndrome. CG = control group (central tendency and variability).

Variables	β	Confidence Interval 95%		Significance
		Inferior	Superior	
Joviality				
Insult by Classmates	−30.689	−51.196	−10.182	0.004
Group	−22.500	−37.510	−7.490	0.004
Interaction	24.014	−2.230	50.258	0.072
Social Competence and Integration				
Insult by Classmates	−26.511	−39.092	−13.930	<0.001
Group	−19.216	−28.343	−10.089	<0.001
Interaction	28.474	12.420	44.528	0.001
Depression				
Insult by Classmates	26.622	12.950	40.294	<0.001
Group	0.380	−9.539	10.299	0.9539
Interaction	−25.066	−42.512	−7.619	0.006
Personal Resources				
Insult by Classmates	−23.622	−35.892	−11.352	<0.001
Group	−18.327	−27.229	−9.426	<0.001
Interaction	25.870	10.213	41.528	0.002

Lastly, regarding the variable "Afraid of a classmate", just one significantly different effect was found depending on group, in self-care ($p = 0.014$). To this effect, the girls in the CG who were afraid of a classmate presented worse means compared to their peers who were not afraid of a classmate in self-care (absence $\overline{x} = 92.50 \pm 26.24$ versus presence $\overline{x} = 55.00 \pm 0$ $p < 0.001$). No significant difference in means was found in the group of girls with FXS in self-care (absence $\overline{x} = 78.42 \pm 17.24$ versus presence $\overline{x} = 89.17 \pm 20.35$ $p = 0.279$). In the absence of being afraid of a classmate, the participants in the FXS group started with a lower score in social competence and integration, personal resources, joviality, and self-care, while the two groups started with a similar score in depression (Figure 5 and Table 9).

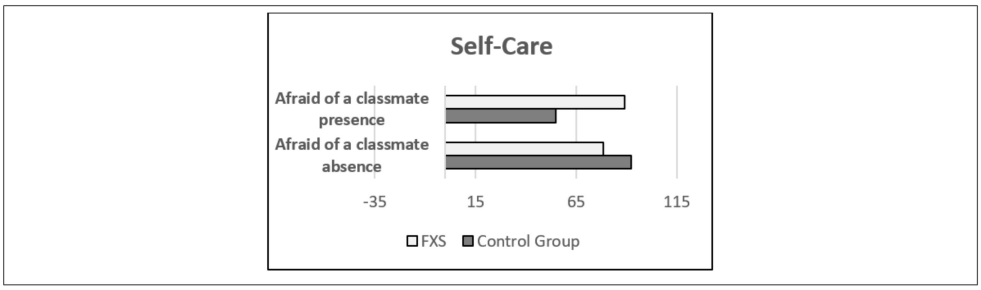

Figure 5. Interaction "Afraid of a classmate" with Group on Self-care with Group. FXS = Fragile X Syndrome. CG = control group.

Table 9. Interaction "Afraid of a classmate" with Group on Self-care with Group. FXS= Fragile X Syndrome. CG = control group (central tendency and variability).

Variables	β	Confidence Interval 95%		Significance
		Inferior	Superior	
Self-care				
Afraid of a classmate	−37.500	−69.597	−5.403	0.023
Group	−14.079	−29.575	1.417	0.074
Interaction	48.246	10.595	85.896	0.014

4. Discussion

The aim of the present work was to study the ratio shown by girls with Fragile X who had suffered bullying in the role of victim and the effect this has had on their adaptive behavior, socialization style, and emotional state.

First, it was observed that although the ratio of the girls with FXS who had suffered bullying at school according to their parents' assessment was similar to that of the girls in the control group, there was discrepancy between the two groups in the type of bullying suffered. Among the girls with FXS, a higher ratio was found in lack of social support and isolation by classmates. These findings coincide with results previously published in the scientific literature, which identify social exclusion as the form of bulling most frequently suffered by people with some type of disability (physical, intellectual or social) or special needs [4,11,12]. Conversely, the girls in the CG presented a higher ratio of insults from classmates.

Second, it was found that the girls who had suffered bullying showed more symptoms of depression, lower levels of joviality and personal resources, and more difficulties with self-care and social competence and interaction. On analyzing the influence of the components of bullying on each of the variables studied, it was observed that the risk of suffering bullying was related to worsening levels of joviality, personal resources, social competence and integration, and depressive symptoms; lack of social support was associated with lower levels joviality, personal resources and social competence and integration; isolation by classmates negatively affected the subjects' social competence and integration; suffering insult from classmates negatively affected their personal resources, depressive symptoms, and social competence and integration; and being afraid of a classmate was associated with lower levels of self-care.

In all the interactions among the group and the different forms of bullying, a similar pattern was observed: in the presence of different forms of bullying, the girls in the CG showed a more pronounced worsening than the girls in the FXS group. The girls with FXS tended to present ASD traits such as deficits in social communication and interactions, stereotypic behavior, and poor eye contact [18]. To this effect, difficulties in social communication and interaction could lead to difficulties in interpreting social signals and correctly identifying situations of bullying, which would mean a lowered awareness of the situation and, therefore, a decreased effect on their levels of joviality, personal resources, self-care, and social competence and integration in comparison with the girls in the control group. It is important to note that presenting difficulties in identifying situations of bullying does not imply the absence of it. This fact could place girls with FXS in a hugely vulnerable situation given that faced with a situation of bullying they would not be able to correctly identify the signals and, therefore, would not be able to adequately manage and resolve the situation. This finding concurs with results previously reported in the literature by different authors, who point out that girls with disabilities can present a lack of or a delay in developing social skills, which increases their vulnerability to bullying [12,23,24].

Strenghts and Limitations

One of the limitations of this study is the relatively small size of the sample. However, despite having only 26 girls with FXS participating in the study, it is the largest sample of girls of child-juvenile age collected to date in Spain, and one of the largest at an international level. The person responsible for carrying out the investigations travelled to different parts of the country over a period of four years to reach the highest possible number of participants. Other limitations were the great difficulty we had in finding a large number of girls for the CG, and the fact that groups are very heterogeneous. This could somehow bias the results. Nonetheless, there were no significant differences between the groups in terms of the control variables, age and IQ. Furthermore, although the girls with ID in the control group had undergone a genetic analysis which had ruled out FXS, the girls without ID did not undergo a genetic study for ethical reasons. However, the participants were evaluated clinically to assess whether they presented symptoms compatible with FXS (physical traits, cognitive-behavioral

characteristics), and they were asked specifically about any previous family history of FXS. Lastly, it must be remembered that the presence of bullying was ascertained using questionnaires administered by participants' parents. In future research, this information should be extended by adding data from assessments made by both teachers and the girls themselves.

5. Conclusions

Last, it must be noted that the present findings could indicate, that when planning interventions for girls with FXS in situations of bullying, apart from mediating and intervening in the immediate situation, there must be a more specific focus on direct work with the girls themselves, placing special emphasis on developing their social skills, and on mitigating any deficits in their social communication and interaction.

Author Contributions: L.J.-E.: Conceptualization, methodology, formal analysis, validation, investigation, resources, data curation, writing, original draft preparation, writing—Review and editing, visualization, funding acquisition, project administration. C.B.-G.: Conceptualization, methodology, writing—Review and editing. M.-L.J.: Conceptualization, methodology, writing—Review and editing. C.J.: Conceptualization, methodology, writing—Review and editing. A.R.-M.: Conceptualization, methodology, writing—Review and editing. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest: The authors declare no conflict of interest.

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6. DISCUSIÓN

6. Discusión:

6.1. Aspectos globales:

La presente tesis se estructura en base a 4 artículos. Éstos representan el núcleo de la investigación que tiene como objetivos principales estudiar la relación entre diferentes áreas del perfil neurocognitivo y la conducta adaptativa en chicas con el diagnóstico de SXF; así como el riesgo de sufrir acoso escolar en el papel de víctima y su relación con su nivel de adaptación funcional. Todos ellos cuentan con una muestra de 26 chicas con SXF y 14 chicas de GC emparejadas por edad y CIT, con edades comprendidas entre los 7 y los 16 años.

El estudio neuropsicológico se realizó con los siguientes instrumentos de medida: WISC-V. Escala de Inteligencia Wechsler para niños-V (Wechsler, 2015); Test de Denominación de Boston *(*Kaplan et al., 2005); Peabody Test de Vocabulario en Imágenes (Lloyd et al., 2006); Test de Clasificación de Tarjetas de Wisconsin (Robert k. et al., 2009); NEPSY-II. Batería Neuropsicológica Infantil (Korman et al., 2014); Torre de Londres (Culbertson et al., 2005); SENA. Sistema de Evaluación de Niños y Adolescentes (Fernández-Pinto et al., 2015); ADHD Rating Scale DuPaul (DuPaul et al., 1998); BAS-2. Batería de Socialización (Silva et al., 2018); BRIEF-2. Evaluación conductual de la función ejecutiva-2 (Gioia et al., 2017); ABAS-II. Sistema de Evaluación de la Conducta Adaptativa-II (Harrison et al., 2013).

6.2. Artículo 1: "Pilot Study of Socio-emotional factors and Adaptive Behavior in young females with Fragile X Syndrome".

En el artículo 1 titulado *"*Pilot Study of Socio-emotional factors and Adaptive Behavior in young females with Fragile X Syndrome*",* se estudió la relación entre: la capacidad intelectual (medida mediante el CIT) y la conducta adaptativa; la percepción social y la ansiedad social; la ansiedad social y la conducta adaptativa, funciones cognitivas y el estado emocional. Asimismo, se valoró si la ansiedad social era más prevalente en las chicas del grupo SXF en comparación con las chicas del GC.

Respecto a la capacidad intelectual, en el grupo de chicas con SXF, el 3,84% de las participantes obtuvieron puntuaciones de CIT en el rango de la DI moderada (CIT 35-40 a 50-55), el 46,15% en el rango de la DI leve (CIT 50-55 a 70), el 38,46% en el rango límite (CIT 70-85) y un 11,53% en el rango medio (CIT > 85). Una vez realizada la comparación de medias mediante la prueba *t* de Student no se objetivaron diferencias estadísticamente significativas entre las variables de control edad, CIT, síntomas TDAH y nivel socioeconómico.

Los resultados obtenidos mostraron que en ambos grupos se daba una relación positiva del CIT con las habilidades de comunicación, las habilidades académicas, el uso de recursos comunitarios, la capacidad de autodirección, la salud y seguridad, la vida social, el nivel de adaptación conceptual y nivel de adaptación total. Al estudiar las diferencias entre ambos grupos, el análisis de los datos mostró varias diferencias estadísticamente significativas entre las chicas con SXF y las chicas del GC. En primer lugar, se observó que, en comparación con el GC, el grupo de chicas con SXF mostraba una relación positiva más fuerte entre el CIT y dos áreas de la conducta adaptativa: la habilidad de autodirección y el nivel de adaptación social. Estos resultados son consistentes con los hallazgos de Glaser et al., según los cuales el CIT está fuertemente asociado con el comportamiento adaptativo en niñas con SXF

(Glaser et al., 2003). En este sentido, se objetivó que en el grupo de chicas con SXF, un CIT más alto está estrechamente relacionado con una mejor capacidad de autodirección y un mejor nivel de adaptación social. Según la Asociación Americana de Psicología, la inteligencia se refiere a la capacidad de entender la información, adaptarse al medio ambiente y aprender de la experiencia. En este sentido, es lógico encontrar que cuanto mejor sea el CIT de las participantes, mejor será su nivel de adaptación funcional. El hecho de que en el grupo de chicas con SXF se haya observado una relación más fuerte entre el CIT y la capacidad de autodirección y la adaptación social que en el GC podría situar al CIT como un indicativo del valor pronóstico de estas dos áreas de la conducta adaptativa en chicas con el diagnóstico de SXF.

En segundo lugar, las chicas con SXF mostraron una asociación positiva más estrecha entre el reconocimiento de emociones y las siguientes habilidades: capacidad de liderazgo, nivel de jovialidad y grado de adaptación social. Una mejor capacidad para reconocer las emociones en los demás es esencial para ser capaz de saber cómo se sienten, y para ser capaz de actuar en consecuencia y adaptar nuestro comportamiento a sus necesidades. Una persona que posee estas habilidades es más propensa a ser percibida como líder y, en consecuencia, a tener una mejor adaptación social y un mayor nivel de jovialidad. Estos resultados están en línea con la investigación de Hatton, en la que se objetivó que los participantes con menos rasgos TEA tuvieron un mejor desempeño en todas las áreas de comportamiento adaptativo (Hatton et al., 2003)

Por último, se constató que, tal y como se describe en la literatura previa (Bartholomay et al., 2019; Visootsak et al., 2005), el grupo de chicas con SXF presentó un mayor nivel de ansiedad social y timidez en comparación con las chicas del GC.

6.3. Artículo 2: "Language in Young females with Fragile X Syndrome: Influence on the Neurocognitive profile and adaptive behavior"

En el artículo 2 titulado "Language in Young females with Fragile X Syndrome: Influence on the Neurocognitive profile and adaptive behavior" se estudió la relación entre las funciones lingüísticas y las siguientes habilidades: funciones ejecutivas, percepción social, razonamiento cuantitativo, estilo de socialización y conducta adaptativa. Los resultados obtenidos objetivaron diferencias estadísticamente significativas entre ambos grupos en la relación de algunas variables estudiadas. Así pues, se observó que, en comparación con el GC, las chicas con SXF mostraron una relación positiva más estrecha entre el vocabulario expresivo y la capacidad de abstracción verbal con la habilidad de teoría de la mente. Esto puede deberse a que en la tarea de Teoría de la Mente Verbal deben realizarse inferencias de la situación planteada mediante el uso de la capacidad de abstracción verbal, ya que se debe analizar la información lingüística proporcionada sobre cada situación. En este sentido, coincidimos con las investigaciones de Raspa (Raspa et al., 2017) que describieron el vocabulario expresivo como una habilidad relativamente preservada del perfil de chicas con SXF.

En este mismo sentido se observó en el grupo de chicas SXF una asociación positiva más fuerte entre el vocabulario comprensivo con la adaptación social, la adaptación conceptual y la habilidad de autodirección; y de la comprensión de instrucciones con la capacidad de autodirección. La conducta adaptativa hace referencia al grado de independencia que alcanza una persona en su vida cotidiana y los resultados de la presente investigación evidencian que una mayor capacidad para comprender las instrucciones revierte en una mejor habilidad para autogestionarse de forma autónoma ya que no será necesario depender de la guía externa de una tercera persona para realizar las tareas cotidianas. Si bien es cierto que estudios anteriores apuntaban al vocabulario comprensivo como una habilidad preservada en las chicas con SXF (Sterling y

Abbeduto 2012), en estos trabajos no se había valorado la posible relación de este aspecto con su nivel de autonomía diaria.

En el área de lenguaje expresivo también se observó una asociación entre la capacidad de denominación y las habilidades académicas. Estos resultados concuerdan con los obtenidos en un estudio realizado por Shaffer, en el que encontraron que un lenguaje más inteligible se relacionaba con mejores habilidades adaptativas (Shaffer et al., 2020).

Por lo que respecta al área de las funciones ejecutivas se objetivó que en el grupo de chicas con SXF había una fuerte relación positiva entre el vocabulario expresivo y la comprensión de instrucciones con la memoria de trabajo auditiva, la flexibilidad cognitiva, la capacidad de inhibición y la velocidad de procesamiento, de la misma manera que en la relación entre la comprensión de instrucciones y la memoria de trabajo. Históricamente y desde un punto de vista evolutivo, el lenguaje se ha considerado como una herramienta indispensable para la autorregulación de los sujetos (Stuss & Benson, 1986; Vygotsky, 1962). En este sentido es lógico pensar que un mejor nivel de vocabulario expresivo y de comprensión de instrucciones es una herramienta básica para que la persona pueda autogestionarse de forma más eficaz y ser más hábil en la regulación de su capacidad de inhibición y de flexibilidad cognitiva mediante el uso de estrategias lingüísticas.

Respecto al estilo de socialización, se observaron diferencias estadísticamente significativas entre ambos grupos en la relación entre las habilidades de denominación y vocabulario expresivo con la capacidad de liderazgo. Desde un punto de vista básico, las habilidades lingüísticas de los niños contribuyen a su habilidad para comprender las instrucciones de las tareas cognitivas que deben realizar (Fletchet, 2011). Al ser el lexicón un área del lenguaje (Hoover et al., 2011), podría deducirse que una mayor facilidad para

acceder al lexicón junto con un mejor conocimiento del vocabulario son aspectos que favorecen positivamente los intercambios comunicativos entre las personas.

En lo referente al razonamiento cuantitativo se observó una fuerte asociación en sentido positivo entre el vocabulario expresivo y la comprensión de instrucciones con la aritmética. En la literatura científica previa se ha considerado que las alteraciones en el razonamiento matemático, descritas anteriormente por otros autores en chicas con SXF, eran debidas a una mayor dificultad a nivel de las funciones visoespaciales (Bartholomay et al., 2019; Raspa et al., 2017, Kemper et al., 1968). Por el contrario, en el presente estudio se ha objetivado una importante influencia de la capacidad de abstracción verbal y la comprensión de instrucciones sobre el componente de aritmética del dominio de razonamiento cuantitativo. Una posible explicación de este hallazgo sería que, para la correcta realización del cálculo aritmético requerido, es necesario primero descifrar y entender de forma correcta el enunciado del problema matemático que se plantea. No se observaron diferencias entre ambos grupos en el subtest de Balanzas del dominio razonamiento cuantitativo, que mide el proceso de razonamiento que puede expresarse matemáticamente basándose en la lógica inductiva o deductiva. Es importante resaltar que en el subtest de Balanzas los procesos lingüísticos tienen un menor peso, ya que la información se presenta mediante estímulos visuales y el sujeto tan solo debe seleccionar la respuesta correcta entre varias opciones que se le plantean. Teniendo en cuenta todo esto, y en contraposición a lo publicado anteriormente, los resultados obtenidos nos llevan a plantear la conclusión de que la peor ejecución de las chicas del grupo SXF en la tarea de aritmética puede deberse a una alteración en el procesamiento de la información lingüística, más que a una alteración pura del razonamiento matemático inductivo / deductivo.

Así pues, los resultados obtenidos indican que, en comparación con el GC, en el grupo de chicas con SXF las funciones lingüísticas muestran una asociación mayor de la esperada con algunas de las funciones ejecutivas, el

razonamiento aritmético, la percepción social, la conducta adaptativa y el estilo de socialización.

6.4. Artículo 3: "Fragile X Syndrome in Young Females: Influence of Executive Function on the Neurocognitive Profile and Adaptive Behavior".

El artículo 3, titulado **"**Fragile X Syndrome in Young Females: Influence of Executive Function on the Neurocognitive Profile and Adaptive Behavior", se planteó con el objetivo de estudiar la relación entre las Funciones Ejecutivas (FE) y el rendimiento en las áreas de lenguaje, estilo de socialización, percepción social, razonamiento cuantitativo, perfil conductual y conducta adaptativa. Los resultados obtenidos mostraron que, en comparación con el GC, las chicas con SXF mostraron una relación más estrecha entre algunas de las FE estudiadas y ciertas áreas de lenguaje, del estilo de socialización, la percepción social, el razonamiento cuantitativo, el perfil conductual y la conducta adaptativa.

En primer lugar, se observó una relación positiva entre la capacidad de abstracción verbal y la teoría de la mente (verbal y total) del dominio percepción social, siendo esta influencia mayor en el grupo de chicas SXF. En el caso de la teoría de la mente verbal (TMV) esta relación puede deberse a que en la tarea planteada hay que realizar inferencias de la situación expuesta mediante el uso de la capacidad de abstracción verbal, ya que la información necesaria para analizar cada situación se proporciona de forma verbal. Por otro lado, en el subtest de Teoría de la mente Total (TMT) se utilizan estímulos en los que la información es procesada tanto a nivel verbal como visual. Sin embargo, a la hora de calcular una puntuación estandarizada, los baremos tan sólo permiten obtener una puntuación total que engloba los ítems verbales y visuales. Si, a pesar de incluir los estímulos visuales en la tarea TMT, seguimos encontrando una influencia de la capacidad de abstracción verbal se infiere que el

componente verbal tiene un peso importante. En este sentido, los resultados obtenidos coinciden con investigaciones anteriores que describieron el lenguaje como un punto fuerte en el perfil cognitivo de chicas con el SXF (Raspa et al. 2017).

En la literatura científica previa se consideraba que las alteraciones en el razonamiento matemático típicamente descritas en chicas con SXF, eran secundarias a alteraciones en las funciones visoespaciales (Kemper et al., 1986; Bunney et al., 2017; Bartholomay et al., 2019). En la presente investigación se observó que el grupo de chicas con SXF presentaba una fuerte asociación entre la capacidad de abstracción verbal y la variable de aritmética del dominio Razonamiento Cuantitativo. No se hallaron diferencias entre grupos al analizar la relación entre la capacidad de abstracción visual (subtest Matrices) con la habilidad de realizar razonamientos matemáticos basándose en la lógica inductiva o deductiva (subtest Balanzas) y la aritmética (subtest aritmética). Una vez descartados otros procesos cognitivos implicados en la prueba de aritmética, como la memoria de trabajo (MT), se observó una fuerte influencia de la capacidad de abstracción verbal sobre ella. Una explicación sería que, para la correcta realización del cálculo aritmético requerido, primero es necesario ser capaz de analizar y abstraer la información del enunciado que se presenta de forma oral. Así pues, los resultados obtenidos nos llevan a plantear que la peor ejecución de las chicas del grupo con SXF en la tarea de aritmética puede deberse a una alteración en la capacidad de abstracción verbal, más que a una alteración pura del razonamiento matemático. Estos hallazgos van en la línea de las investigaciones de Rivera y Klabunde en las que detectaron un patrón de activación aberrante del córtex frontal cuando personas con SXF realizaban operaciones matemáticas (Rivera et al., 2002; Klabunde et al., 2015).

Respecto al área conductual y estilo de socialización se objetivaron diferencias entre ambos grupos, siendo el grupo de chicas con SXF el que mostraba una mayor influencia de algunas de las FE sobre ciertas variables conductuales. Se observó que una mejor capacidad de abstracción verbal y de

seguimiento de la norma se relaciona con una mayor habilidad de liderazgo. De la misma forma, una peor destreza en la MT y en la planificación/organización repercute de forma negativa en la capacidad de liderazgo. Es lógico pensar que las chicas con una mejor habilidad para procesar la información de forma más abstracta y con un buen rendimiento en MT puedan presentar una mayor facilidad para entender la comunicación verbal, ya que podrán mantener dicha información en su mente el tiempo necesario para poder procesarla y entenderla correctamente. Así mismo, si son capaces de seguir las normas establecidas y tienen una buena habilidad para planificar, pueden constituirse como un modelo a seguir entre sus compañeras. Estos factores pueden llegar a facilitar que sean consideradas como un referente por sus iguales.

En la misma línea, se observó que una escasa habilidad de supervisión de uno mismo y de regulación de la propia conducta se relaciona con un bajo nivel de sensibilidad social. La capacidad de supervisarse a uno mismo es fundamental para ser consciente de los propios errores y corregirlos. Esta dificultad en la detección de los errores cometidos puede llevar a una mala gestión de la regulación conductual que podría ser interpretada como una falta de sensibilidad social, debido a la incapacidad de adaptar el propio comportamiento a las demandas sociales.

También se objetivó que una peor ejecución en regulación emocional y flexibilidad cognitiva conlleva niveles más altos de ansiedad y timidez y que un rendimiento peor en MT se relaciona con niveles más bajos de ansiedad y timidez. Tanto la flexibilidad cognitiva como la regulación emocional son importantes para conseguir un buen nivel de aceptación social ya que permiten poder adaptarnos a las demandas del ambiente. El presentar dificultades en estas habilidades puede llegar a generar conflictos en situaciones sociales, lo cual podría desencadenar un mayor nivel de ansiedad como respuesta a una situación de estrés y una tendencia a la timidez como mecanismo de defensa para intentar no exponerse a una situación estresante y conflictiva para ellas. Por el contrario, una baja capacidad de MT conlleva una mayor dificultad en la

identificación de los errores cometidos y por consiguiente una menor conciencia de dichos errores. Esta falta de conciencia de los errores cometidos repercute en un menor nivel de ansiedad y timidez. En un estudio anterior se encontró que las mujeres con SXF necesitan un mayor número de ensayos para la consolidación de la memoria (Keysor & Mazzocco, 2002). La MT es fundamental para la generación de recuerdos a medio y largo plazo. Una hipótesis explicativa sería que una baja habilidad en la MT dificultaría la consolidación de la información y la generación de recuerdos. Así pues, la persona tendría una menor conciencia de sus dificultades en la interacción social y, por lo tanto, se generaría una menor respuesta de ansiedad anticipatoria que a su vez conllevaría un mecanismo de defensa menos intenso y presentarían un menor grado de timidez. Dada la novedad de estos hallazgos y la falta de literatura previa al respecto se necesitarán nuevas investigaciones en las que se estudie la posible relación entre la MT y la ansiedad en chicas con SXF.

Otro aspecto a destacar es que una peor habilidad de organización de materiales está relacionada con mayores niveles de ansiedad social y que una buena capacidad para mantener la actitud y una buena regulación emocional influyen de forma positiva en la capacidad de integración y competencia social. Las chicas con una mayor habilidad para regular sus emociones, mantener su actitud y ser constantes en lo que están haciendo tienen un mayor nivel de aceptación social ya que estas habilidades mejoran su competencia social y por lo tanto su capacidad de integración.

En lo referente a la conducta adaptativa se observó que una mejor capacidad de abstracción verbal repercute de forma positiva en el nivel de adaptación conceptual. Este dominio de adaptación conceptual está compuesto por las habilidades académicas, de comunicación y de autodirección. Un mejor rendimiento en el razonamiento abstracto verbal es básico para poder organizar el pensamiento mediante el lenguaje, lo cual repercute en una mejora de la autodirección. Así mismo, el ser capaces de realizar un procesamiento más abstracto de la información verbal favorece la comunicación ya que nos ayuda a

poder interpretar los dobles sentidos y las ironías. En esta misma línea, una buena capacidad de abstracción verbal es fundamental para obtener la información importante de un texto, entender los enunciados y razonamientos matemáticos, las metáforas... aspectos que van muy ligados al rendimiento académico.

De igual forma, una mejor capacidad de inhibición, de supervisión de sí mismo, de control emocional y de MT repercute de forma positiva en el grado de adaptación social y la capacidad de autodirección. Tanto la habilidad para suprimir una respuesta automática y los distractores ambientales como el control emocional y la capacidad de autocrítica (supervisión de uno mismo) son habilidades que nos ayudan a adaptarnos a las demandas del ambiente. En consecuencia, cuanto más capaces sean de adaptarse a dichas demandas mayor nivel de adaptación conseguirán.

Así mismo las chicas con mejores habilidades organizativas (planificación/organización y organización de materiales) mostraron una mayor capacidad de autodirección. A mejores habilidades para la planificación/organización y organización de materiales menos necesidad de depender de otra persona que las ayude en la gestión y planificación de sus objetivos, por lo que serán chicas más autónomas en su día a día.

También se observó que un mayor nivel de regulación emocional y conductual conlleva una mejor adaptación social. Cuanto más capaces sean de regular sus emociones y sus conductas más hábiles serán también para adaptarse a las demandas sociales y por lo tanto mostrarán una mayor autonomía a nivel social. De igual modo, una mayor flexibilidad cognitiva mejora la capacidad de autodirección, adaptación social y adaptación conceptual. La habilidad para cambiar entre estados mentales, operaciones o tareas es una de las más importantes de todas las FE para conseguir adaptarse al entorno cambiante.

6.5. Artículo 4: "Bulling victimization in young females with Fragile X Syndrome"

Por último, para estudiar el riesgo que presentan las chicas con SXF de sufrir acoso escolar en el papel de víctima, así como su efecto sobre su capacidad de adaptación, estilo de socialización y estado emocional, se redactó el artículo 4 "Bulling victimization in young females with Fragile X Syndrome".

En primer lugar, se observó que si bien la ratio de chicas con SXF que había puntuado en la escala de "riesgo de acoso escolar" según la valoración de los padres era bastante similar al de las chicas del GC, se observó una tendencia diferente en el tipo de acoso sufrido en función del grupo. En el caso de las chicas con SXF se halló una mayor ratio de falta de apoyo social y aislamiento por parte de los compañeros (también denominado acoso indirecto). Estos hallazgos coinciden con lo publicado en la literatura previa en la que se describe que la exclusión social es la forma de acoso escolar experimentada más frecuentemente por las personas con algún tipo de discapacidad (física, intelectual o social) o con necesidades especiales (Stang et al., 2020; Maïano et al., 2016; Mayo et al., 2019). Por el contrario, las chicas del GC presentaron una mayor ratio de insultos por parte de los compañeros (acoso de tipo directo). Si bien es cierto que se observó esta tendencia, la diferencia entre ambos grupos no llegó a ser estadísticamente significativa, muy probablemente debido al tamaño reducido de la muestra.

En segundo lugar, se objetivó que las chicas que habían sufrido acoso escolar presentaban más síntomas depresivos, menores niveles de jovialidad y de recursos personales, más dificultades en el autocuidado y más dificultades en su integración y competencia social. Al analizar la influencia de los componentes del acoso escolar sobre cada una de las variables estudiadas, se observó que el riesgo de sufrir acoso escolar estaba relacionado con un empeoramiento en el

nivel de jovialidad, los recursos personales, la integración y la competencia social y los síntomas depresivos; la falta de apoyo social se asociaba con niveles más bajos de jovialidad, recursos personales e integración y competencia social; el aislamiento por parte de los compañeros mostraba una relación negativa con la integración y la competencia social; el hecho de sufrir insultos por parte de los compañeros repercutía negativamente en los recursos personales, los síntomas depresivos y la integración y competencia social; y el tener miedo de un compañero de clase se asoció a una menor habilidad de autocuidado.

En todas las interacciones encontradas entre el grupo y las diferentes formas de acoso escolar destacó un mismo patrón, en el que ante la presencia de las diferentes formas de acoso las chicas del GC mostraban un empeoramiento mucho más pronunciado que las chicas del grupo SXF. Las chicas con SXF suelen presentar rasgos de un Trastorno del Espectro Autista tales como déficits en la interacción y comunicación social, estereotipias y pobre contacto ocular (Visootsak et al., 2005). En este sentido, las dificultades en la interacción y comunicación social podrían llevar a una dificultad para interpretar las señales sociales e identificar las situaciones de acoso escolar de forma correcta, lo cual conllevaría una menor conciencia de la situación y, por lo tanto, un menor grado de afectación en sus niveles de jovialidad, recursos personales, autocuidado e integración y competencia social en comparación con las chicas del grupo control. Es importante destacar que el presentar una dificultad para la identificación de las situaciones de acoso escolar no implica la ausencia de las mismas. Este hecho puede colocar a las chicas con SXF en una situación de gran vulnerabilidad ya que ante una situación de acoso escolar no serán capaces de identificar las señales correctamente y, por lo tanto, no podrán gestionar y solventar la situación de forma adecuada. Esto concuerda con lo descrito anteriormente en la literatura por diferentes autores que destacan que los niños con discapacidades pueden presentar una falta o retraso en el desarrollo de las habilidades sociales que incrementa su vulnerabilidad ante el acoso escolar (Bourke, 2010; Dixon 2006; Stang 2020).

Por último, es importante destacar que los hallazgos realizados nos podrían estar indicando que a la hora de planificar las intervenciones con chicas con SXF en situaciones de acoso escolar, aparte de realizar un trabajo de mediación e intervención sobre el ambiente, debemos centrarnos de forma más específica en el trabajo directo con las propias chicas haciendo hincapié en el entrenamiento de las habilidades sociales, así como en la intervención sobre los déficits en la interacción y comunicación social.

6.6. Consideraciones finales:

Por lo que respecta a la capacidad intelectual, podemos concluir que la muestra estudiada es representativa de la población diana, ya que la distribución del CIT de la misma coindice con lo descrito previamente en la literatura científica. En este sentido, la literatura previa describe que un 50% de las mujeres con SXF presentan DI entre leve y moderada y el otro 50% presenta una capacidad intelectual en los rangos límite y medio (Keysor et al., 2002; Ferrando et al., 2004). En la muestra estudiada se reflejan estos valores con un 50% de participantes con un CIT en el rango de la DI leve-moderada (3,84% DI moderada y 46,15% DI leve) y un 50% de participantes con un CIT en los rangos límite y medio (38,46% límite y 11,53% medio). Al estudiar con mayor detenimiento las puntuaciones CIT obtenidas, vemos que el grueso de la muestra se encuentra en el rango de la DI leve y CIT límite. Este es un dato relevante y que debe ser destacado, ya que en la práctica clínica aún nos encontramos con la creencia extendida de que las chicas con SXF no tienen una afectación importante a nivel de capacidad cognitiva. Y nada más lejos de la realidad ya que según los datos obtenidos, tan solo un 11,53% de la muestra obtiene unas puntuaciones de CIT en el rango medio de la normalidad, mientras que el 88,45% restante obtiene puntuaciones de CIT a partir una desviación estándar por debajo de la media.

Respecto a las funciones cognitivas en las chicas con SXF (en comparación con las chicas del GC), se observó que tanto el lenguaje como las funciones ejecutivas juegan un papel importante en determinadas áreas de la conducta adaptativa, el estilo de socialización, la percepción social y el razonamiento aritmético. Así pues, los resultados muestran que en el caso de la Teoría de la Mente (Verbal y Total) existe una relación con la capacidad de abstracción verbal y el vocabulario expresivo. En el caso de la habilidad de liderazgo esta relación se da con la capacidad de abstracción verbal, la memoria de trabajo, la capacidad de planificación y organización, el seguimiento de la norma, la denominación, el vocabulario comprensivo y el reconocimiento de emociones. En la sensibilidad social se objetivó una asociación con la habilidad de supervisión de uno mismo, la regulación conductual y el reconocimiento de emociones.

Por otro lado, la ansiedad social guardaba una relación con la capacidad de organización de materiales; la habilidad de integración y competencia social con la regulación emocional y el mantenimiento de la actitud y la ansiedad-timidez con la memoria de trabajo, la regulación emocional y la flexibilidad cognitiva.

En lo respectivo al nivel de adaptación funcional o conducta adaptativa se observó que la habilidad de autodirección guarda relación con la supervisión de uno mismo, la memoria de trabajo, la capacidad de planificación-organización, la organización de materiales, la regulación emocional, la flexibilidad cognitiva, el control inhibitorio, la comprensión de instrucciones, el vocabulario expresivo y el CIT. La adaptación social está relacionada con la supervisión de uno mismo, la memoria de trabajo, la regulación emocional y conductual, el control inhibitorio y el vocabulario comprensivo. Y la adaptación conceptual se relacionó con el vocabulario comprensivo.

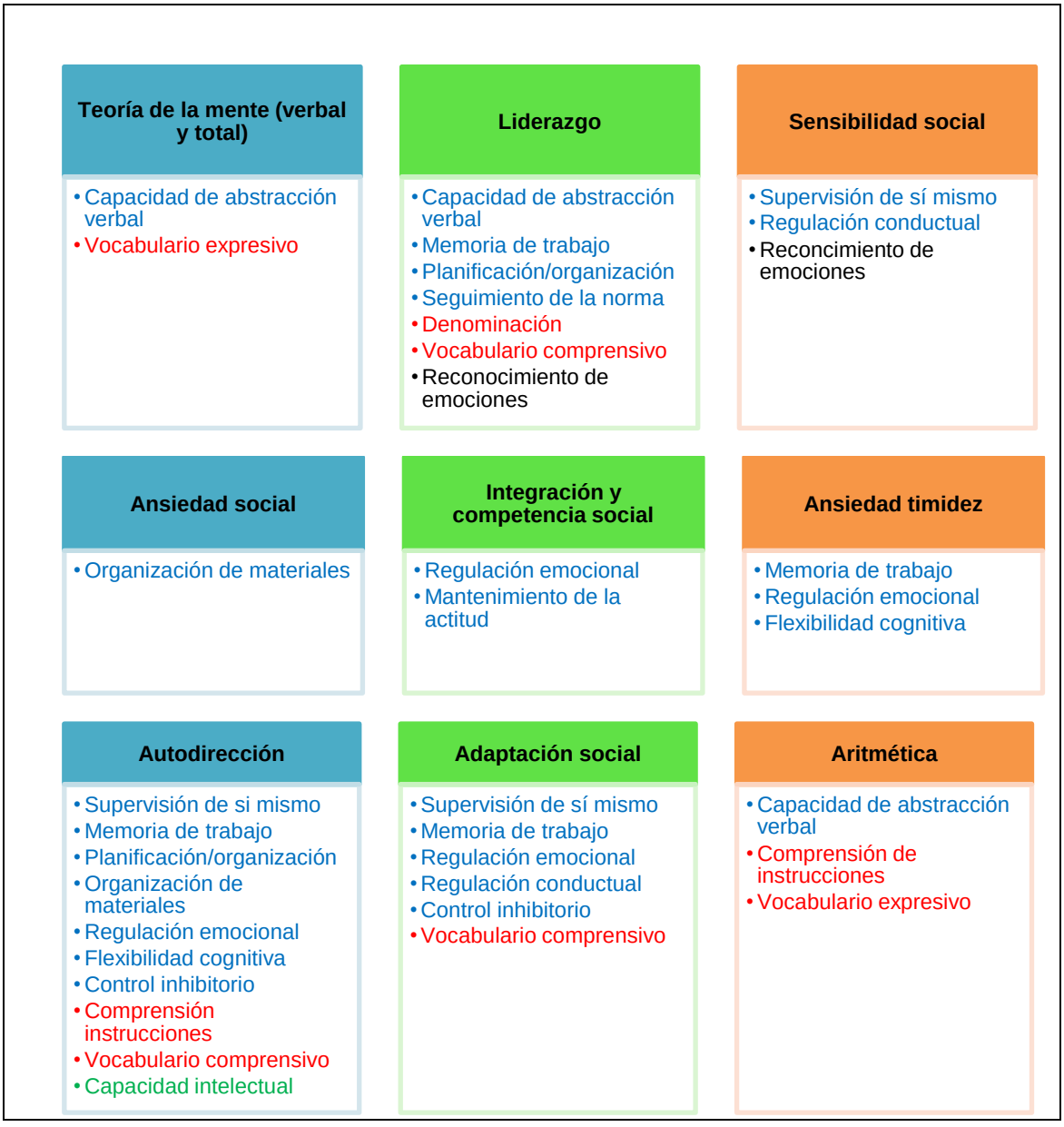
Las habilidades académicas guardaron relación con la habilidad de denominación. Así mismo, respecto a las dificultades en las matemáticas descritas ampliamente en la literatura previa, los hallazgos realizados muestran que éstas pueden ser debidas a una dificultad en la capacidad de abstracción verbal, en la comprensión de instrucciones y en el vocabulario expresivo y no a una alteración en las funciones visoespaciales. Estos hallazgos apuntarían hacia la necesidad de dar un mayor peso a las terapias de logopedia para estimular, potenciar y asentar ciertas áreas del lenguaje sobre las que después se sustentarán una serie de habilidades académicas.

Tomando en conjunto todos los resultados obtenidos en el análisis de las variables cognitivas, podemos concluir que las funciones ejecutivas tienen un peso importante en la gran mayoría de las áreas evaluadas, siendo así en el caso de la teoría de la mente, la habilidad de liderazgo, la autodirección, la sensibilidad social, la adaptación social, la integración y competencia social, la ansiedad-timidez, etc. (estos resultados están resumidos en la figura 5). En este sentido, sería importante implementar programas de intervención basados en la estimulación de las funciones ejecutivas para ayudar a las chicas con SXF a alcanzar un mayor grado de autonomía en su vida diaria, así como para mejorar en su estilo de socialización y en el razonamiento aritmético.

Por último. Es importante destacar que la habilidad de reconocimiento de emociones mostró una relación muy estrecha con la capacidad de liderazgo y la sensibilidad social. Las chicas con SXF no presentaron un mayor riesgo de sufrir acoso escolar que las chicas del GC, pero sí difirieron en el tipo de acoso sufrido que fue del tipo indirecto. Los hallazgos muestran que ante una situación de acoso escolar las chicas del GC experimentaron un empeoramiento más pronunciado en su estado emocional, estilo de socialización y conducta adaptativa, lo cual puede estar sugiriendo una dificultad en el grupo de chicas con SXF de identificar la situación de acoso y ser consciente de la misma. Este

hecho las sitúa en una posición de extrema vulnerabilidad y debe hacer extremar las precauciones a la hora de detectar una situación de posible acoso escolar ante cualquier pequeño cambio en su conducta o estado emocional.

Figura 5. Resumen de las relaciones entre las habilidades cognitivas y las variables de conducta adaptativa, estilo de socialización, aritmética y percepción social.



Azul = Función ejecutiva; Rojo = funciones lingüísticas; Negro = reconocimiento de emociones; Verde = capacidad intelectual.

7. CONCLUSIONES

7. Conclusiones:

- ✓ El grupo de chicas con SXF presentaron mayores niveles de ansiedad social que las chicas del grupo control.

- ✓ En el grupo de chicas con SXF:
  - Las funciones ejecutivas presentaron una asociación más fuerte con diferentes aspectos de la conducta adaptativa, el estilo de socialización y la integración y competencia social.
  - Las habilidades lingüísticas presentaron una fuerte relación con el razonamiento aritmético.
  - Se objetivó una importante asociación entre el reconocimiento de emociones con la capacidad de liderazgo y la sensibilidad social.

- ✓ No se observaron diferencias significativas entre ambos grupos al analizar la relación entre las funciones visoespaciales y el razonamiento cuantitativo (inducción matemática y aritmética).

- ✓ Respecto al riesgo de sufrir acoso escolar, a pesar de que ambos grupos presentaron la misma ratio difirieron en el tipo de acoso sufrido. Las chicas con SXF presentaron un tipo de acoso escolar indirecto, mientras que las chicas del grupo control eran más propensas a sufrir un acoso escolar directo.

- ✓ Ante una misma situación de acoso escolar las chicas del grupo control presentaron un empeoramiento más pronunciado en: síntomas depresivos, niveles de jovialidad, recursos personales, nivel de autocuidado e integración y competencia social.

- ✓ La presencia de rasgos TEA en las chicas con SXF pueden llevar a una dificultad en la interpretación de las situaciones sociales, entre ellas, el sufrir acoso escolar. Esta dificultad puede llevar a la falta de detección de

la situación de acoso escolar y, por lo tanto, a la falta de conciencia de la misma.

- ✓ Esta falta de identificación de la situación de acoso puede situar a las chicas con SXF en una situación de gran vulnerabilidad.

8. LIMITACIONES

8. Limitaciones.

Una de las limitaciones de la presente investigación, es el tamaño relativamente reducido de la muestra. Este hecho condiciona de forma importante el análisis estadístico de los resultados y ha podido repercutir a la hora de no encontrar un mayor número de diferencias estadísticamente significativas entre el grupo de chicas con SXF y el grupo control.

A pesar de que sólo se pudo contar con la participación de 26 chicas con SXF, es la mayor muestra de población femenina en edad infanto-juvenil recogida hasta la fecha en España y una de las mayores a nivel mundial. A lo largo de 4 años, la doctoranda viajó a diferentes puntos de España para conseguir incorporar el mayor número de participantes posible.

Otra limitación fue la gran dificultad encontrada para conseguir un mayor número de participantes para el grupo control. A pesar de esto, no existen diferencias significativas entre los grupos en las variables de edad, capacidad intelectual, síntomas TDAH y nivel socioeconómico.

Por otro lado, aunque todas las chicas del grupo control con DI contaban con un análisis genético que descartaba la presencia del SXF, en el caso de las chicas sin DI no se realizó el estudio genético por motivos éticos. Aun así, se hizo una evaluación clínica de las participantes para valorar si presentaban síntomas compatibles con el SXF (rasgos físicos, características cognitivo-conductuales) y se recabaron los antecedentes familiares preguntando de forma específica por la existencia de algún familiar con SXF.

Por último, es importante tener en cuenta que la valoración realizada mediante cuestionarios se limitó a los contestados por los padres de las participantes.

9. CONSIDERACIONES FINALES E INVESTIGACIONES FUTURAS

9. Consideraciones finales e investigaciones futuras.

Debido a las limitaciones de tiempo no fue posible ampliar el tamaño total de la muestra, ni administrar los cuestionarios en forma de entrevista a las participantes con DI. De cara a futuras investigaciones sería interesante ampliar y complementar la información obtenida mediante los cuestionarios de los padres con la información que pudieran aportar tanto los profesores como las propias participantes.

De los resultados obtenidos, se deduce que las funciones ejecutivas tienen un papel muy importante en áreas de las habilidades sociales y la conducta adaptativa como la capacidad de liderazgo, la teoría de la mente, la sensibilidad social, la adaptación social, etc. En este sentido, sería muy interesante realizar una intervención específica para estimular las funciones ejecutivas y ver si, mediante esta intervención, mejoran otras áreas del funcionamiento diario de las chicas con SXF.

En este mismo sentido, otra línea de investigación que podría iniciarse sería la de realizar una intervención logopédica para estimular la capacidad de abstracción verbal, la comprensión de instrucciones y el vocabulario expresivo y ver si dicha intervención repercute en una mejora en su rendimiento en tareas de razonamiento aritmético.

Respecto a los resultados que indican que una peor habilidad en memoria de trabajo se relaciona con niveles más bajos de ansiedad, sería interesante ampliar el estudio de esta relación.

Por último, teniendo en cuenta los resultados que apuntan a una dificultad en la detección de una posible situación de estar sufriendo acoso escolar, sería importante realizar un trabajo preventivo con las chicas con SXF centrándonos en trabajar las habilidades sociales, así como la interpretación e identificación de situaciones sociales de riesgo.

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11. ANEXOS

ANEXO 1.

LORENA JOGA ELVIRA - Re: American Journal of Medical Genetics: Part A

De: Ben Solomon <solomonbenjamind@gmail.com>
A: <ljoga@tauli.cat>
Fecha: 9/5/2021 16:29
Tema: Re: American Journal of Medical Genetics: Part A

Thanks - I have no objections.

Best,
Ben

On Sun, May 9, 2021 at 9:15 AM Lorena Joga-Elvira <onbehalfof@manuscriptcentral.com> wrote:

> 09-May-2021
>
> 20-0178.R2 - LANGUAGE IN YOUNG FEMALES WITH FRAGILE-X SYNDROME: INFLUENCE ON THE NEUROCOGNITIVE PROFILE AND ADAPTIVE BEHAVIOR.
>
> Dear Dr Solomon:
>
> I am currently doing my thesis and wanted to ask if it is possible to put a copy of the published paper "Language in Young Femlaes with Fragile X Syndrome: influence on the neurocognitive profile and behavior" as part of the dissertattion.
>
> The final version of the dissertation will be published in the repository of the Univertat Autònoma de Barcelona.
>
> Paper information:
> Article ID: AJMGA62130
> Article DOI: 10.1002/almg.a.62130
> Internal Article ID: 17010566
> Article: Language in Young Femlaes with Fragile X Syndrome: influence on the neurocognitive profile and behavior
>
> Sincerely,
> Mrs. Lorena Joga-Elvira
> American Journal of Medical Genetics: Part A

ANEXO 2

Re: Author query RIDD RIDD-D-20-00440R1 [210509-008697]

De: "Research in Developmental Disabilities" <ridd@elsevier.com>
A: LJOGA@tauli.cat; ridd@elsevier.com
Fecha: lunes - 10 mayo, 2021 11:31
Tema: Re: Author query RIDD RIDD-D-20-00440R1 [210509-008697]
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Best regards,

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Journal title: Research in Developmental Disabilities

Article title: FRAGILE X SYNDROME IN YOUNG FEMALES: INFLUENCE OF EXECUTIVE FUNCTION ON THE NEUROCOGNITIVE PROFILE AND ADAPTIVE BEHAVIOR

Manuscript number: RIDD-D-20-00440R1

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LORENA JOGA ELVIRA - RE: [EXTERNAL] Fwd: Child Neuropsychology

De: Jacobus Donders <Jacobus.Donders@maryfreebed.com>
A: "ljoga@tauli.cat" <ljoga@tauli.cat>
Fecha: 11/5/2021 13:47
Tema: RE: [EXTERNAL] Fwd: Child Neuropsychology
CC: William MacAllister <dr.bill.macallister@gmail.com>

Dear Ms. Lorena Joga:
That would be no problem, as long as you include a reference to published article.
Thanks for asking.
Best regards,

Jacobus Donders, PhD, ABPP |
Associate Editor, Child Neuropsychology
jacobus.donders@maryfreebed.com

---------- Forwarded message ---------
From: **Child Neuropsychology** <onbehalfof@manuscriptcentral.com>
Date: Sun, May 9, 2021 at 7:22 AM
Subject: Child Neuropsychology
To: <dr.bill.macallister@gmail.com>

09-May-2021

CNY-OA 20-136.R2 - Pilot Study of Socio-emotional factors and Adaptive Behavior in young females with Fragile X Syndrome

Dear Dr William MacAllister:

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Sincerely,
Ms Lorena Joga
Child Neuropsychology

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