Universitat Autònoma de Barcelona

SÍNDROME DE X FRÁGIL Y SÍNDROME DE DOWN: Problemas de comportamiento, competencia social y factores ambientales

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Tesis dirigida por:

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Agradecimientos

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Presentación

La Discapacidad Intelectual es inherente a la especie humana, sin embargo es un constructo social que ha ido cambiando a lo largo del tiempo y dependiendo de la aproximación y definición social que se le otorgaba en cada momento de la historia se configuraban las aproximaciones y las actuaciones que se realizaban con las personas con dicha condición. En la actualidad, ostentamos una concepción en la cual se considera que las dificultades con las que cuentan las personas con discapacidad intelectual pueden ser analizadas y tras ello, intervenidas de manera externa fomentando y ayudando a conseguir el máximo nivel de desarrollo individual que pueden alcanzar dichas personas. Asimismo, se considera que no solo los factores genéticos son los responsables de las dificultades que presentan, sino que también los factores ambientales determinan e interactúan con esas variables individuales lo que conlleva al nivel de desarrollo que obtienen los individuos.

En esta tesis, se analizan dos síndromes que producen discapacidad intelectual, en concreto, el Síndrome de Down y el Síndrome de X Frágil. Específicamente, se abordan tanto los problemas de comportamiento como de competencia social en ambos síndromes así como los diferentes factores que influyen en dichos problemas. Para ello, la tesis se desarrolla en tres capítulos:

En el primer capítulo se realiza una introducción sobre el estado actual y las diferentes variables de las que se va a hablar a lo largo de la tesis, incluyendo una descripción de ambos síndromes, los problemas que conllevan y los factores que influyen sobre ellos.

En el segundo capítulo se describen los tres estudios (2 artículos y un estudio enviado a una revista) que se han llevado a cabo, así como se realiza un análisis y una discusión de los resultados. El primer artículo ha sido publicado en la revista "Research in Developmental Disabilities" en diciembre de 2018 siendo un estudio empírico sobre la relación entre una actitud parental, la emoción expresada, y cómo ésta se relaciona con los problemas de comportamiento en sus

descendientes con Síndrome de Down y Síndrome de X Frágil. En el Anexo I se muestra la aprobación por parte de la revista para la aparición del artículo en la tesis doctoral. El segundo artículo es una revisión sobre los problemas de comportamiento y competencia social en individuos con Síndrome de X Frágil teniendo en cuenta tanto factores ambientales como trayectorias de desarrollo de dichos problemas. Ha sido publicado en la revista "Genes" en enero de 2022. En el Anexo II muestra la aprobación por parte de la revista para la aparición del artículo en la presente tesis. El estudio 3 es una revisión sobre problemas de comportamiento y competencia social en individuos con Síndrome de Down nuevamente focalizado tanto en el ambiente como en las trayectorias de desarrollo y ha sido enviado a la revista "Journal of Intellectual & Developmental Disabilities" en febrero de 2022. En el Anexo III se muestra la recepción del artículo en la revista.

Finalmente, en el tercer capítulo, se realiza una discusión general, unas conclusiones y se analizan las fortalezas y dificultades de los estudios realizados así como se plantean futuras líneas de investigación.

Presentation

Intellectual Disability is inevitably present in the human condition. However, it is a social construct that has changed during humankind's existence depending on people's beliefs and its definition. Which, in turn, also configured the attention and the treatment given to people with intellectual disabilities. Currently, it is believed that difficulties in people with developmental disabilities could be analyzed and supported by external aids to help them develop and achieve their greatest level of development by partially supplying those difficulties. Thus, along with genetic factors, environmental factors could determine and interact with the biological factors leading to the developmental level seen in individuals with intellectual disabilities.

This thesis analyzes two syndromes that cause intellectual disability, specifically Down syndrome and Fragile X syndrome. Particularly, behavior problems and social competence are addressed in both disabilities as well as factors that might influence behavior and social problems. The thesis compiles three chapters:

The first chapter provides a rationale and description of intellectual disability and the two syndromes, along with the different variables related to behavior problems and social competence.

The second chapter includes three studies (2 published papers and a study sent to a journal) developed to assess the objectives of the thesis. All of them include results and discussions about the findings. The first paper was published in the journal “Research in Developmental Disabilities” in December of 2018. It is an empirical study that addresses the association between a specific parental attitude, expressed emotion, and behavior problems in individuals with Down syndrome and Fragile X syndrome. In Appendix I, the confirmatory mail of the journal for using the article in the present thesis is displayed. The second paper is a systematic review of Fragile X Syndrome, which summarizes the main results of studies conducted during the last 20 years concerning behavior problems and social competence considering environmental factors and developmental trajectories. It was published in the “Genes” journal in January of 2022. In Appendix II, a

confirmatory email for including the paper on the present thesis is displayed. The third study is a structured review focusing on behavior problems and social competence in individuals with Down syndrome, considering environmental factors and developmental trajectories. It was submitted to the "Journal of Intellectual & Developmental Disabilities" in February of 2022. In Appendix III, the email from the journal stating they have received the study is shown.

Finally, in the third chapter, a general discussion, conclusions, limitations and strengths of the studies developed are shown along with future research lines.

Capítulo 1

1.1. Introducción

1.1.1. Discapacidad Intelectual

La Discapacidad Intelectual (DI) ha estado presente durante toda la existencia de la humanidad, si bien la comprensión de su naturaleza y el diagnóstico de la misma se ha ido desarrollando lentamente (Verdugo, 1994). Al ser una construcción social definida arbitrariamente por las personas, el constructo DI ha ido cambiando a lo largo de los años (Landesman y Ramey, 1989). Pasando en 1992 de un modelo de deficiencia, en el cual se consideraba a la DI como una condición estática que no podía modificarse, a un modelo de apoyos en el cual tanto los factores ambientales como los personales podían interactuar produciendo mejoras en el desarrollo de los individuos con DI (Reiss, 1994; Luckasson et al., 1992). La representación gráfica del modelo de apoyos (Luckason et al., 2002) se encuentra en la figura 1.

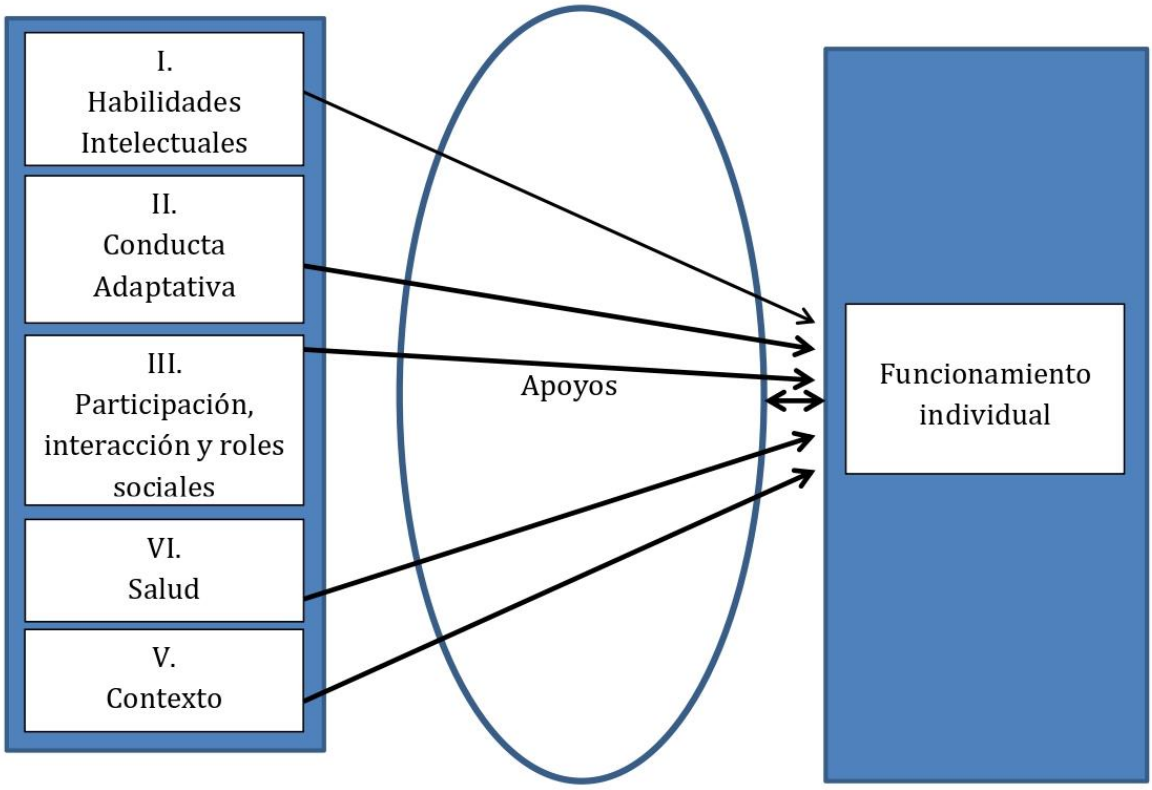

Figura 1. Modelo de apoyos. Adaptado de *Mental retardation: Definition, classification, and systems of supports* (p. 10), por R. Luckasson et al., 2002, American Association on Mental Retardation.

Este fue el punto de partida a partir del cual se comenzó a considerar que los apoyos ambientales (del hogar, la comunidad o la escuela) podían mejorar el funcionamiento de los individuos con DI así como sus capacidades para conseguir una mejor vida (Luckasson et al., 1992; American Association on Intellectual and Developmental Disabilities [AAIDD], 2021). Considerando que una vez identificados los factores ambientales que influyen en su funcionamiento, se podrían modificar y por lo tanto reducir aquellas dificultades asociadas a la DI (Schneidert et al., 2003). En la actualidad, la definición de DI de acuerdo con la AAIDD (2021) incluye limitaciones significativas en dos áreas principales: el funcionamiento intelectual y comportamiento adaptativo, afectando las habilidades sociales y prácticas del día a día que se originan antes de los 22 años de edad. Sin embargo, diferentes individuos con diferentes síndromes que causan DI no muestran las mismas dificultades o deterioros en los mismos dominios sino que más bien muestran perfiles mixtos en los cuales dependiendo de cada síndrome, hay un patrón de fortalezas y debilidades en sus habilidades (Fidler et al., 2009). Dos de los síndromes que causan DI son el Síndrome de X Frágil (SXF) y el Síndrome de Down (SD) (American Psychiatric Association, 2021).

1.1.2. Síndrome de X Frágil

El Síndrome de X Frágil es la principal causa hereditaria de DI con una prevalencia de 1 entre 4.000 hombres y 1 entre 8.000 mujeres (Crawford et al., 2001; Bear et al., 2004; Coffee et al., 2009), aunque prevalencias mayores han sido reportadas por la National Fragile X Syndrome Foundation (2021) señalando que 1 de cada 3.600/4.0000 hombres y 1 de cada 4.000/6.000 mujeres tienen SXF. Las personas con SXF suelen mostrar deterioro de las funciones cognitivas de medio a moderado así como problemas clínicos, físicos y comportamentales (Hagerman, 2002). Aunque en mujeres, el deterioro cognitivo suele ser medio debido al segundo cromosoma X que poseen, y que no se ve afectado por la enfermedad, permitiéndoles compensar parcialmente la afección que provoca el SXF mediante la producción de la proteína FMRP, aunque no completamente (Cornish et al., 2008; Tassone et al., 1999). Prácticamente todos los hombres con SXF y aproximadamente un tercio de las mujeres tienen DI (Rousseau et al., 1994).

El SXF es causado principalmente por una expansión del número de repeticiones de Citosina Guanina Guanina (CGG) en la cadena del cromosoma X (Symons et al., 2003; Verkerk et al., 1991). La expansión de la cadena inactiva el gen *FMR1* no permitiendo que el mismo produzca la proteína FMRP que es necesaria para el desarrollo neuronal normal (Bassell y Warren, 2008). En la población que no está afectada por el síndrome, los alelos normales del gen tienen entre 6 y 44 repeticiones CGG, siendo dichas repeticiones estables (Maddalena et al., 2001; Nolin et al., 2003). Sin embargo en los individuos que poseen alelos con la premutación, es decir que cuentan con entre 55-200 repeticiones, hay una tendencia hacia la expansión en el número de repeticiones llegando a la mutación completa, más de 200 repeticiones, en una generación (Nolin et al., 2003; Fu et al., 1991). El SXF afecta a aquellos individuos con la mutación completa cuyos alelos son silenciados debido al número de repeticiones y no pueden producir la proteína lo que causa el síndrome propiamente (Hagerman et al., 2008; Basuta et al., 2015). Existe también un fenotipo que ocupa los alelos de la zona intermedia (zona gris) con individuos que poseen entre 45 y 54 repeticiones de la cadena CGG, que en ocasiones debido al tamaño del número de repeticiones, pueden expandirse en futuras generaciones, si bien, la mutación completa en una sola generación es altamente improbable en individuos con alelos en la zona intermedia (Maddalena et al., 2001; National Fragile X Syndrome Foundation, 2021). En más del 98% de los casos, la causa del SXF es el número de repeticiones CGG aunque en ocasiones, raras mutaciones y variaciones genéticas pueden causar SXF sin la expansión de la cadena CGG (Collins et al., 2010).

Las personas que tienen la premutación no tienen SXF propiamente, sin embargo no están exentas de dificultades asociadas con tal condición. Si bien en los inicios de estudio del síndrome se creía que las personas con la premutación no mostraban signos de afectación psicológica, considerando como única condición el hecho de que sus descendientes pudieran heredar la mutación completa (Johnson et al., 2020), varias dificultades como déficits de aprendizaje, ansiedad social y aislamiento social se han relacionado con la premutación (Hagerman, 2002). Del mismo modo, revisiones como la de Wheeler et al. (2014) señalan como posibles condiciones asociadas a la premutación los déficits en funciones ejecutivas, afectaciones en la memoria, trastornos afectivos, trastornos de ansiedad y

síntomas de Trastorno por Déficit de Atención e Hiperactividad (TDAH) entre otras condiciones. Además, las personas con la premutación pueden desarrollar lo que se denomina el síndrome de temblor y ataxia asociado al síndrome de x frágil (FXTAS por sus siglas en inglés) que es un síndrome neurodegenerativo que afecta al 46% de los hombres y el 17% de las mujeres con la premutación (Garcia-Arocena y Hagerman, 2010). Dicho síndrome además de producir ataxia como su propio nombre indica, incluye otros síntomas como parkinsonismo y deterioro cognitivo, particularmente de las funciones ejecutivas, neuropatía periférica y disfunción autonómica (Leehey et al., 2008). Tanto hombres como mujeres pueden tener la premutación, sin embargo, quitando contadas excepciones, los padres no transmiten la mutación completa a sus descendientes sino que es la premutación la condición que es heredada. En el caso de las mujeres, éstas tienen un 50% de probabilidades de transmitir la mutación completa o la premutación a su descendencia (Bangert et al., 2021).

1.1.3. Síndrome de Down

El Síndrome de Down es la principal causa genética de DI (Presson et al., 2013). De acuerdo con la National Down Syndrome Society (2021), la prevalencia estimada es de 1 por cada 700 bebés nacidos en Estados Unidos. El SD fue descrito por primera vez por John Langdon Down en 1866 siendo el síndrome cromosómico humano mejor conocido (Sierra-Romero et al., 2014). Su causa es una copia extra del cromosoma 21 (trisomía 21) aunque alrededor del 1% de los individuos con SD tienen mosaicismo para la trisomía y en torno a otro 4% se producen por la translocación de parte del cromosoma 21 a otro cromosoma (National Down Syndrome Society, 2022). Debido al cromosoma extra hay un incremento en la expresión de las proteínas lo cual afecta al desarrollo neuronal de los niños, provocando en última instancia cambios estructurales en el cerebro y cambios comportamentales en las personas con SD (Patterson, 1995). Esta circunstancia se ve reflejada en la DI de los individuos con SD que se establece entre la profunda y la límite, siendo la media de cociente intelectual de 50 puntos y exhibiendo puntuaciones que oscilan entre los 30 y los 70 puntos en general (Vicari et al., 2005).

Entre las personas con SD que tienen edades superiores a los 45-50 años existe un riesgo aumentado de desarrollar demencia (Farriols-Danés, 2012). La prevalencia del deterioro cognitivo en población con SD se ha estimado en torno al 55% de individuos con edades entre los 40-49 años y hasta el 77% de aquellos que tienen entre 60-69 años (Ballard et al., 2016). La demencia más frecuentemente asociada al SD es la enfermedad de Alzheimer (Farriols-Danés, 2012). Son las propias características del SD las que conllevan a una mayor frecuencia en la enfermedad de Alzheimer en comparación con la población general (Ballard et al., 2016). Debido al tercer cromosoma 21, hay una producción excesiva de la proteína precursora de amiloides (Lott y Head, 2019) que lleva a la formación de placas seniles por acumulación de β-amiloides en el cerebro, facilitando en última instancia el desarrollo de demencia (Glenner y Wong, 1984). Se considera que en torno al 80% de individuos con SD mayores de 40 años poseen los signos neuropatológicos de la enfermedad de Alzheimer, sin embargo, la aparición de la sintomatología asociada no es inmediata sino que puede retrasarse unos años (Bittles et al., 2006).

1.1.4. Comorbilidades

Los individuos con DI tienen un mayor riesgo de sufrir comorbilidades con otros trastornos mentales como TDAH, trastornos del estado de ánimo, trastorno del desarrollo generalizado, trastornos de estereotipia… entre otros y en comparación con individuos de desarrollo típico (American Psychiatric Association, 2022; Brue y Wilmshurst, 2016). Por ello, no es extraño que los individuos con SXF y SD muestren ciertas comorbilidades. En particular, las comorbilidades más frecuentes asociadas con el Síndrome de Down incluyen autismo (7-8%), Trastorno de Espectro Autista (TEA; 19%) y TDAH (6-44%) (Kent et al., 1999; Dykens, 2007; Ekstein et al., 2011; Moss et al., 2012). Algunos problemas de comportamiento en el SD han sido asociados a la comorbilidad con autismo como un mayor aislamiento social, pobre contacto ocular, fijaciones por partes específicas de objetos, intereses restringidos, aleteo de manos, comportamientos compulsivos y balanceos del cuerpo (Kent et al. 1999). De acuerdo con Ghaziuddin (1992) si bien la comorbilidad con el autismo normalmente ocurre en un bajo porcentaje de casos con SD, puede que éste sea más común en aquellos individuos con elevados

problemas de comportamientos. Por lo que respecta al SXF, el autismo, la ansiedad y los problemas de atención son las condiciones comórbidas en las que un mayor número de estudios se han centrado (Raspa et al., 2017). De hecho, el SXF es la principal causa de autismo (García-Nonell et al., 2006; Hagerman, 2002) con una comorbilidad estimada del 30% (Harris et al., 2008). Dada la elevada comorbilidad y a que más del 90% de los varones con SXF presentan sintomatología autista (Harris et al., 2005), existe un gran debate relativo a si los comportamientos presentes en individuos con SXF son parte del autismo o dependen de mecanismos diferentes (Thurman et al., 2014). En cuanto a las estimaciones de TDAH, éstas rondan el 73% de los varones con SXF, lo que supera en un 40% la comorbilidad que presentan los individuos de desarrollo típico (Baumgardner et al., 1995) y en el caso de la ansiedad, un 51.6% de los adolescentes con SXF muestran trastorno de ansiedad según Ezel et al. (2019).

1.1.5. Problemas de comportamiento

En esta tesis entendemos dentro del conjunto de problemas de comportamiento aquellos identificados como externalizantes por Achenbach y Edelbrock (1993) incluyendo comportamientos agresivos, impulsivos, de agitación psicomotora, de desobediencia y comportamiento antisocial. Así como los problemas de comportamiento internalizantes como la ansiedad, el retraimiento, la depresión y los sentimientos de inferioridad (Achenbach et al., 1993). Si bien, en las dos revisiones realizadas en la presente tesis (artículo 2 y estudio 3), agrupamos los comportamientos internalizantes dentro de la competencia social debido a la abundante conexión en la literatura entre síntomas internalizantes y competencia social en etapas de niñez y adolescencia (Bornstein et al., 2010). El origen de los problemas de comportamiento (internalizantes y externalizantes) en las personas con DI estaría en las dificultades de procesamiento de la información, problemas orgánicos, factores culturales y/o familiares y en las dificultades sensoriales (Eaton y Menoslacino, 1982). En conjunto, el origen resultaría de una compleja interacción entre factores biológicos, psicológicos, sociales y del desarrollo (Jones et al., 2008). Los problemas de comportamiento se relacionan con la etapa de desarrollo y también ocurren en individuos sin DI (Coronel, 2018) llegando a suponer una gran dificultad en las relaciones con el entorno e interferir con el

desarrollo tanto emocional como social e intelectual (Brian-Sulkes, 2020). En las personas sin DI conforme se van desarrollando, sus problemas de comportamiento disminuyen o llegan a desaparecer (Mangrulkar et al., 2001), sin embargo, en los individuos con DI, dichos problemas de comportamiento tienden a mantenerse en etapas de desarrollo posteriores (Coronel, 2018). El interés por los problemas de comportamiento en los síndromes que causan DI es apoyado por los estudios que encuentran que particulares síndromes exhiben un mayor número o una mayor frecuencia de problemas de comportamiento que los individuos de desarrollo típico (DT) emparejados por edad de desarrollo (Bodifish y Lewis, 2002). Así como por las implicaciones que algunos problemas de comportamiento tienen en la calidad de vida, el desarrollo y la competencia social de los individuos con DI (Holden y Gitlesen, 2006).

Por añadido, las comorbilidades presentes en ambos síndromes pueden dar lugar a una mayor gravedad en los problemas de comportamiento que en individuos no comórbidos. Así, se ha encontrado en individuos con SD con autismo comórbido, una mayor intensidad en conductas estereotípicas, e hiperactividad (Moss et al., 2012). Y del mismo modo, es probable que la comorbilidad de autismo y SXF lleve a un mayor número de problemas de comportamiento (Razak et al., 2020). De hecho un mayor número de comportamientos repetitivos y desafiantes se han encontrado en adultos y adolescentes con SXF y autismo en comparación con aquellos que solo tenían SXF (Smith et al., 2012).

1.1.6. Competencia social

Desde hace mucho tiempo, se considera la competencia social como una parte definitoria de la DI, anteriormente denominada retraso mental, haciendo hincapié en las carencias que presentaba el concepto de edad mental para definir la DI sin considerar el funcionamiento social (Doll, 1936). Sin embargo, la competencia social ha estado enmascarada bajo el concepto de funcionamiento adaptativo (García-García, 1997). Dicho concepto, es referido a la eficiencia con la que una persona puede responder de manera adecuada a las demandas naturales y sociales de su ambiente (Dressler et al., 2010). Por lo tanto abarca de manera amplia aquellas actividades del día a día necesarias para la actividad personal y social. Y aunque ha habido modelos que proponen una separación entre las conductas

adaptativas referidas al funcionamiento académico y aquellas más sociales (Schaefer, 1981) en la actual definición de la AAIDD (2021) todavía se hace referencia al funcionamiento adaptativo con el término "comportamiento adaptativo". Por lo tanto en la actualidad sigue sin establecerse una división clara entre aspectos muy interrelacionados como la inteligencia y las habilidades sociales como ya señaló Reschly (1985).

El constructo competencia social hace referencia tanto un fenómeno asociado con el desarrollo que cambia a lo largo de los años mientras el individuo crece (ontogénesis) como a las características de una situación social específica en un momento concreto (microgénesis) capturando la relación cambiante entre factores de desarrollo, cognitivos y sociales (Iarocci et al., 2008). Solo puede ser definido teniendo en consideración a "los otros" al estar inherentemente asociado a las interrelaciones entre personas y grupos (Keung-Ma, 2012). De acuerdo con Stichter et al. (2012), la competencia social implica más que las habilidades sociales, es fundamental para desarrollar las interacciones sociales y establecer y preservar los vínculos afectivos con los otros. De hecho, de acuerdo con el modelo de competencia social de Vaughn y Hogan (1990), son cuatro los constructos que se deben tener en cuenta: las relaciones con iguales o las relaciones positivas con otros individuos, la cognición social acorde a la edad de desarrollo, los problemas de comportamiento y las habilidades sociales efectivas. De hecho, en la revisión de Hukkelberg et al. (2019) realizada en población general se ha encontrado una correlación negativa con un tamaño medio de efecto entre los problemas de comportamiento y la competencia social. Por lo tanto bajo el término competencia social se incluirían habilidades como la empatía, el compartir con otros (posesiones, experiencias y emociones), interactuar, sentir compasión y ayudar a otros (Jędrzejowska, 2020). Sin embargo, la amplitud de términos y conceptos incluidos bajo los constructos competencia social y conducta adaptativa dificultan lograr una evaluación adecuada, así como la relatividad contextual inherente a la competencia social pues lo competente en unas ocasiones no lo es en otras (Peredo-Videa y Ángeles, 2016). De modo que por lo general, se considera a un individuo como socialmente competente cuando este consigue ajustarse a una demanda social (Crick y Dodge, 1994).

Tradicionalmente, el desarrollo social de los individuos con SD se ha considerado un área de relativa fortaleza (Gibbs y Thorpe, 1983) consistentemente con el estereotipo de que los niños con SD son muy sociables (Wishart y Johnston, 1990). Dicha concepción era apoyada por estudios que mostraban que los individuos con SD mostraban una mayor disposición a la interacción social que individuos con otras DI (Kasari et al., 1995; Kasari y Freeman, 2001). De hecho, en comparación con otras áreas personales como la cognición o el lenguaje, el desarrollo social se sigue considerando un área de fortaleza en individuos con SD (Guralnick et al., 2011). Sin embargo, que el área social sea una fortaleza no significa que no se hayan encontrado diferencias en comparación con individuos de DT, de hecho son numerosos los estudios que han señalado que los individuos con SD tienen unas habilidades sociales más pobres que los individuos de DT emparejados por edad mental, aunque en ciertas áreas sociales específicas como el juego interactivo, el comportamiento prosocial o el funcionamiento comunitario no se han encontrado diferencias en comparación con individuos DT (Naess et al., 2017). De hecho, recientes estudios demuestran que el desarrollo social en los individuos con SD muestra una tendencia a seguir un patrón similar al de los pares de DT aunque a un ritmo más lento (Grieco et al., 2015), llevando a importantes diferencias en comparación con los individuos de DT con el paso de los años (Cebula et al., 2010).

Respecto a los individuos con SXF tanto la ansiedad social como las dificultades sociales no autistas son características frecuentemente señaladas en su fenotipo (Grau et al., 2015). Dicha ansiedad social se ve reflejada en los comportamientos de los individuos con SXF como las estereotipias, las conductas agresivas y/o disruptivas o la agitación psicomotriz (Cornish et al., 2001). Y específicamente hay ciertos déficits sociales únicos identificados en SXF (Bruno et al., 2014) como la evitación del contacto ocular que se ha demostrado que son una manifestación de la aversión que sienten los individuos con SXF ante la iniciación del contacto ocular en oposición a los individuos con autismo que a veces parecen insensibles a la mirada social (Cohen et al., 1989). Del mismo modo, una mayor ansiedad social en población general se ha relacionado con menores habilidades sociales y viceversa (Caballo et al., 2014). De hecho, los déficits sociales en el Síndrome de X Frágil así como su timidez y su angustia ante las situaciones de interacción social, se atribuyen en gran medida a la ansiedad social que experimentan y no a una

reducción en el interés social o a la presencia de indiferencia que sí ocurre en el espectro autista (Hong et al., 2019; García-Nonell et al., 2006).

Por añadido a estas deficiencias mostradas en ambos síndromes, la presencia de comorbilidades que presentan los individuos con SXF y SD con por ejemplo el autismo, impactan las áreas de competencia social que son características propias del espectro autista afectando tanto el inicio como el mantenimiento de las interacciones sociales (Hale y Tager-Flusberg, 2005). Esto se ha observado particularmente en individuos con SXF y autismo comórbido en los cuales se aprecian mayores deterioros en la comunicación social que en los individuos que solo tienen SXF (Razak et al., 2020; Smith et al., 2012) y también en individuos con SD y autismo comórbido en cuanto a habilidades de socialización mostrándose menos competentes que los individuos con SD únicamente (Dressler et al., 2011).

1.1.7. Fenotipos conductuales

Los fenotipos conductuales pueden ser entendidos como patrones cognitivos, de personalidad, comportamentales, motores, lingüísticos, psiquiátricos y sociales que caracterizan un síndrome específico o trastorno biológico (Flint y Yule, 1994; Cassidy y Morris, 2002). Incluyen por lo tanto patrones específicos de comportamiento que se relacionan con trastornos genéticos en los que genes específicos estarían implicados en el desarrollo de determinados fenotipos conductuales (O'Brien, 2006; Hall et al., 2006). De modo que personas con un determinado síndrome exhiben con una mayor probabilidad uno o más de esos patrones comportamentales en comparación con individuos con otros síndromes (Dykens, 1995). Aunque un mismo comportamiento puede ser compartido por varios síndromes no siendo específico a un único síndrome (Fidler, 2005). Tanto el SXF como el SD cuentan con fenotipos conductuales definidos (Smith et al., 2012; Backes et al., 2000; Chapman y Hesketh, 2000).

Dentro del fenotipo conductual de los individuos con SD se encuentra una relativa fortaleza en el funcionamiento social (Wishart y Johnston, 1990), menores problemas adaptativos que otros individuos con DI (Chapman y Hesketh, 2000) y menores problemas de comportamiento que otros individuos con DI como la hiperactividad (Waltz y Benson, 2002). El fenotipo conductual del SXF incluye comportamientos como la agresión, conductas autolesivas, hiperactividad,

inatención y comportamientos estereotípicos (Hatton et al. 2002). Trastornos comórbidos como el TDAH, el espectro autista o la ansiedad (Cicaccio et al., 2017; Bailey et al., 2008). Y específicamente, la evitación de la mirada en el SXF se ha considerado como una manifestación del síndrome casi específica de individuos con SXF (Hall et al., 2006). En las mujeres con mutación completa en concreto el fenotipo conductual incluye aislamiento, evitación social timidez y trastornos comórbidos como la ansiedad, fluctuaciones del estado de ánimo y depresión (Chun-Hui et al., 2009).

1.1. 8. Ambiente

Los comportamientos de los individuos con DI no solo dependen de sus fenotipos conductuales sino que también sus características individuales interactúan con los factores contextuales pertenecientes a la familia, los pares, la escuela, la comunidad y la cultura produciendo variabilidad en el desarrollo de los individuos (Iarocci et al., 2008). De hecho, los fenotipos conductuales no son algo estable sino que más bien, se vuelven aparentes conforme el individuo se desarrolla, no es algo que se aprecie desde el nacimiento sino que tanto componentes genéticos, epigenéticos y ambientales influyen en cómo el fenotipo se expresa en cada persona (Karmiloff-Smith, 2016). Tal y como determina el modelo bioecológico de Bronfenbrenner y Ceci (1994), los genotipos parentales y los fenotipos influencian la genética y consecuentemente los fenotipos observados en los niños pero también los procesos proximales, entendidos como las interacciones con en el entorno, personas, objetos y símbolos pueden modificar las características genéticas del niño. De ese modo, el niño selecciona, modifica y construye su propio mundo como se aprecia en la figura 2. En dicha imagen, se puede observar como los procesos proximales correspondientes a pobres entornos no permitirán que el individuo desarrolle todo su potencial genético (baja actualización del potencial genético), mientras que los procesos proximales de entornos enriquecidos ayudarán a que desarrolle su potencial al máximo nivel (potencial de actualización más alto).

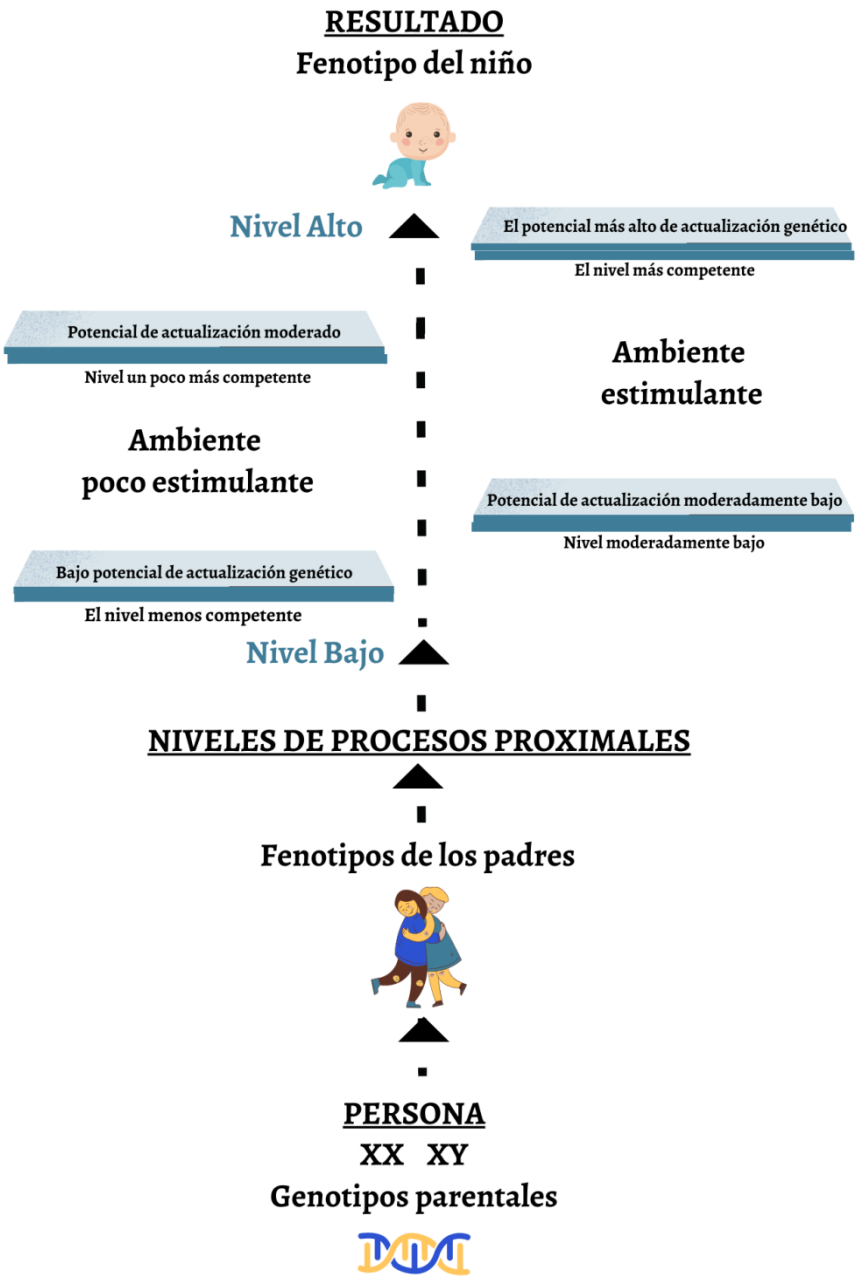

Figura 2. Adaptado de "Nature-nurture reconceptualized in Developmental perspective: A bioecological model" (p. 581), por U. Bronfenbrenner y S. J. Ceci, 1994, *Psycological Review*, *101*(4), 568–586.

De acuerdo con este modelo, se ha visto que factores ambientales como altos niveles de cohesión familiar, armonía y un entorno familiar orientado a los niños con DI se han relacionado con mayores niveles de comportamiento adaptativo, un menor número de problemas de comportamiento y un menor aislamiento social en la descendencia (Mink et al., 1983). Del mismo modo, en individuos de DT el afecto parental y el apoyo se han relacionado con menores problemas externalizantes

(Caspi et al., 2004). Sin embargo según Phillips et al. (2017) las madres de niños con SD utilizan un mayor estilo autoritario y en menor medida un estilo permisivo que las madres de niños de DT. Y un mayor nivel de conflicto familiar ha sido observado en familias de individuos con SXF en comparación con SD (Lewis et al., 2006) pese a que el conflicto familiar puede interferir con el afecto parental y el vínculo que caracteriza la cohesión en la familia (Eisenberg et al., 2005). Del mismo modo, se ha visto que los comportamientos de los padres como los cuidados parentales, tal y como sucede con niños de DT, pueden contribuir a la mejora del desarrollo en niños con autismo y por lo tanto son una parte fundamental de las intervenciones con niños con trastorno del espectro autista (Crowell et al., 2019).

Los fenotipos conductuales además de interferir en el desarrollo de los niños con síndromes genéticos también producen cambios en el contexto familiar y social cambiando las percepciones y las reacciones de las personas que los rodean (Hodapp, 1997). A esto se le denomina "efecto indirecto" referido al efecto que un individuo causa en su propio entorno produciendo percepciones específicas de los padres debido a sus comportamientos fenotípicos particulares (Hodapp, 2003). Son diversos los patrones de reacciones y percepciones en padres que se han encontrado dependiendo del tipo de discapacidad en lo referido al estrés y al apoyo en las familias de individuos con diferentes síndromes (Fidler et al., 2000). Por todo ello, la crianza de individuos con discapacidad suele ser un reto complejo para los padres (Fielding-Gebhardt et al., 2020) así como el cuidado de adultos que se dificulta aún más cuando los mismos cuentan con elevados problemas de comportamiento (Haveman et al., 1997).

Al mismo tiempo, las características de los padres también pueden influir en los comportamientos de su descendencia. De acuerdo con el estudio de Mak et al. (2020) realizado con individuos de DT el estrés parental se asoció con estilos educativos parentales negativos que mediaron la relación entre el estrés parental y problemas de comportamiento en sus hijos. Del mismo modo, el estrés parental se ha asociado con comportamientos internalizantes y externalizantes en muestras de individuos con DI durante 15 años de estudio (Woodman et al., 2015). Además en madres de individuos de DT, la emoción expresada, un constructo referido al clima emocional en las familias, se ha identificado como predictor del

comportamiento antisocial en la descendencia (Caspi et al., 2004) y niveles más elevados de emoción expresada han sido encontrados en madres de individuos con DI en comparación con madres de individuos de DT (Beck et al., 2004). Además, se han encontrado efectos bidireccionales entre el bienestar psicológico de las madres de individuos con DI y los problemas de comportamiento de los mismos en estudios longitudinales, estableciendo relaciones entre los síntomas depresivos en madres y los comportamientos internalizantes en su descendencia y el afecto positivo en las madres y los problemas de comportamiento asociales en su descendencia (Orsmond et al., 2003). Sin embargo, tal y como señalan Laghezza et al. (2010), son escasas las investigaciones que se centran en los estilos parentales en individuos con DI. Más bien, las investigaciones se suelen centrar en cómo los problemas de comportamiento de los descendientes afectan a las características parentales (Woodman et al., 2015).

Particularmente, en el caso de los individuos con SXF, las madres son portadoras de la premutación de dicho síndrome o pueden poseer la mutación completa. Los problemas clínicos que pueden experimentar las madres afectan tanto a las condiciones de la madre como a las de sus descendientes con SXF (Bangert et al., 2021). Influyendo también en su relación con sus hijos dado que específicamente, en el caso de mujeres con la premutación, se han encontrado rasgos clínicos importantes como una mayor timidez, ansiedad y fobia social en aproximadamente el 25% de mujeres portadoras (Artigas-Pallares et al., 2001; Cornish et al., 2008). Además en las madres de niños con SXF se ha observado una percepción de menor cercanía en la relación con sus hijos en comparación con las madres de SD (Abbeduto et al., 2004), siendo dicha percepción de poca cercanía mayor todavía en aquellas madres de niños con SXF y autismo comórbido (Lewis et al., 2006). Del mismo modo, las madres de individuos con SXF en comparación con aquellas de SD fueron más pesimistas en el estudio de Lewis et al. (2006). Por todo ello, las madres de individuos con SXF se encuentran en una posición de mayor vulnerabilidad en comparación con las madres de individuos con SD.

La figura 3 representa de una manera visual y simple cómo se configurarían todos estos factores considerados en la presente tesis doctoral. Los individuos con discapacidad partirían con una genética determinada, heredada de sus padres, la

cual conlleva unas tendencias a desarrollar ciertas comorbilidades, ciertos problemas de comportamiento y una cierta competencia social que se expresarán de manera fenotípica en función del ambiente (apoyos, características del hogar, pares, escuela, programas de intervención que reciban, padres, etc.) en el que los individuos se desarrollan. Dichos problemas de comportamiento y de competencia social serían la manifestación fenotípica individual de las dificultades que presentaría la persona con discapacidad en el entorno en el que se desarrolla. Los problemas de comportamiento como la hiperactividad o el retraimiento, además de producir dificultades en los individuos por sí mismos también afectarían la capacidad de competencia social de los individuos con discapacidad. Y a su vez los problemas de comportamiento y la competencia social exhibida por los individuos con DI, pueden provocar efectos indirectos en los padres o cuidadores más cercanos (flechas azules curvas) los cuales también modificarán la interacción de los padres con los individuos con discapacidad. El ambiente en el que se desarrolla el individuo viene representado por un óvalo que envuelve las expresiones fenotípicas de los individuos con discapacidad debido a que cualquier influencia ambiental va a determinar potencialmente las expresiones que se observen en los individuos. En cuanto al rombo de las comorbilidades, este se encuentra entre el óvalo del ambiente y el exterior debido a que gran parte de las mismas viene determinada genéticamente, como ocurre en el caso del autismo con una heredabilidad estimada del 90% (Zafeiriou et al., 2006), si bien las variables ambientales tendrán la capacidad de moderar o no dichas comorbilidades e incidir en el modo en el cual afectan a los problemas de comportamiento y de competencia social de los individuos con discapacidad. El tiempo y las trayectorias de desarrollo representadas en el esquema por el reloj es otra de las variables a considerar puesto que las expresiones fenotípicas comportamentales apreciadas en los individuos con discapacidad se van modificando con el tiempo, no siendo estables

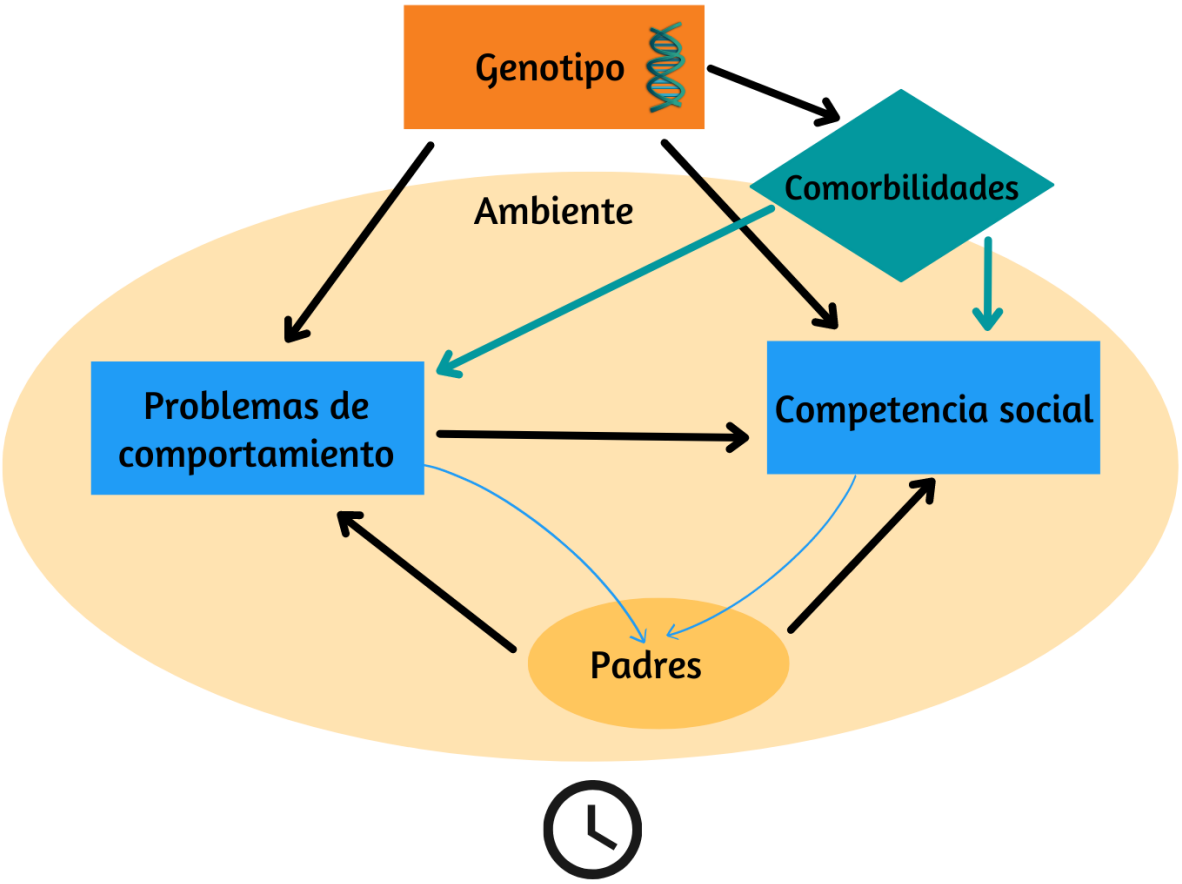

Figura 3. Interacción entre los diferentes factores ambientales e individuales y los problemas de comportamiento y competencia social en individuos con DI.

1.2. Justificación

Una vez identificados los múltiples factores implicados tanto en los problemas de comportamiento como en la competencia social de los individuos con SXF y SD y basándonos en la idea del modelo de apoyos (Luckasson et al., 2002), que considera que el funcionamiento individual puede estar mediado por aquellos apoyos provenientes del entorno, parece claro lo fundamental y lo relevante que se hace el considerar tanto las variables ambientales como las características fenotípicas y sus interacciones en el estudio de los problemas de comportamiento y la competencia social en individuos con DI. Puesto que el estudio de los problemas de comportamiento en niños con DI requiere incidir sobre diferentes factores etiológicos como el contexto, la genética, la familia y las interacciones entre todos ellos (Coronel, 2018). Y de una manera similar, el desarrollo interpersonal y la competencia social no dependen en exclusiva de las circunstancias biológicas sino también de los factores ambientales haciéndose necesaria la descripción de los factores ambientales que pueden ayudar a desarrollar intervenciones adecuadas en individuos con DI (Cebula et al., 2010). Sin embargo, pese al cambio de paradigma y la actual concepción de la DI, son pocos los estudios que se centran en observar cómo ciertas variables del entorno pueden afectar a la DI (McCarthy, 2008). Por ello, resulta fundamental continuar investigando para comprender las relaciones entre el ambiente familiar y el desarrollo comportamental en individuos con SXF así como sus cambios a lo largo del tiempo (Smith et al., 2016). Además, de acuerdo con Foley et al. (2014) son escasos los estudios que consideran el ambiente y cómo afecta a los individuos con SD. Así se hace necesario compilar y ampliar la información procedente de los diferentes estudios referidos a problemas de comportamiento y competencia social en individuos con Síndrome de X Frágil y Síndrome de Down buscando tanto factores genéticos/biológicos/personales como aquellas variables ambientales que influyen en los mismos.

Del mismo modo, aunque se han descrito los diferentes fenotipos conductuales correspondientes a ambos síndromes, debido a la complejidad del fenotipo del SXF por sus diferentes condiciones asociadas y comorbilidades, en la actualidad existe una necesidad de discernir si existen diferentes fenotipos conductuales en SXF en

lo referido a problemas del comportamiento (Raspa et al., 2017). Además autores como Dykens (2007) han destacado la necesidad presente en el SD de describir y conectar el estatus psiquiátrico y diagnóstico a lo largo del desarrollo, incluyendo la adolescencia, así como examinar procesos asociados como la sociabilidad, la ansiedad o la atención y de descubrir y examinar los factores protectores y de riesgo que pueden incrementar o disminuir la psicopatología en el SD. Y dado que los fenotipos conductuales no son estables, considerar el desarrollo de los problemas de comportamiento y competencia en ambos síndromes y en especial en etapas de la adolescencia es vital. De hecho, la evolución y la cronicidad de los trastornos de conducta así como de los factores de riesgo ha recibido atención insuficiente en la literatura sobre la DI (McCarthy, 2008).

1.3 Objetivos

1.3.1. Objetivo general

Por todo lo descrito con anterioridad, el objetivo general de la presente tesis es recopilar, sintetizar y extender la información sobre problemas de comportamiento y de competencia social en individuos con SD y SXF, focalizando no solamente en las variables biológicas, sino también en variables ambientales que puedan influir sobre dichos problemas, otorgando al mismo tiempo una visión de desarrollo.

Para ello, se han concebido tres objetivos específicos que se han materializado en la realización de tres estudios:

1.3.1.1. Objetivo específico 1: Extender el conocimiento sobre los problemas de comportamiento y de competencia social en individuos con SD y SXF en relación con variables ambientales.

Para ello, se ha realizado el artículo 1. Se trata de un estudio empírico que aborda la relación entre la emoción expresada y la impulsividad en madres de individuos con SXF y SD y la relación con los problemas de comportamiento en su descendencia. Cuenta con una muestra de 41 individuos con SXF y 21 con SD.

1.3.1.2. Objetivo específico 2: Recopilar, resumir y revisar la información que concierne a los problemas de comportamiento y competencia social en SXF teniendo en cuenta la comorbilidad con autismo y reuniendo la información concerniente a las trayectorias de desarrollo y los factores ambientales que inciden sobre los problemas mencionados.

Para ello, se ha llevado a cabo el artículo 2. Se trata de un estudio de revisión realizado mediante la búsqueda sistemática de problemas de comportamiento y competencia social en individuos con SXF en tres bases de datos. El estudio recoge los resultados de 51 estudios y aúna la información referida a la comorbilidad entre SXF y autismo así como ofrece una perspectiva del desarrollo en dichos problemas y recoge las variables ambientales que influyen en ambos problemas.

1.3.1.3. Objetivo específico 3: Recopilar, resumir y revisar la información referida a problemas de comportamiento y competencia social en SD relativa no solo a factores biológicos, sino también ambientales que pueden influir en los dichos problemas estableciendo también una perspectiva de desarrollo.

Para ello, se ha llevado a cabo el estudio 3. Se trata de un estudio de revisión del SD sobre problemas de comportamiento y competencia social. Dicho estudio se ha llevado a cabo mediante la búsqueda en tres bases de datos y la realización de una búsqueda hacia atrás desde la bibliografía encontrada llevando a un total de 44 estudios revisados. El estudio recoge la información referida a los problemas de comportamiento y competencia social, así como la información relacionada con las trayectorias de desarrollo, factores de riesgo y variables ambientales.

Capítulo 2

Artículo 1

Cregenzán-Royo, O., Brun-Gasca, C., and Fornieles-Deu, A. (2018). Expressed emotion and impulsiveness in mothers of children with Fragile X Syndrome and Down Syndrome: The relation to behavioral problems in their offspring. *Research in Developmental Disabilities*, *83*, 179–189. https://doi.org/10.1016/j.ridd.2018.08.016

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Expressed emotion and impulsiveness in mothers of children with Fragile X Syndrome and Down Syndrome: The relation to behavioral problems in their offspring

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ABSTRACT

Background: Fragile X Syndrome (FXS) and Down Syndrome (DS) are common causes of Intellectual Disability (ID). Mothers of individuals with FXS sometimes have the premutation condition which makes them display neurocognitive signs, such as impulsiveness impairments, while mothers of DS individuals, as a group, do not have impairments. Although behavior problems in individuals with ID may be related to high Expressed Emotion (EE) in parents, parenting in families with ID members has been little explored.

Aim: To explore the relationship between a mother's EE and impulsiveness, in mothers of individuals with FXS and DS, with behavior problems in their offspring.

Method: A questionnaire was developed to collect data about impulsiveness and EE in mothers, along with information about behavior problems in ID individuals.

Results: EE scores were associated with behavior problems in their offspring for both samples. Mothers with the premutation showed higher scores in EE than mothers of DS individuals. However, impulsiveness scores were not different between both parental groups, and were related to EE scores.

Conclusions: EE is a parental feature that is possible to modulate and seems to be related to behavior problems in ID individuals. More research should be carried on to create interventions to reduce this attitude in parents of ID individuals.

What this paper adds?

On the one hand, this paper adds information about behavior problems of individuals with ID by not only focusing on their phenotypic characteristics but also on other environmental factors, such as EE in their mothers, which may influence their behavioral problems. This study shows that EE in mothers of ID individuals is related to the main behavior problems in their offspring reported by mothers. Moreover, mothers of ID individuals seem to have high scores in EE, and this variable influences the way the child is raised. This means that it is important to design interventions to reduce this attitude in parents of individuals with ID and explore whether reducing EE in parents will decrease behavioral problems in their offspring.

On the other hand, this paper adds information of the phenotypic characteristics of mothers with the FXS premutation condition.

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As both groups of mothers did not differ in impulsiveness scores, the paper supports that phenotypic impulsiveness linked to the premutation condition is not only related to the premutation, in spite that it may be affected by other variables, such as the number of CGG repeats or the percentage of methylation. Moreover, differences between both groups of individuals with ID are shown.

Finally, to our knowledge this is the first study that shows that impulsiveness in mothers of individuals with ID is related to some behavioral problems in their offspring. As a consequence further research should be carried in this area.

1. Introduction

Intellectual disability (ID) is a condition that originates before the age of 18 and is characterized by significant limitations in both intellectual functioning and adaptive behavior, which covers a range of everyday social and practical skills (American Association of Intellectual & Developmental Disabilities, 2016). Two syndromes that cause ID are Down Syndrome (DS) and Fragile X Syndrome (FXS) (American Psychiatric Association, 2000). Furthermore, there are a large number of affected individuals in the world suffering from these problems. A recent meta-analysis (Maulik, Mascarenhas, Mathers, Dua, & Saxena, 2011) estimated the prevalence of ID as10.37/1000 population.

FXS is the most common inherited cause of ID (Bear, Huber, & Warren, 2004; Hagerman, Rivera, & Hagerman, 2008; Siomi, Siomi, Nussbaum, & Dreyfuss, 1993). It is associated with an unstable expansion of a polymorphic CGG repeats within the 50 untranslated region of the fragile X mental retardation 1 gen *FMR1* (Verkerk et al., 1991). FXS affects individuals with more than 200 CGG repeats (full mutation; FM) in *FMR1* (Basuta et al., 2015). In unaffected populations, the repeat is stable, with repeat sizes varying from 6 to 50, although some individuals have what is called an “intermediate” or gray area sized allele. These alleles with 45–54 CGG repeats are not considered to be mutations. However, the intermediate alleles have a small chance of becoming unstable, and may expand to a premutation in future generations. As there is no reported risk for an individual with an intermediate sized allele to have a child with a full mutation and intermediate alleles according with the National Fragile X Foundation (2017), it does not appear to be associated with any clinical or medical issues, developmental disabilities, or social/emotional difficulties. However, other studies have shown phenotypes associated with gray zone or intermediate allele sizes (Hall, 2014), such as dopamine responsive and motor fluctuations, and dyskinesia from dopaminergic medications or premature ovarian insufficiency (Bodega et al., 2006).

Another phenotypic feature of the FXS is the premutation (PM) alleles which have 55–200 repeats that are known to be unstable, and tend to expand to the FM in some family members (Nolin et al., 2003). The frequency of the PM in the total population is 1:291 women and 1:855 men (Hunter et al., 2014). In addition, it is well known that carriers of FMR1 premutation alleles are at risk of developing fragile X-associated tremor/ataxia syndrome (FXTAS), a late-onset neurodegenerative disorder (Hashimoto, Backer, Tassone, Hagerman, & Rivera, 2011). Until recently, individuals with PM alleles of *FMR1* gene were believed to be psychologically unaffected (Hessl et al., 2005). However, the emerging neurocognitive implications of the PM and the high frequency of carriers highlights the necessity of investigating the effects of the PM on cognitive function, especially during adult development (Goodrich-Hunsaker et al., 2011).

That is why in recent years, the PM has received considerable attention and there is now an emerging consensus that despite intellectual functioning being within the average range, PM men present with subtle executive function impairments that include poor inhibitory control (Grigsby et al., 2014; Kogan & Cornish, 2010). Inhibitory control is the process of suppressing or restraining an action, sensation, feeling, thought, or desire (Hooker & Knight, 2006), as well as the ability to suppress irrelevant information and actions, or to inhibit a predominant response (Barkley, 1997; Durston et al., 2002). The cognitive phenotype of male carriers of the *FMR1* PM is relatively well understood (Grigsby et al., 2014). However, the neuropsychological phenotype in the PM female was controversial in the past (Hunter et al., 2008; Hunter, Abramowitz, Rusin, & Sherman, 2009). Nonetheless, there have been some advances in this respect, such as Shelton et al. (2014), who found poorer inhibitory control in group comparisons for female carriers on ocular motor tasks, suggesting that impaired inhibitory control may represent a phenotype characteristic in PM women. Furthermore, self-reported inattention and impulsivity in PM women have been positively associated with CGG repeat length (Hunter et al., 2008). Moreover, Cornish, Hocking, Moss, and Kogan, (2011) found that CGG repeat length moderates the relationship between age and inhibitory control. Inhibitory control develops through childhood, and becomes more efficient with age (Durston et al., 2002). However, children with FXS have a relatively specific vulnerability to poor inhibitory control compared with other neurodevelopmental disorders (Tonnsen, Grefer, Hatton, & Roberts, 2015). In a non-clinical population, child impulsivity or inhibitory control will be enhanced by the parents serving as a model and by parents reinforcement on the child`s behavior. However, an impulsive parent may find their child`s impulsivity to be aversive, and punish the child for it, leading to a situation that breeds conflict because it is the opposite to what children see in their parents (Buss, 2014). In contrast, mothers of children with DS, as a group, do not have any impairment related to their offspring’s disease, because DS condition does not involve phenotypic problems in their mothers, as it is produced by a mutation in the hereditary mechanisms. Moreover, in addition to the many stressors of raising children with significant intellectual and behavior disabilities, mothers of children with FXS have the emotional burden of passing on the gene mutation to their children (Coleman, 2010).

Since 1992, ID has been defined as a condition that could be improved by providing support, rather than being only considered as a static lifelong disability (AAIDD, 2016). That is why environmental factors such as maternal adaptation, maternal stress, depressive symptoms, anxiety, and quality of life have been associated with child behavior problems in FXS (Bailey, Golden, Roberts, & Ford,

2008). However, in 2010 Laghezza, Mazzeschi, Di Riso, Chessa & Buratta (2010) showed that very little attention had been paid to the parenting relationship in families with ID members. Expressed emotion (EE) is a construct used to measure the emotional climate within families (Griffith, Hastings, Petalas, & Lloyd, 2015). The initial basis for EE research was the finding that adult schizophrenic patients from families characterized by high levels of emotional over-involvement, hostility, or criticism (later collectively labeled 'EE') were more likely to relapse than their counterparts from families with low scores in these characteristics (Brown, Monck, Carstairs, & Wing, 1962). Research data support that EE is linked to the relationship a mother has with individual children, rather than being evidence of the character disposition of mothers (Griffith et al., 2015), and seems to be a parental feature that is possible to modulate (Laghezza, Mazzeschi, Di Riso, Chessa, & Buratta, 2010). Hastings and Lloyd (2007) suggest that there is support for the hypothesis that behavior problems in children and adults with ID may be related to high EE in parents, and a causal effect of high EE on maintaining or exacerbating behavior problems. Furthermore, in 2010, Coleman reported initial findings that provided striking information on the high number of PM mothers of children with FXS, who met criteria for high EE, particularly emotional over-involvement. Greenberg et al. (2012) also found that the presence of warmth and positivity, and the absence of criticism were associated with fewer behavior problems in children and adults with FXS. Finally, Coleman (2010) suggests that a comparison of EE between mothers of children with FXS and mothers of children with other ID, such as DS would be crucial to sort out the differences between the FXS phenotype and environmental effects within the relationship between EE and FXS.

Therefore, the aim of the present study is to explore the relationship between the mother's scores on EE and impulsiveness with the scores on the behavior problems in their offspring in mothers of individuals with FXS and DS.

2. Method

In order to develop the study, an online questionnaire was used to collect data. This questionnaire included self-reported data of demographic variables, the mother's impulsiveness and EE scores, and any behavior problems on their offspring. A total of 36 mothers of individuals with FXS answered the online questionnaire; however just 12 mothers of DS answered it. Thus, in order to increase the sample collected, the questionnaires were printed, and researchers went to the family groups in Aragon (Spain) to ask for more participants. As a result, 11more mothers of individuals with DS answered the questionnaires.

2.1. Sample

A total of 36 biological mothers of individuals with FXS answered the questionnaires, as well as 24 biological mothers of individuals with DS.The mothers of FXS with only one offspring with FXS (N = 28) were between 35–70 years old (M = 47 years; SD = 9.52). The mothers of two individuals with FXS (N = 7) were between 41–57 years (M = 52 years; SD = 5.97), with the mothers with DS offspring (N = 23) being between 36–72 years (M = 49 years; SD = 8.82. Fig. A1 in Appendix A presents the flowchart of the sample size. Table B1 in Appendix B presents the information of the mothers that participated in the study, and Table C1 in Appendix C shows the information of the offspring of the study, including the type of condition that individuals with FXS had. It is important to highlight any mother of FXS sample that met criteria to have FXTAS disease, as it is an important condition that could have affected the results of the study.

2.2. Procedure

Recruitment efforts included contact by mail with the Spanish, Chilean, and Argentinean Federations of FXS as well as with the Spanish DS Federation. Moreover, we contacted family groups of Aragon for both conditions. After the first contact with the groups, a joint letter was written, which was sent to all the family groups in all countries. Before the tasks were sent to participants, some native psychologists from the countries that were going to participate in the research had read the questionnaire to ensure that all questions would be understood by participants. These included a Chilean psychologist and two Argentinean psychologists. Some clarifications were added in brackets in the questions that were hard to understand by any of the reviewers. Furthermore, all participants signed an informed consent, in which the confidential use of their data was guaranteed. Moreover, when tasks were sent to the study participants, they received a note in which the confidentiality of their data was explained. Later, we went to Zaragoza FXS family group, as well as the Barbastro and Monzón DS family groups to find more participants. Finally, after the end of the study all groups that had participated in the study received an explanatory note about the overall results of the study.

2.3. Measurement tools

Each mother that participated on the research completed an *ad hoc* questionnaire about their demographic and personal data, which included their date of birth, whether they had any other diagnosed disorders (status of illness variable that included: depression, anxiety, attention deficit. and fibromyalgia, among others), as well as the number of offspring with the disorder, the intelligence quotient of their affected children, a question about whether their children had any another co-morbid disease, the number of healthy offspring, a question about whether their children were biological or adopted, and their socioeconomic level. Only in the case of mothers of children with FXS did they have to report the number of CGG repeats that they had as mothers, to be sure

that the mothers presented with the premutation condition. They also had to report the number of CGG repeats of their offspring in order to discern if the affected individual had the FM condition, the premutation, or the mosaicism condition. This questionnaire also included all measurements, which are going to be described in the measurements section, and was developed by putting the questions on demographic, personal data and the questions in all the measurement tools of the study in the Google Forms platform. Access to the platform was only available to the participants of the study. All mothers of FXS offspring completed the *ad hoc* questionnaire through the internet. However, ten mothers of DS children completed it on paper by printing the questionnaire. Regardless of this, assessment tools were administered in the same order to all the participants of the study. Apart from the online *ad hoc* questionnaire, two subgroups of mothers that had answered the online questionnaire were assessed with *in situ* measurements, in order to determine if both groups of mothers were comparable in intelligence and impulsiveness. Therefore, 9 Mothers of individuals with FXS and another subgroup of 10 mothers of individuals with DS were also evaluated *in situ*.

2.4. Measurements

The measurements used in the *ad hoc* questionnaire are summarized in Table D1 in Appendix D.

It is important to note that all mothers were assessed using the tools mentioned in Table D1. However, a subgroup of 9 mothers of individuals with FXS, and 11 mothers of individuals with DS were also evaluated *in situ,* and these *in situ* measurements are summarized in Table E1 in Appendix E.

3. Data analysis

Before the statistical analyses were conducted, all the quantitative variables (demographic, EE, impulsiveness, and behavior problems) were examined for normality using Saphiro-Wilks tests. Several tests were not significant, indicating that the variables were normally distributed and suitable for parametric analysis. However, there were a few variables from the Child Behavior Check List (CBCL) scale that were not normally distributed, so it was decided to perform a non-parametric analysis on the correlations with all variables. Moreover, it was determined whether the scores in *ad hoc* questionnaires answered by mothers of DS individuals that answered the questionnaire *in situ* (N = 11) were different from the scores of mothers that answered it online. The results showed that no significant differences were found between both groups of mothers in EE scores ($t_{(21)}$ = -0.05; p = 0.10), or in impulsiveness scores ($t_{(21)}$ = -1.39; p = 0.18), or in CBCL total problems reported by mothers ($t_{(19)}$ = 0.15; p = 0.89;)..

CBCL generates separated data by age (1.5–6 years and older than 6 years). However, each scale produce standardized t-scores derived from age-based norms, making scores for each form comparable. As a consequence, all scores were computed together using t-scores on CBCL variables.

It is important to highlight that all analyses performed in the study for the FXS sample were only computed with individuals with the full mutation condition, in order to avoid differences in the sample, due to the different phenotypes in the three different conditions.

Although no differences were found in the level of EE in mothers of FXS as regards the gender of their children, as well as not finding any differences in Internalizing symptoms, Externalizing, or Total Problems in FXS individuals concerning gender, we decided to compute only the data of the male participants with FM condition due to the large amount of evidence that shows that the behavioral phenotype is different for boys and girls inside the FXS spectrum (Cornish et al., 2004; Hagerman et al., 2009; Pierpont, Richmond, Abbeduto, Kover, & Brown, 2011). In the case of DS sample, we did not find any differences between the mothers levels of EE regarding the gender of their offspring, and no differences were found about gender in internalizing symptoms, externalizing, or total problems. Moreover, as previous evidence had not shown gender differences as a consequence, it was decided to compute all data without taking into account the gender of the sample. Results are shown in Appendix F in Table F1.

All analyses were conducted using the STATA statistical package, version 13 (StataCorp, 2013).

4. Results

To determine if mothers of individuals with FXS had higher levels of EE than mothers of DS offspring, it was decided to include only mothers with one child with FXS, as mothers of two children may present more EE due to the burden assumed when they have to raise two children with ID. Statistical analysis shown that, as a group, mothers of one child with FXS condition (N = 22) had 7.79 points more on EE than mothers of DS individuals (N = 19) ($t_{(39)}$ = 3.46; p < 0.01; 95% CI [3.24–12.35]).

To determine whether there are any differences by groups of mothers on impulsiveness scores, the same decision taken in the last analysis was taken for this one. After comparing scores for both groups with just one offspring with ID, results showed that there were no differences between groups of mothers on impulsiveness scores measured with the Barrat Impulsiveness Scale (BIS) ($t_{(40)}$ = 0.57; p = 0.57; 95% CI [-3.60-6.46]). Neither differences were found between impulsiveness scores or intelligence assessed with *in situ* measures, results are shown in Appendix G Table G1. In addition, no association was found between mother's age and impulsiveness scores assessed with BIS in PM mothers (ρ = -0.08; p = 0.61). However an association with age was found with the *in situ* assessments although it was not significant for any of the measurements (Stroop ρ = -0.34; p = 0.37; TMT ρ = 0.50; p = 0.17).

To examine the relationship between EE and impulsiveness scores with behavior problems in their offspring for both groups of

mothers, it was decided to include, in the PM mothers group, EE and impulsiveness scores of mothers that had two sons with FXS, as there were no differences in impulsiveness ($t_{(33)} = 0.48$; $p = 0.64$; 95% CI [-5.76-9.34]) or EE scores ($t_{(6.85)} = 0.87$; $p = 0.41$; 95% CI [-6.91-14.91]) between mothers of one individual with FXS compared to mothers with two. The results show that most of the CBCL variables were significantly related to some subscales of EE, at least for one of the samples; however impulsiveness in mothers assessed with the BIS scale was not associated with internalizing, externalizing, or with total problems for both samples of ID. The results of the analysis are shown in Table H1 in Appendix H. All CBCL variables are included in the Table, except the somatic problems variable, which was deleted because it did not show any significant result in any of the samples. It is important to mention that impulsiveness in mothers of FXS individuals was significantly related to some CBCL variables, such as social problems ($p = 0.45$*), thought problems ($p = 0.38$*), attention problems ($p = 0.36$*), and ADHD problems ($p = 0.34+$), if girls were include in the FXS group ($N = 33$). Moreover impulsiveness in PM mothers assessed with *in situ* measurements, specifically TMT, for the FXS sample with girls, showed correlations higher than 0.40 for the same behavior problems, with the ones for ADHD being significant. The correlations higher than 0.60 were also found for Externalizing symptoms, Anxious Depressed, and Rule Breaking Behaviors. In addition, significant correlations in the DS sample were found. TMT measurements showed correlations higher than 0.60 for Anxious Depressed, Aggressive Behavior, ADHD Problems, and ODP problems, and Stroop measurements showed correlations higher than 0.48 for Social Problems and Attention Problems.

Furthermore, mean differences in behavior problems for both samples were tested using the *t*-test for Internalizing, Externalizing and Total Problems of the CBCL. A difference ($p < 0.05$) was found between these variables in FXS and DS sample. Additionally, results showed that FXS individuals had more problems reported by mothers for each behavior problem than DS individuals. Results are shown in Table I1 in Appendix I.

We also explored the association between EE and impulsiveness scores. Higher impulsiveness scores assessed with the BIS scale were related with higher EE scores on PM mothers ($N = 35$; $\rho = 0.55$; $p < 0.01$), however this association was not found in mothers of DS individuals ($N = 23$; $\rho = -0.7$; $p = 0.08$). Likewise Stroop measures showed an association between impulsiveness and EE in mothers of FXS 0.49, however it was not significant ($p = 0.18$; $N = 9$). A correlation of 0.40 was also found between the Stroop measure and EE in mothers of DS individuals, but this was not significant ($p = 0.29$; $N = 9$).

Finally, an association between EE and a worse illness status was found in PM mothers ($N = 35$), with the more conditions a mother reported, the more EE she had ($\rho = 0.36$; $p = 0.03$). The same positive association between a worse illness status and EE was found in mothers of individuals with DS, but it was not significant ($N = 17$; $\rho = 0.34$; $p = 0.19$).

5. Discussion

The results of the study show that PM mothers had higher levels of EE than mothers of DS sample. The burden of passing the disorder to their offspring, the emerging neurocognitive profile, or the higher behavior problems in their offspring, could be explanations for these results. However, Greenberg et al. (2012) previously reported that levels of EE in PM mothers were no different compared with mothers of children with autism. Nevertheless, having an offspring with autism is different to having one with DS, with FXS individuals often showing co-morbidity with autism.

In contrast with other studies that found inhibitory differences in PM-carriers individuals compared with controls(Kraan et al., 2014), we did not find more impulsiveness in PM mothers compared to mothers of DS individuals. Nor was there any relationship found between mother's age and impulsiveness scores on PM mothers using the BIS scale. However, when *in situ* measures were used to test impulsiveness, it showed an important association, in spite of the fact that the sample was small. The small sample size, the different nature of the measurements used in each study, or the low alpha coefficient found in our sample with the BIS scale could explain these results. More studies should be carried out with tasks and self-report tools to confirm if there are any differences in the female phenotype of impulsiveness.

Significant associations were found in both samples between EE and internalizing symptoms, total problems, and 16 of 17 subscales of the CBCL. To our knowledge, this is the first study conducted with mothers of DS individuals on EE, and results of this sample must be taken with caution as exploratory results. The associations found in the DS sample were stronger than the ones found in the FXS sample, showing correlations of 0.80 in some variables. The stronger correlations in DS sample could be explained by the complexity of both disorders. It seems that as FXS is a complex genetic disorder with higher behavior problems than DS disorder. Thus, FXS individuals could receive less effect of the family environment than DS individuals in shaping their behavioral phenotype. However, as is known from recent studies on autism (Greenberg, Seltzer, Hong, & Orsmond, 2006), EE has bidirectional effects with behavioral problems, so EE not only influences behavior problems but also behavior problems influence EE in mothers. Alternatively, and in contrast with a previous study (Greenberg et al., 2012), we did not find associations between CC and Externalizing problems in FXS individuals, and our measurement of emotional over-involvement was related to some variables of the CBCL scale. However, there were sample differences with the other studies, such as age of individuals and different tools to measure EE. Nevertheless, we found associations previously reported in general population (St. Jonn-seed & Weiss, 2002) and clinical populations with Attention-Deficit/Hyperactivity-Disorder (ADHD; Christiansen, Oades, Psychogiou, Hauffa, & Sonuga-Barke, 2010). Finally, it is important to highlight that the strongest relationship was found between Affective Problems subscale of the CBCL, which was significantly associated with both subscales of EE and total EE in both samples. Moreover, thought problems were related to both subscales of EE and total EE in FXS sample, and for both criticism and total EE in the sample of DS. As a consequence, it seems that both affective

problems and thought problems may be nuclear in the EE construct of mothers. As Hastings and Lloyd (2007) suggested, it seems that behavior problems in individuals with ID are related to high EE in parents.

A new result is that impulsiveness in PM mothers assessed with BIS was significantly associated with social, thought, attention, and ADHD problems in their offspring when including the girl subsample with FM in the sample of FXS. Also the same associations, among others, appeared with the *in situ* measurements. However these associations did not appear when only boys were considered. As all variables associated seem to be related with impulsiveness in children or a deficit in inhibitory control mechanisms, an explanatory hypothesis of these results could be that, even knowing that girls and boys have different phenotypes, coping strategies or the upbringing in families may have lead their children to show more behavior problems related to impulsiveness. This is an interesting result, because in this sample, PM mothers were no different from mothers of DS individuals in impulsiveness scores when assessed with the BIS or with*in situ* measurements. However, when checking for associations with*in situ* measurements, some behavior problems of DS individuals were significantly associated with impulsiveness scores in their mothers. So it seems that, for both samples of offspring, problem behaviors may affect impulsiveness scores in mothers. Or maybe mothers with higher scores in impulsiveness reported more problem behaviors in their offspring. Consequently, further studies should be carried out to discover the underlying mechanism that leads to more behavior problems in FXS and DS in relation to their mother's impulsiveness. To our knowledge, this is the first finding in this direction.

A significant association has been found between EE and impulsiveness in PM mothers with the BIS scale. Although it was not significant with *in situ* measurements, the same association was found for both groups of mothers. That could be explained by the fact that impulsiveness in mothers could induce them to respond to the questionnaires in a biased way, thus leading them to have higher scores in EE.

Finally, despite that females with FXS FM usually have milder behavior problems than males (Chonchaiya, Schneider, & Hagerman, 2013), we did not find any differences in EE levels of mothers as regards the gender of their offspring. This could be explained by the fact that the sample of females with the FM (N = 9) was lower than that of the males (N = 24).

6. Implications and future research

As EE seems to be a parental attitude that has an influence on behavior problems in their offspring, and is a feature that could be reduced through specific interventions, there is a need to create or apply interventions for this group of mothers that are at high risk to develop this attitude. Moreover, as Hastings and Lloyd (2007) said, another challenge would be demonstrating whether EE predicts, over time, the putative causal effect of high EE, maintaining or exacerbating behavior problems. Therefore, interventions should assess whether, as a result of reducing this attitude in mothers, behavior problems in their offspring also decrease. In addition, EE in mothers of ID individuals in this study showed the strongest associations with affective and thought problems. As a consequence, this relationship should be explored in future studies. Moreover, further analyses should be carried out to determine if EE in PM mothers is related to impulsivity levels, because to our knowledge, this variable has never been considered in studies carried out on EE. *In situ* measurements showed that a relationship between the two variables may exist, and it seems that if the samples had been larger, a significant association would have appeared between EE and impulsiveness in both groups of mothers.

7. Limitations

It must be taken into account that both samples consisted of volunteers, and were small samples. Moreover, the FXS sample included more individuals from several countries, while DS sample was mainly from one community of Spain (Aragon). Consequently the representativeness of the sample and generalizability of the findings are not known. We tried to determine the intelligence quotient of each offspring, in order to control this variable, due to the fact that it could influence behavior problems in ID individuals, but it was not possible. Moreover, autism symptoms were not assessed and therefore not controlled in the study. Some individuals (FXS N = 12; SD N = 8) measured with the CBCL were older than the highest age admitted in the CBCL scale, but as they have ID we, as other authors (Perez-García, Granero, Gallastegui, Pérez-Jurado & Brun-Gasca, 2011), considered that this tool can be used even in the older sample. Finally, we could not use Five Minute Speech Sample (FMMS), which is the most used tool to measure EE, because is not adapted to Spanish.

8. Conclusions

EE scores in mothers have been related to behavior problems in their offspring, showing that the more EE a mother has the more behavior problems the child has. However, EE shows bidirectional effects with behavioral problems, so it is not only that EE influences behavior problems, but also behavior problems influence EE in mothers. As EE is an environmental factor that seems to be associated with behavior problems in individuals with ID, and is a parental feature that is possible to modulate, interventions should be performed in order to reduce this attitude in parents, and to demonstrate whether by reducing the attitude, the behavior problems in their offspring also decrease. Moreover, it is important to highlight that the study does not try to blame the mothers of individuals with ID, but just means to protect ID individuals from environmental factors that could affect their development.

This study did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

Appendix A

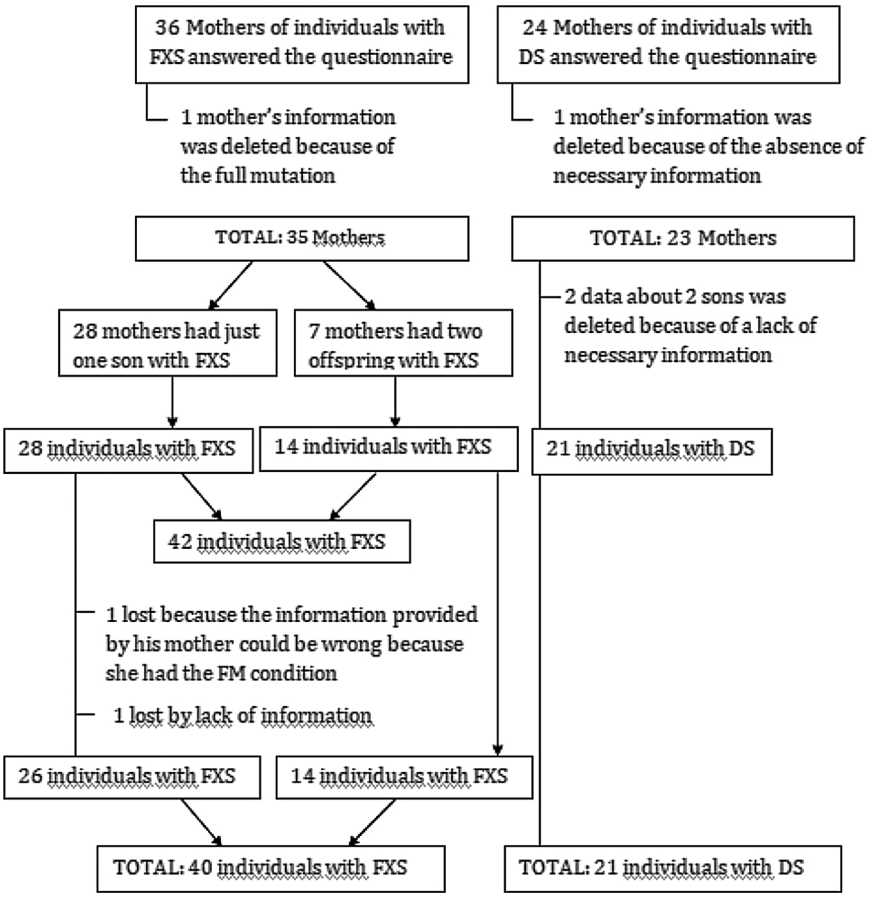

Fig. A1. Flowchart of the sample.

Appendix B

Table B1
Descriptive information for mothers.

	Mothers of one offspring with FXS		Mothers of 2 offspring with FXS		Mothers of offspring with DS	
Countries	N	Percentage	N	Percentage	N	Percentage
Spain	21	75	6	85.71	23	100
South America	7	25	1	14.29		
Civil Status						
Married	24	85.71	7	100	22	95.65
Divorced	4	14.29			1	4.35
SES						
High	4	15.38			3	13.04
Medium	21	80.77	4	57.14	17	73.91
Low	1	3.85	3	42.86	3	13.04
Illnes Status						
Healthy	12	42.86	3	42.89	12	57.14
1 CD	8	28.57	4	57.14	9	42.86
2 CD	4	14.29				
3 CD	4	14.29				

Note, FXS = Fragile X Syndrome; DS: Down Syndrome; SES = Socioeconomic Status; CD = Condition Reported (status of illness variable).

Appendix C

Table C1
Descriptive information of the offspring.

	FXS individuals N = 40		DS Individuals N = 21	
	Mean	SD	Mean	SD
Age	16.2	9.05	11.66	7.20
Gender				
Male	29	72.50	14	66.67
Female	11	27.50	7	33.33
Genetic FXS status	N	Percentage		
Full Mutation	33	82.50		
Mosaicism	3	7.50		
Premutation	2	5		
Unknown	2	5		

Note, FXS: Fragile X Syndrome; DS: Down Syndrome.

Appendix D

Table D1
Measurements included in the online *ad hoc* questionnaire.

Tool	Construct	Author
Family Questionnaire	Expressed Emotion	(Wiedemann, Rayki, Feinstein, & Hahlweg, 2002). Spanish validation (Sepulveda et al., 2014).
Barrat Impulsiveness Scale	Impulsiveness	(Patton, Stanford, & Barratt, 1995). Adapted version from (Oquendo et al., 2001).
Child Behavior Checklist 1-5 years	Behavior Problems	(Achenbach & Rescorla, 2000).
Child Behavior Checklist 6-18 years	Behavior Problems	(Achenbach & Rescorla, 2001).
Hollinshead	Socioeconomic status	(Hollingshead, 1975).
Illness questions in the ad hoc questionnaire	Status of illness	

Appendix E

Table E1
Measurements included in the *in situ* assessment.

Tool	Construct	Author
Wechsler Adults Intelligence Scale-III-Revised	Intelligence	(Wechsler, 1997)
Stroop Color-Word Task	Impulsiveness	(Golden, 1999)
Trail Making Test	Impulsiveness	(Reitan, 1992)

Appendix F

Table F1
Mean differences depending on sample's sex.

Mean differences	N	t	fd	p	IC [95%]
EE in mothers of FXS individuals depending on their offspring's sex	Female = 9, Male = 24	−0.27	31	0.79	[−8.10-6.21]
Internalizing symptoms in FXS sample by sex	Female = 9, Male = 24	0.31	31	0.76	[−10.65-8.04]
Externalizing symptoms in FXS sample by sex	Female = 9, Male = 24	−0.54	31	0.59	[10.76-6.23]
Total problems in FXS sample by sex	Female = 9, Male = 24	−0.30	31	0.77	[−13.20-10.07]
EE in mothers of DS individuals depending on their offspring's sex	Female N = 7, Male= 14	1.07	19	0.30	[−3.58-11.15]
Internalizing symptoms on DS sample by sex	Female N = 7, Male= 14	0.58	19	0.57	[-6.09-10.80]
Externalizing symptoms in DS sample by sex	Female N = 7, Male= 14	0.75	19	0.46	[−5.47-11.61]
Total problems in DS sample by sex	Female N = 7, Male= 14	1.15	19	0.26	[−4.02-13.87]

Note: EE = Expressed Emotion; FXS = Fragile X Syndrome; DS = Down Syndrome.

Appendix G

Table G1
Mean differences between mother's groups on *in situ* measures.

Mean differences	N	Statistics	fd	p	IC [95%]
Impulsiveness measured with Trail Making Test	N = 9 mothers of FXS offspring N = 9 mothers of DS offspring	t = -0.57	16	0.58	[−38.93 22.40]
Impulsiveness measured with Stroop*	N = 9 mothers of FXS offspring N = 9 mothers of DS offspring	u = 41.5		0.69	
Intelligence assessed with Wechsler	N = 7 mothers of FXS offspring N = 7 mothers of DS offspring	t = 0.023	12	0.98	[−13.59-13.87]

* Due to the fact that samples were not symmetric, to assess impulsiveness measured with Stroop we did the non-parametric test Mann-Whitney as a consequence, there are not IC neither t or fd values.

Appendix H

Table H1
Spearman correlations between Child Behavior Checklist Variables with Expressed Emotion on mothers. FXS boys with FM N = 24, SD boys and girls N = 21.

CBCL Variables	EE	EOI	CC	Impulsiveness
Internalizing	P	P	P	P
FXS	0.41*	0.29	0.47*	−0.05
DS	0.66**	0.67**	0.44*	−0.17
Externalizing				
FXS	0.25	0.28	0.32	−0.02
DS	0.72**	0.49*	0.79**	−0.08
Total Problems				
FXS	0.38	0.35	0.51*	0.05
DS	0.88**	0.73**	0.75**	−0.02
Anxious-Depressed				
FXS	0.28	0.13	0.49*	0.05
DS	0.53*	0.58*	0.36	−0.10
W-D				
FXS	0.26	0.27	0.14	0.00
DS	0.38	0.47*	0.20	0.11
Somatic Complains				
FXS	0.33	0.28	0.27	−0.18
DS	0.53*	0.53*	0.25	−0.11
Social Problems				
FXS	0.37	0.39	0.36	0.14
DS	0.50+	0.40	0.45	−0.14
Thought Problems				
FXS	0.51*	0.46*	0.53*	0.20
DS	0.76**	0.45	0.69**	−0.05
Attention Problems				
FXS	0.34	0.28	0.48*	0.08
DS	0.65**	0.46*	0.68**	0.01
RBB				
FXS	0.34	0.40	0.37	0.04
DS	0.72**	0.60*	0.59*	−0.24
Aggressive Behavior				
FXS	0.20	0.20	0.33	0.07
DS	0.65**	0.43+	0.71**	0.04
Affective Problems				
FXS	0.47*	0.52**	0.41*	0.03
DS	0.68**	0.68**	0.49*	0.28
Anxiety Problems				
FXS	0.22	0.12	0.38	0.21
DS	0.44+	0.45*	0.32	−0.08
ADHD Problems				
FXS	0.34	0.29	0.49*	0.21
DS	0.74**	0.54*	0.71**	−0.09

(*continued on next page*)

Table H1 (*continued*)

CBCL Variables	EE	EOI	CC	Impulsiveness
ODP				
FXS	0.06	0.06	0.18	−0.08
DS	0.43+	0.22	0.59**	0.11
Conduct Problems*				
FXS	0.38	0.47*	0.46*	0.03
DS	0.70**	0.49	0.65**	−0.20

Note, FXS = Fragile X Syndrome; DS = Down Syndrome; CBCL = Child Behavior Checklist; EE = Expressed Emotion; EOI = Emotional Over-involvement; CC = Criticism; W-D = Withdrawn-Depressed; RBB = Rule Breaking Behavior; ODP = Oppositional Defiant.
*In Conduct Problems variable, as CBCL variable for individuals with less than 6 years do not have an scale for this variable, only 14 individuals of DS sample and 17 individuals of FXS sample were computed to do the analysis with EE, EOI and CC; +p = .05 *p < .05, **p < .01.

Appendix I

Table I1
t-test for CBCL variables. FXS sample in first place and DS sample in second. FXS (N = 24), DS (N = 21).

CBCL variables	$t_{(df)}$	p	CI 95%
Internalizing	$4.62_{(43)}$	0.00	5.79-14.75
Externalizing	$2.65_{(43)}$	0.02	1.69-12.49
Total Problems	$4.83_{(43)}$	0.00	6.81-16.58

Note, FXS: Fragile X Syndrome; DS: Down Syndrome; CBCL: Child Behavior Checklist.

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Artículo 2

Cregenzán-Royo, O., Brun-Gasca, C., & Fornieles-Deu, A. (2021). Behavior Problems and Social Competence in Fragile X Syndrome: A Systematic Review. *Genes, 13,* 280. https://doi.org/10.3390/genes13020280

genes

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Review

Behavior Problems and Social Competence in Fragile X Syndrome: A Systematic Review

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Abstract: Fragile X syndrome (FXS) causes intellectual disability and is the known leading cause of autism. Common problems in FXS include behavior and social problems. Along with syndromic characteristics and autism comorbidity, environmental factors might influence these difficulties. This systematic review focuses on the last 20 years of studies concerning behavior and social problems in FXS, considering environmental and personal variables that might influence both problems. Three databases were reviewed, leading to fifty-one studies meeting the inclusion criteria. Attention deficit hyperactivity disorder (ADHD) problems remain the greatest behavior problems, with behavioral problems and social competence being stable during the 20 years. Some developmental trajectories might have changed due to higher methodological control, such as aggressive behavior and attention problems. The socialization trajectory from childhood to adolescence remains unclear. Comorbidity with autism in individuals with FXS increased behavior problems and worsened social competence profiles. At the same time, comparisons between individuals with comorbid FXS and autism and individuals with autism might help define the comorbid phenotype. Environmental factors and parental characteristics influenced behavior problems and social competence. Higher methodological control is needed in studies including autism symptomatology and parental characteristics. More studies comparing autism in FXS with idiopathic autism are needed to discern differences between conditions.

Keywords: behavior problems; social competence; fragile X syndrome; autism; anxiety; aggressive; socialization; attention; withdrawn

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1. Introduction

As one of the most frequent inherited reasons for intellectual disability (ID) [1,2], fragile X syndrome (FXS) is caused by silencing of the fragile X gene FMR1 due to large expansions of non-coding CGG repeats [3]. The trinucleotide expansion inactivates the FMR1 gene, resulting in an absence of the fragile X mental retardation protein (FMRP), which is fundamental for natural neural development [4]. Repeat sizes conditioning the development of the different phenotypes vary in the unaffected population from 6 to 50 repeats, while individuals with the premutation (PM) have repeat sizes between 55 and 200. As a result of genetic inheritance, these PM alleles tend to expand to a full mutation in family members [5]. Consequently, the members with the full mutation (FM) expansions, which implies more than 200 CGG repeats of the gene, have a silenced gene, resulting in the absence of the FMRP protein and the full development of FXS [2].

Until recently, individuals with PM alleles were believed to be psychologically unaffected [6]. However, several implications of this condition have been found, including a significant contribution to the risk of attention deficit hyperactivity disorder (ADHD), subtle white matter structural changes, diminished brain activation in the amygdala

and several brain areas that mediate social cognition, and long-term verbal memory recall deficits [7–10]. In fact, via increased FMR1 mRNA production and toxicity, the PM alleles can produce a family of neurodevelopmental phenotypes (ADHD, autism spectrum disorder, seizure disorder) and neurodegenerative phenotypes (fragile X-associated tremor/ataxia syndrome) [3].

The FXS FM phenotype occurs in both genders, although males tend to show greater cognitive impairment than females [11,12], with considerable variability in the degree of ID [13]. Females with FXS are usually less affected due to the extra X chromosome that partially compensates for the problem of the affected chromosome [14,15]. However, variability in females is even greater, with 1/3–1/2 of FM females exhibiting normal intellectual functioning [16]. Recent estimates of the prevalence of males and females with FXS are around 1 in 3600 to 4000 and 1 in 4000 to 6000, respectively [17].

1.1. Comorbidities

FXS individuals show comorbidities with other disorders such as ADHD, autism spectrum disorder (ASD), and anxiety [18]. ADHD estimates of comorbidity have been established at 73% [19], with almost 60% of juvenile cases continuing in adulthood [20]. ADHD symptoms are the most prevalent recognized behavior problem in FXS for the majority of boys and many females [19,21–23], hindering social relationships at both home and school [24]. Regarding ASD, mutations in the FMR1 gene are a contributing cause to ASD as a part of the broader FXS phenotype [2]. Recent studies have stated a prevalence of comorbid FXS+ASD that varies from 30% to 67% [25–28]. Moreover, it has been estimated that among the population with autism (Aut), 2–6% of children have FXS [29]. Around 90% of individuals with FXS present atypical behaviors, as do nonsyndromic ASD individuals, such as motor stereotypies (i.e., hand flapping), self-injury, eye avoidance, or social avoidance [30–33]. However, controversy remains about the overlap between ASD and FXS [34]. Some authors claim that autism seen in FXS and idiopathic autism (IA) have considerable similarities, sharing changes in the neurobiology of facial emotion processing, with individuals with IA and comorbid individuals with FXS and autism showing behavioral problems similar to those of individuals with IA [18]. In contrast, others state that there are substantial differences, making comorbid subjects more vulnerable, with greater communication and social reciprocity impairments and higher levels of repetitive and challenging behaviors than individuals with FXS only [35], and with different neurobiological substrates of the behavioral impairments [36]. Comorbid individuals with FXS and autism have shown outcomes inferior to those of individuals with FXS without autism [26,37]. Last, regarding anxiety, symptoms are recognized as an outstanding feature of the phenotype of individuals with FXS [38], with 70% of males and 56% of females receiving treatment for anxiety symptoms or with a comorbid anxiety diagnosis [39].

1.2. Behavior Problems

Behavioral implications in FXS have been explored since 1943, with the description of Martin and Bell [40]. A particular behavioral phenotype, understood as a greater probability of exhibiting particular behavior due to the syndrome, has been observed for individuals with FXS, although there is some variability in behavioral symptoms [41,42]. They include cognitive difficulties, language problems, social anxiety, gaze aversion, hand stereotypies [31], repetitive and self-injurious behavior [43], and aggressive behavior [44], in addition to autistic-like features such as motor stereotypies and perseverative behavior [45]. A standard indicator of the intersection between ASD and FXS is repetitive behaviors [46]. In this regard, the same behaviors are shared in FXS and ASD phenotypes, although there is evidence signaling different phenotypes between FXS individuals and idiopathic autism (IA) [47]. Other authors have also found similar behavior difficulties in both groups [48]. Thus, determining behavioral phenotypes is valuable for identifying individuals with FXS at the early stages and for starting interventions and assessments as soon as possible [49].

However, there is still a need to address whether there are different phenotypes of FXS concerning behavior problems or self-injury, and how they develop as individuals get older, and specifically in transition stages at school and when entering employment [50]. Furthermore, scarce studies have focused on trajectories of behavior problems across adolescence and adulthood in individuals with FXS [51].

1.3. Social Skills and Social Competence

Social competence is a broad construct referring to adequately dealing with the demands of a social situation [52]. Four components could be addressed when considering this construct: peer relations, social cognition, behavior problems, and effective social skills [53]. Social skills could be defined as abilities associated with the development that contributes to the general level of social competence, including perspective taking, interpersonal problem solving, moral judgment, self-control, and communication facility [54]. To this effect, social skills are particular behaviors exhibited by an individual to be competent in a social task [55]. Since the ID definition includes both limitations in intellectual functioning and adaptive behavior in daily social and practical skills [56], it is not striking that individuals with FXS show deficits in social competence. As described above, autistic features, social anxiety, and pragmatic deficits in language are part of the social deficits included in the full mutation phenotype [57]. People with FXS are particularly characterized by social avoidance [23], with one of their most prominent features being eye contact avoidance, finding this an aversive stimulus, which is associated with changes in skin conductance, cortisol reactivity, and pupillary reactivity [58–60]. Social withdrawal is also considered part of FXS individuals' clinical profile [61]. Considering the fact that ASD individuals show poor social skills as a prominent feature, with impairments in social communication, it is understandable that comorbid individuals with FXS and ASD are more avoidant than individuals with FXS without autism comorbidity [43,62]. In the same line, anxiety and autism symptoms have been found to be risk factors for reduced social skills in individuals with FXS [34]. Similarly, autism symptoms have been associated with reduced socialization skills in FXS [63].

1.4. Environmental Factors

ID was considered a lifelong disability of an individual's characteristics until 1992 when the American Association on Intellectual and Developmental Disabilities stated a definition that considered environmental supports to improve individual functioning [56]. Considering ID as a state of functioning allowed discrepancies between person and environment to be considered when conducting ID studies [64]. In this scenario, providing support to individuals with ID could enhance their functioning in their environment, leading to a fuller life [56]. Supports are understood as assets and strategies that strive to facilitate the developmental and learning processes and interests and quality of life of persons trying to improve personal functioning. [65]. Moreover, changes in the family, educational, or home environment might help reduce or increase behavior problems in FXS [66]. However, parenting a child with FXS can be very challenging due to their behavioral phenotype, and even when they try to do their best, parents can be defeated trying to maintain a responsive parenting style [67].

Additionally, challenging behaviors in individuals with FXS are known to impact family functioning such as the mother's mental health [68]. Some studies point to a higher susceptibility to stress for mothers with the PM condition [69,70]. Consequently, a highly stressed family environment could negatively influence the development of the offspring's self-regulation and social competence, subsequently affecting the entire family system bidirectionally [71], with the family environment potentially affecting a child's social and emotional functioning, and the child's behavior possibly influencing their parents. Thus, bidirectional effects are well recognized in the general literature [72].

1.5. Current Study

This is a systematic review of the last 20 years of research focusing on behavior problems and social competence problems in individuals with FXS. Specifically, we want to address phenotypic differences between individuals with FXS, individuals with comorbid FXS and ASD, and IA individuals. Although a behavioral phenotype has been identified, there is a need to clarify the differences between individuals with FXS and ASD and non-syndromic ASD individuals in terms of anxiety, manic/hyperactive behavior, and obsessive compulsive behavior [73]. Further, it seems that important information concerning differences between the FXS spectrum and IA might be masked by just relying on a categorical diagnosis of ASD [36]. Furthermore, other comorbidities contributing to both behavior problems and social competence are considered. Environmental factors that contribute to the observed problems in social competence and behavior problems are also addressed in this review since they might influence both variables. The specific questions addressed by this review are as follows:

1. What behavior problems have been researched in individuals with fragile X syndrome in the last 20 years?
2. What social competence problems have been researched in individuals with fragile X syndrome in the last 20 years?
3. What differences have been found in behavior problems and social competence when comparing individuals with fragile X syndrome with typically developing individuals (TD) and individuals with other IDs?
4. What differences have been found in behavior problems and social competence when comparing individuals with fragile X syndrome with comorbid individuals with fragile X syndrome and autism?
5. How might environmental factors affect behavior and social problems in individuals with fragile X syndrome?

2. Materials and Methods

This review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [74]. It has been registered in the PROSPERO database with ID number 284267, although due to the current pandemic, it has not yet been assessed by the resident professionals.

Search Strategy

Three databases were searched: PsycINFO, PubMed, and Web of Science. The exact string search included "Fragile X Syndrome or FXS" in the title or in the abstract and the title depending on the defaults of the database, and "social skills OR social abilities OR social interaction OR social behavior OR social behaviour OR interpersonal skills OR social functioning OR social competence OR socialization OR problem behavior OR problem behaviour OR disruptive behavior OR disruptive behaviour OR dysfunctional behaviour OR dysfunctional behavior OR challenging behavior OR challenging behaviour OR behavioral problems OR behavioural problems OR externalizing OR internalizing OR aberrant behavior OR aberrant behaviour OR phenotype OR phenotypes OR maladaptive behavior OR maladaptive behaviour." A preliminary search was conducted on 1 December 2019, and the main search was carried out on 1 October 2021. The databases were last searched on or before 10 October 2021. Term selection was carried out using MesH terms of PubMed and by consulting studies in the bibliographies related to social competence and behavior problems. Filters included in the searches were the date, only including studies from 2000 onwards, journal articles, and Spanish and English languages.

The inclusion criteria for papers to be considered in the review, apart from the filters included in the search, were as follows. The study had to focus empirically on behavior problems or social competence in individuals with FXS. Nevertheless, studies focusing on other variables were considered if they addressed behavior problems or social competence in their results. Only full-text papers were included, meaning that if a study could not be wholly retrieved, it would be excluded from the review. Moreover, the studies had to focus on individuals with FXS with the full mutation. The exclusion criteria were documents other than original research such as reviews, congress abstracts, books, single case studies, studies focusing on participants with IDs other than FXS (if the study addressed different groups, this exclusion criterion did not apply), and studies focusing on other phenotypes such as premutation, and comorbidity of individuals with FXS and fragile X-associated tremor/ataxia syndrome (FXTAS) or dementia. This search strategy led to a total of 1538 papers eligible for inclusion. After checking for duplicates, 785 papers were considered.

The titles and abstracts of the 785 papers that remained after checking for duplicates were screened by a researcher. An Excel matrix was developed to record why each study was excluded according to the exclusion criteria. Different categories were developed, and labels explaining the reason for exclusion were assigned. These were case studies, language, reviews, interventions, studies focusing on drug treatments, animal models, brain/metabolism (including neurotransmitters, hormones, cognitive functions, or neuroimaging studies), validation tools, other phenotypes (the premutation condition and FXTAS), and a category to include the articles that could not be categorized in the others called "Not in line with the topic" (sleep problems, epilepsy, supplements, dental studies). All the articles were thereby classified into categories according to their title and abstract, leaving 143 papers. A researcher assessed the full text of the 143 papers, leading to 64 more being excluded, leaving 79 papers (51 included in the review and 28 with lower scores).

The 79 papers were reviewed using a matrix adapted from another study, which assesses the quality of the studies that addressed phenotypes [49]. The only modification made to the matrix was in the second line, corresponding to autism comorbidity or symptom control in individuals with FXS. The researcher assessed all the documents twice within two weeks. If discrepancies were found between the assessments, two other researchers decided what score was most fitting. The matrix and discrepant decisions are depicted in Appendix A, Table A1. The discrepant decisions are indicated in Table A1 with an asterisk (*) when a study was correspondingly discrepant. After assessing the 79 papers using the matrix, only those in the upper third were included in the review, leaving the studies that scored 12 or more points. However, since most of these studies pertained to the social competence category (n = 26), and only 14 studies pertained to behavior problems, studies with scores of 11 and 10, which belonged to the behavior problems category, were also included in the review. This strategy led to 26 studies assessing social competence and 25 studies assessing behavior problems. The data from the studies included in this review can be found in Supplementary Table S1. The PRISMA flowchart depicted in Figure 1 is a visual description of the process of filtering the initial 1538 papers down to the 51 reviewed.

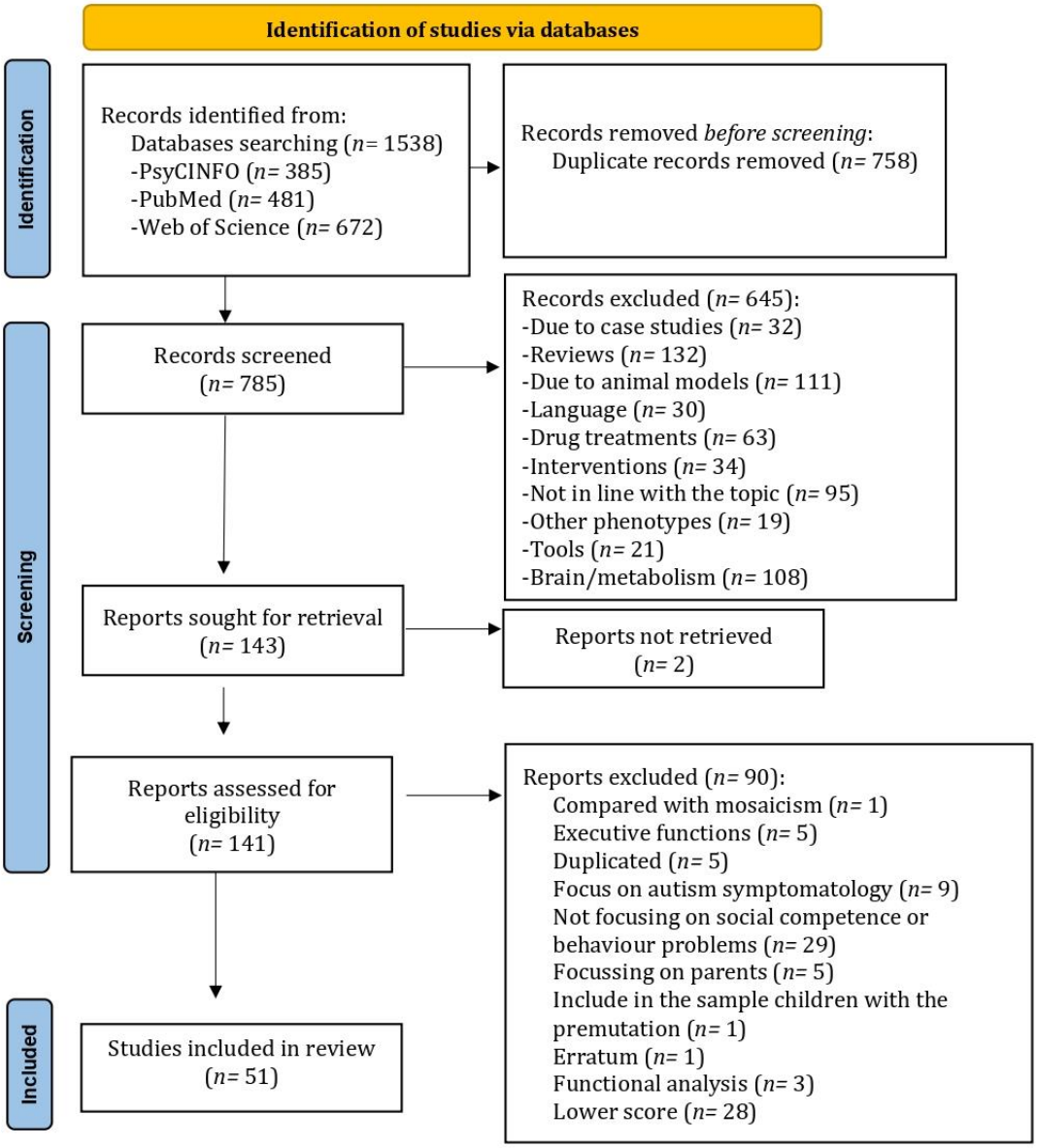

Figure 1. Based on PRISMA flowchart [74].

3. Results

3.1. Researched Profile in Behavior Problems

The main behavior problems researched represented a consistent behavioral phenotype in FXS, including attention deficit, hyperactivity, impulsivity, anxiety, repetitive, perseverative, stereotypic behaviors, affect, aggression, and self-injurious behavior [75]. The prevalence of the behavior problems indicated in the studies reviewed is summarized in Appendix A, Table A2. As expected in light of previous reviews, the highest prevalence and percentage scores of clinical concern were found for attention problems and ADHD comorbidity in boys and girls aged between 4 and 30 years [76]. The percentages of this behavior in the clinical range across studies varied from 15 to 73.5% in boys, as the table shows. The lowest percentages in the clinical range corresponded to the samples with the highest age range [77,78]. Furthermore, almost all the boys with FXS aged between 5.7 and 16.1 years were inattentive and easily distracted (98–100%, respectively), followed by over-active and impulsive [79]. Supporting these findings using a mood scale, the highest scores for boys between 4 and 10 years were for manic/hyperactive [73].

Less prevalent behavior problems of clinical concern for individuals aged between 4 and 12 years were thought problems and withdrawn and aggressive behavior problems in girls, withdrawn and aggressive behavior in boys [66], and aggressive behavior in boys and girls at 6 years [78]. Depression problems were the least reported psychiatric concern, and their prevalence was very low in children and low in adolescents (1.2–16%, respectively) [63], although these percentages were slightly higher in other studies [73,78].

Four of the studies reviewed contribute with results on disruptive behaviors. In boys aged between 11 and 18 years, stereotypy showed the highest prevalence and happened most often with a daily median frequency, although it was the least severe behavior problem [80]. Aggression was the most severe reported behavior problem by parents, followed by property destruction, which was also reported in the moderate zone but as the least prevalent behavior. Both behavior problems exhibited a weekly median frequency. The daily prevalence for aggression was between 20% and 40%. A slightly higher daily prevalence (50%) for aggression was found for boys in the same age range, and 25% of caregivers reported this behavior as a significant threat to health and safety [77]. In an older sample of males aged between 6 and 47 years, 21.5% exhibited persistent aggressive behavior, and higher impulsivity scores were associated with an increased probability of exhibiting aggressiveness over time [81]. Aggression was also found to be the most prevalent behavior problem and was the behavior problem with fewer boys not showing it between 5 and 21 years old [82].

Regarding self-injurious behavior, over eight years, almost 50% of boys aged between 16 and 25 years exhibited this behavior, with 32.4% of them exhibiting it persistently [81]. Higher scores in restricted, repetitive, and stereotyped behaviors predicted an increased probability of exhibiting continuous self-injury behavior across all the assessment points. A higher percentage (70.6%) of self-injurious behavior was found in individuals aged between 11 and 18 years [80]. However, in boys aged between 6 and 10 years, self-injury was the least reported behavior problem and was also less problematic [42].

Developmental Trajectories in Behavior Problems

Some studies have found decreasing trajectories of behavior problems such as physical aggression and tantrum scores until age 19 years, although they were not associated with age after this point [83]. The prevalence and severity of aggression also declined from 40% to 20% and 30% to 10% in boys aged between 11 and 12 years and 17 and 18 years [80], respectively, and a decreased proportion of aggressive behaviors in the clinical range was found from age 6 to 18 years in boys and girls [78]. Moreover, self-injury frequency was lower in boys aged between 17 and 18 years than in the age group 11–12 years [80], and boys and girls showed decreased percentages of attention problems in the clinical range from age 6 to 18 years [78]. Furthermore, higher rates of total behavior problems were found in both children and adolescents than in adults [84]. However, stability in aggressive behaviors in males aged between 6 and 47 years over 8 years has also been found [81].

Other behavior problems showed stability in longitudinal studies, including verbal aggression in males and females from 5 to 40 years [83], total problems assessed with the Child Behavior Checklist [85] in boys aged between 4 and 12 years [22], externalizing behaviors over three years in males and females aged between 12 and 48 years [86], and total and externalizing behaviors in a cross-sectional sample when comparing boys under 10 years old and boys over 11 years old [87]. No difference by age was found in attention/hyperactivity or opposition in individuals with FXS aged between 3 and 30 years [77]. Over-activity and impulsive speech remained stable in individuals aged between 6 and 54 years [88]. Trajectories of behavior problems are visually described in Appendix A, Figure A1.

Trajectories of behavioral problems were affected by ASD comorbidity in two longitudinal studies. Decreases in attention problems and aggressive behaviors in individuals aged between 6 and 18 years were smaller for those with autism comorbidity than those with FXS only [78]. Moreover, in individuals aged between 6 and 54 years, impulsivity

and repetitive questioning scores decreased only for the group with low levels of autistic symptomatology, and not for the comorbid FXS+ASD group [88].

3.2. Researched Profile in Social Competence

The researched social competence profile is less unitary than that for behavior problems. Studies have mainly assessed social behavior profiles, social avoidance, social approach behavior, and many specific variables that do not respond to a unitary theoretical approach to social competence, but rather to specific behaviors associated with it. The studies switched between parent-reported measures and task measures to address this area. Concerning prevalence, 81% of males exhibited social avoidance between ages 4 months and 25 years [89]. Regarding problems associated with social competence in the clinical range, between 15 and 35% of individuals with FXS aged between 3 and 30 years experienced social issues, anxiety, and adaptive social problems in the clinical range [77]. Withdrawal problems appeared in 21.5% and 17.5% of the sample of boys and girls, respectively, between the ages of 6 and 17 years in [66], and for 17% of boys aged between 4 and 12 years in [22]. Social problems appeared in the clinical range for 40% and 41.8%, respectively, of boys and girls [66] and for 26% of boys [22].

Developmental Trajectories in Social Competence

Some studies found positive trajectories for social competence over the years in individuals with FXS. These included reduced discomfort in older individuals with FXS when conducting a social task in a sample aged between 6 and 17 years [59], positive correlations between chronological age (CA) and social responsiveness in boys with a mean age of 15 years [90], higher scores in social skills in older individuals in a sample of boys aged between 3 and 7 years [34], and a positive correlation between social motivation and age in boys with FXS with a mean age of 23 years [91].

Regarding socialization, the longitudinal studies reviewed found different trajectories across ages. Significant declines between ages 2 and 14 years, which stabilized between 14 and 18 years, in boys were found, in addition to stability for girls [91]. However, in studies controlled by ASD symptomatology, boys aged between 1 and 12 years steadily improved their socialization scores [92]. Increasing socialization was found between ages 2 and 9.5 years, which were restrained around 7.5 years, with many infants tending to show declines at this age [93]. Furthermore, socialization scores decreased over three years in boys with a mean age of 4.7 years [94].

Internalizing symptoms were stable over three years in males and females aged between 12 and 48 years, although older individuals showed slightly fewer internalizing symptoms [86], and they were likewise stable in a cross-sectional sample of boys aged under 10 years and boys over 11 years old [87]. However, in another cross-sectional study, a higher frequency of internalizing symptoms in adolescents than in children was found [84].

Regarding social anxiety and depression, studies have found stability or worsening status. Anxious/depressed scores in girls with FXS aged between 10 and 15 years were found to be stable over three years [95], as were scores in boys and girls aged between 6 and 18 years [78]. Depression and anxiety disorders were also found to be stable until 30 years old [77]. However, social anxiety correlated negatively with age in boys with a mean age of 23 years, and a positive association for social anxiety with age was found in boys, with a mean age of 15 years [90,96].

Other studies have found stability in different variables, including social issues in individuals aged between 3 and 30 years [77] and withdrawal in girls aged between 10 and 15 years over three years [95]. However, in younger boys with a mean age of 4.7 years, increases in withdrawn behaviors with age were found over four years of assessments [93]. Higher increasing avoidance in initial interactions with unfamiliar people has been seen in early childhood (4–72 months) in terms of eye contact, physical approach, and facial expressions, but not in familiar interactions. However, in adolescent and adult samples (10–25 years), social avoidance was not associated with age [89]. Supporting this finding,

eye gaze avoidance in boys between 13 and 22 years was stable [97]. Trajectories of social competence are visually described in Appendix A, Figure A2.

Three studies found autism and anxiety symptomatology to be interaction variables affecting trajectories in social competence. Boys aged between 3 and 14 years with low levels of autism symptomatology showed a significant increase in social skills with age. Those with middle levels of ASD reached higher scores in total social skills earlier in life, showing reduced increases over the years, and those with high levels showed meager total social skills at younger ages, increasing minimally over time [34]. Moreover, girls with FXS with higher scores in autistic symptomatology obtained poorer outcomes and slower development rates in the personal social domain than those with lower scores [98]. Furthermore, higher ASD symptomatology was associated with a slower growth rate in socialization scores in boys at 24 months, while there was no association up to this age [99]. Regarding anxiety, boys with low and medium anxiety symptoms showed significant increases in social skills with age, while the group with higher anxiety scores showed minimal increases in social skills over the years [34].

3.3. Differences in Behavior Problems and Social Competence, Comparing Individuals with Fragile X Syndrome with Individuals with TD and Individuals with Other IDs

3.3.1. Comparison of Behavior Problems between Individuals with FXS and Individuals with TD

The studies found greater behavior problems for individuals with FXS than for TD individuals, including more significant total, internalizing, and externalizing behaviors in boys between 5.7 and 16.10 years with FXS [87]. Boys and girls with FXS with a mean age of 10.9 years showed higher scores in externalizing behaviors than their unaffected siblings [100]. Significantly higher levels of irritability, stereotypic behavior, inappropriate speech, hyperactivity, more symptoms on the attention and hyperactivity scale, and more issues in the repetitive behavior questionnaire were found, in addition to a trend for higher opposition scores in individuals with FXS aged between 3 and 30 years [77]. Furthermore, compared to normative data, adolescents and adults with FXS scored above the clinical cut-off in behavior problems [35]. Interestingly, boys aged between 5 and 8 years with FXS exhibited significantly higher hyperactivity and lower attention scores than CA-matched and mental age (MA)-matched TD boys with good attentional abilities, but they did not differ from CA-matched and MA-matched TD boys with deficient attentional abilities [101].

In some behavior problems, no differences were found between individuals with FXS and those with TD. For boys aged between 6 and 17 years, there were no differences for somatic complaints and delinquent behaviors [66]. No difference was found in somatic complaints and delinquent behavior in boys aged between 4 and 12 years [22], or in aggressive behavior in girls and boys aged between 6 and 17 years [63]. Furthermore, no differences were found in delinquency and aggressive behaviors in boys with FXS and TD individuals with deficient attentional abilities aged between 8 and 15 years [101].

3.3.2. Comparisons of Behavior Problems between Individuals with FXS and Individuals with Other IDs

Regarding Down syndrome (DS) groups, boys aged between 5 and 18 years with FXS scored significantly lower in attention abilities and had higher hyperactivity than the DS group [101]. Significantly higher scores on stereotyped behaviors, repetitive behaviors, insistence on sameness, impulsivity, and over-activity were found for the boys with FXS aged between 6 and 39 years compared to the DS group, but no differences were found in compulsive behavior [102].

Regarding individuals with other IDs, fewer differences were found. There were no differences in the severity or frequency of aggression for boys with FXS between the ages of 11 and 18 years compared to those with other intellectual and developmental disabilities (IDD) matched by CA [103]. There were no differences in the frequency of aggression in boys in the same age range compared to a mixed etiology group, although the aggressive behaviors of the FXS group were rated as less severe [80]. In this study,

stereotypy was also more prevalent and self-injury more frequent in individuals with FXS, but both groups showed the same relative frequency in property destruction and stereotypy. In a study comparing boys with FXS aged between 3 and 6 years and boys with a developmental delay of unknown etiology, no differences were found in general activity, task orientation, attention problems, hyperactivity, rigidity (difficulties with changes), somatic complaints, and irritability [104]. Even after controlling for maternal persistence, distractibility, and irritability, there were no differences in attention, hyperactivity problems, and task orientation. However, when maternal ratings of their activity level were controlled for, a higher general activity level was found for the FXS group [104]. However, activity levels did not differ in males aged between 6 and 39 years compared to individuals with Phelan–McDermid syndrome [102]. This study found a difference in total repetitive, with these behaviors being higher for FXS individuals. Additionally, boys aged between 5 and 16 years showed similarities in the frequency of behavior problems to boys with fetal alcohol syndrome (FAS), particularly in disruptive behaviors such as irritability, abusive/swearing at others, and attention/seeking, as well as overexcited/impulsive, and flick, tap, and twist objects [79]. At the same time, other behavior abnormalities, including autistic-related behaviors such as eye avoidance and self-absorbed behaviors, were more frequent in boys with FXS than in individuals with FAS, tuberous sclerosis, or Prader–Willi syndrome [79].

Comparisons with ASD samples showed no differences or greater behavior problems for FXS groups. There were no differences in the activity level, repetitive behaviors, or compulsive behaviors in males aged between 3 and 39 years [102], or in internalizing and externalizing behaviors in males with a mean age of 21 years [35]. A trend for higher manic/hyperactive behavior was found for FXS boys aged between 4 and 10 years compared to CA-matched boys with ASD. This trend increased until reaching significance when controlled by intellectual quotient (IQ) and ASD symptomatology [73]. A trend for lower obsessive compulsive behaviors for FXS appeared but did not remain when controlled by ASD and IQ. Additionally, in the early stages, 36–95 months, boys with FXS were significantly more distractible than those with an autism diagnosis (AD) [105].

3.3.3. Comparisons of Social Competence between Individuals with FXS and Individuals with TD

A worse profile in social competence was generally found for individuals with FXS than for TD individuals, including lower socialization scores than CA-matched TD boys aged between 3 and 13 years [106], lower adaptive socialization scores in boys over 12 years and in girls aged between 2 and 18 years [91], and a lower growth rate in social development in individuals with FXS compared to TD references aged between 12 and 143 months and in boys aged between 6 and 24 months [92,99]. Higher percentages of social avoidance (eye contact, physical approach, and facial expression) at initial assessments and in the last hour of assessment for boys aged between 4 and 72 months were also recorded [89]. Similar levels of physical approach in the last hour of assessment were found between FXS individuals with a mean age of 4 years and TD individuals [107]. A significantly higher mean proportion of eye avoidance was found in boys with an average age of 16.52 years [97], in addition to impaired eye contact, vocal quality, increased discomfort, and task avoidance during a social task in individuals aged between 6 and 17 years [59]. One study recorded lower scores in social skills in boys with FXS aged between 3 and 7 years [34], and another found more withdrawal and adaptive behavior in a socially desirable way that developed more slowly in boys with FXS aged between 36 and 95 months [105]. One study found significantly lower social scores in adaptive behavior, more significant difficulties with social issues, significantly higher levels of lethargy, and higher anxiety scores in individuals with FXS aged between 3 and 30 years [77]. Girls with FXS aged between 7 and 18 years exhibited significantly greater impairments in identifying the causes and consequences of social problems, and a trend for generating less competent goals and solutions to social problems and performing at lower rates in all social information processing tasks, compared to TD girls [108]. Higher anxiety levels, withdrawal, and social problems in

individuals with FXS than in CA- and MA-matched TD individuals with both good and impaired attentional abilities have been found [101], as have lower facial fear expressions of avoidance compared to TD individuals, resulting in an untypical response to unknown people [109].

However, some behavior problems did not differ among individuals with FXS and TD individuals, including anxiety/depression scores in boys aged between 6 and 17 years [66], and escape behaviors and distress vocalization when exposed to unknown individuals across years in individuals with a mean age of 38 months [109].

3.3.4. Comparisons of Social Competence between Individuals with FXS and Individuals with Other IDs

A more impaired profile is seen in individuals with FXS than in individuals with DS, including lower socialization skills in boys with FXS aged between 3 and 13 years [106], more eye gaze avoidance in a sample aged between 13 and 22 years [97], and higher social anxiety in boys with a mean age of 23 years and boys aged between 5 and 18 years [96,104]. However, in the social composite, a lower percentage of individuals with FXS between 3 and 30 years were in the clinical range [77]. However, differences in social motivation were not found in boys with a mean age of 23 years [96].

Comparisons with individuals with other IDs found similar anxiety/depression scores to individuals with a developmental delay of unknown etiology [104], and similar socialization scores for individuals aged between 5 and 21 years compared to Smith–Magenis syndrome (SMS) and non-specific intellectual and developmental disabilities (NSID) [86]. Furthermore, no differences were found in social motivation in boys with a mean age of 23 years compared to individuals with Cornelia de Lange syndrome (CdLS) and Rubenstein–Taybi syndrome (RTS) [96]. However, significantly more avoidance (to novel situations) and less withdrawal were found in boys aged between 3 and 6 years than in individuals with a developmental delay of unknown etiology [104]. Nonetheless, when controlled by maternal temperament (general activity level and sleep, approach/avoidance, flexibility/rigidity, mood, persistence, and distractibility), the boys with FXS were reported to only have a trend of increased avoidance/approach behavior compared to the boys belonging to the control group, but still exhibiting significantly less withdrawn behavior. Lower eye contact and focus of attention were found in boys with FXS compared to individuals with CdLS but similar levels of eye contact to individuals with RTS in [90].

Compared to individuals with autistic disorders (ADs), a better profile of social competence appears together with higher anxiety levels. Adolescents and adults with FXS have been shown to be almost 12 times more likely to have a mutual friend than those with AD, and when accounting for behavior problems, it seems that the diagnostic group has no influence on friendship, while the level of behavior problems does [110]. Moreover, individuals with FXS were significantly more likely to have a hobby and spend time with friends and neighbors than individuals with AD. One study showed that adults with FXS were more engaged in recreational activities and playing sports than adults with AD, but no differences were found between the adolescent samples. The two groups of teenagers and adults did not differ in time spent with coworkers, attending religious services, social events, or religious groups, or travel. Male infants aged between 36 and 95 months with FXS had a higher developed personal-social domain than AD males (7.8 months lower) [105]. However, higher mean scores in general anxiety were found for individuals with FXS aged between 4 and 10 years than CA-matched ASD individuals even when controlled for verbal IQ and ASD symptomatology [73].

3.4. Differences in Behavior Problems and Social Competence between Individuals with FXS Only and Those with Comorbid ASD

3.4.1. Differences in Behavior Problems

Five studies comparing groups found greater behavior problems for individuals with FXS+ASD than for those with FXS only from childhood to young adulthood. These included higher attention problems [35,46,48,111], internalizing [35,46,48], hyperactivity/over-activity [88,111], aggressiveness or irritability/aggressive behaviors [35,111], repetitive or stereotyped behavior [46,48,88], total problems [35,46], externalizing, thought problems, intrusive thoughts, socially offensive behaviors, uncooperative behaviors, and being more hurtful to others in a sample with a mean age of 21 years [35]. Higher perseverative/obsessive compulsive behavior has been recorded in a sample aged between 0 and 21 years [111], as well as higher impulsivity, lining up, and just right behavior over 19 years old in a sample aged between 6 and 54 years [88]. However, no differences were found between samples in other behavior problems such as destructive to property, hurtful to self, disruptive behaviors, unusual habits [35], and irritability [48].

Furthermore, no differences in behavior by group (FXS or FXS+ASD) were found in a study with a sample group of over 200 individuals aged between 3 and 11 years and over 12 years, although this study assessed comorbidities by requesting information from parents and not by using a validated measure to establish the groups [63]. The only slight difference was higher self-injury behavior in the FXS+ASD group, but there were no differences in attention, hyperactivity, or aggressive behavior.

Three studies comparing behavior problems in individuals with FXS+ASD and those with ASD only showed different results that could be age related. A study conducted on young adults (mean age 21 years) with comorbid FXS+ASD showed higher scores in challenging behavior, total behavior problems, socially offensive behavior, uncooperative behavior, intrusive behaviors, and attention problems. The two groups did not differ significantly in aggressive behaviors, thought problems, externalizing problems, hurtful to self, property destruction, and disruptive behavior. However, the ASD group exhibited significantly lower strengths than the FXS+ASD group [35]. In a study with a juvenile sample (3–5 years), the groups did not differ in stereotypy, self-injury, and insistence on sameness, with the autism group only showing higher impairments in compulsive and ritual behaviors than the FXS+ASD sample [47]. Last, a study comparing young individuals (mean age 4.6 years) with FXS+Aut and those with developmental language delay (DLD) and Aut showed significantly higher scores in the borderline and clinical range in total behavior problems, thought, attention, and aggressive problems [46].

3.4.2. Differences in Social Competence

A more impaired profile in social competence is seen in individuals with comorbid FXS+ASD than in those with FXS only in the studies reviewed, including significantly lower socialization scores in boys with FXS+ASD compared to boys and girls with FXS only aged between 12 and 143 months [92], and lower socialization scores in a small sample of boys aged between 21 and 48 months [26]. A lower developed personal domain in boys aged between 36 and 59 months was also seen [105]. Lower socialization and lethargy/social withdrawal over two years were observed in the FXS+ASD group in individuals with a mean age of 4.7 years, but these differences did not remain in older ages [94]. Higher social withdrawal, withdrawal/lethargy, and greater delays in socialization were seen for boys with FXS+ASD aged between 3 and 8 years [112], as well as higher withdrawal and lethargy/social withdrawal in boys with an average age of 4.7 years [46]. Higher withdrawn/inattentive behaviors were also seen in comorbid FXS+ASD with a mean age of 21 years than in individuals with FXS only [35]. Supporting these results, males and females aged between 2 and 9.5 years with FXS only showed the sharpest increase in socialization scores over the years compared to those with FXS+Aut [93]. Furthermore, in boys aged between 4 and 5 years, increasing impairments in social interaction have been found in the groups FXS only, FXS + pervasive developmental disorder (PDD), and FXS+ASD, in

all measures corresponding to the social behavior profile (withdrawal, lethargy/social withdrawal, socialization, and daily living) [48]. Individuals aged between 5 and 16 years with comorbid FXS+ASD also made significantly fewer non-comprehension signals (more impairment) than the FXS-only group during a social task [113]. Higher anxiety scores for comorbid individuals aged between 12 and 21 years [111] and higher impairments for social information processing tasks (problem identification, goal generation, first solution competency, and chosen solutions) in comorbid girls with FXS+ASD than in FXS-only girls aged between 6 and 17 years were also found [108]. Furthermore, although FXS-only individuals acted similar to those with comorbid FXS+ASD in social approach during the first minute of interaction, the comorbid group exhibited less social approach (more avoidant) in the last hour of assessment [107]. However, in other issues such as mood swings/depression, there were no differences between individuals with FXS only and those with comorbid ASD [111].

Special attention must also be paid to studies comparing comorbid FXS+ASD and individuals with ASD only, although they do not provide a clear picture. In socialization, the FXS+ASD group achieved lower scores that disappeared when controlled for age and IQ [46], while in another study, the lowest personal-social levels were attributed to young boys with AD aged between 36 and 59 months compared to boys with FXS+ASD [105]. Furthermore, for withdrawal and internalizing, lower scores were found for the FXS+ASD group compared to the DLD+Aut group, unlike other studies that have found greater internalizing problems, while non-significant and greater withdrawal/inattentive problems for the FXS+ASD group have also been reported [35,46].

3.5. Environmental Factors Affecting Behavior and Social Problems in FXS

3.5.1. Environmental Factors Affecting Behavior Problems

In several studies, three characteristics of the mothers were associated with behavior problems. Higher maternal criticism was associated with externalizing symptoms in children, adolescents, and adults and with total behavior problems in adolescents, and high criticism in families was associated with a higher severity of behavior problems in individuals aged between 12 and 48 years [84,86]. On the other hand, positive comments were associated with lower externalizing problems in children and adults and total problems in adolescents [84]. Higher maternal warmth was also associated with lower levels of externalizing problems in children and adults, total behavior problems in children and adults, and decreases in behavior problems in individuals aged between 12 and 48 years [84,86]. Another maternal characteristic, flexibility, was associated with attention problem scores, with individuals with more flexible mothers showing greater declines in attention problems over the years [78], while warmth and affect were not significant in this study. This characteristic of the mother combined with ASD comorbidity led to four possible outcomes in an individual's attention problems. Similar scores were achieved by individuals with FXS+ASD with mothers with high flexibility and FXS-only individuals with mothers with low flexibility. Both exhibited medium decreases in attention problems over the years. In contrast, individuals with comorbid ASD and mothers with low flexibility maintained attention problems over the years, and individuals with FXS only with highly flexible mothers showed the highest decreases in attention problems over the years. Higher maternal educational level, apart from predicting total behavior problems, was associated with higher reports of behavior problems and attention problems in their offspring aged between 4 and 12 years [22].

Parental psychopathology was associated with internalizing and externalizing behaviors in boys and girls with FXS, respectively, between 6 and 17 years [66]. However, maternal distress was not associated with behavior problems in individuals with a mean age of 10.9 years [100].

Other positive aspects of the environment (cohesion, expressiveness such as sharing personal problems, achievement orientation, active recreational activities, independence, intellectual-cultural, moral-religious, control as rules, and organization) were not related to behavior problems in individuals with FXS with a mean age of 10.9 years [100].

3.5.2. Environmental Factors Affecting Social Competence

Parental characteristics have also been related to social competence problems in individuals with FXS. More positive comments were associated with lower internalizing behaviors in adults, males, and females [84]. Higher closeness in the relationship with the mother was associated with lower levels of withdrawal and lower anxious/depressed behavior at a trend level in girls aged between 10 and 15 years [95]. Maternal responsivity predicted socialization scores in infants with FXS with or without autism at 30 months, with socialization scores increasing by 0.03 for every point increase in frequency of maternal responsivity behaviors, and maintaining high levels of maternal responsivity reduced the amount of decline exhibited in socialization scores [93]. Strikingly, maternal flexibility was associated with anxious/depressed behavior in their offspring, with higher flexibility associated with higher anxious/depressed behavior [78].

Furthermore, three studies have reported parental mental issues associated with social competence factors. Higher parental psychopathology was associated with internalizing problems in boys aged between 6 and 17 years [66], and higher maternal depressive symptoms between families were associated with higher internalizing symptoms [86]. Higher maternal psychological distress was associated with higher withdrawal levels in girls aged between 10 and 15 years [95].

Regarding home characteristics, the mother's marital status was associated with the probability of having a mutual friend in individuals with FXS, with adolescents and adult sons or daughters of married mothers exhibiting a lower probability of having a mutual friend [86]. Higher home environment (parent responsivity, encouragement of maturity in the child, acceptance of the child, learning materials at home, effort to provide cultural, recreational, or artistic enrichment, family companionship, and quality of physical environment) was also associated with better gaze, vocal quality, and less task avoidance in boys and girls with FXS aged between 6 and 17 years [59]. Living out of the parents' house was significantly associated with more frequent socializing but participating less frequently in religious services and hobbies [110].

4. Discussion

This review summarizes results for behavior problems and social competence profiles in individuals with FXS by selecting the studies that best fit behavioral phenotypes and show the best methodology criteria. Most of the studies that controlled for ASD symptomatology and achieved a good methodological quality were developed in the social competence area, while less methodological quality was found in studies addressing behavior problems. Consequently, to facilitate carrying out this review, more studies addressing behavior problems were included, even though they had lower methodological quality scores. In terms of the age ranges included, eighteen studies assessed childhood stages (up to 10 years), twenty-eight studies assessed stages from childhood to young adulthood (up to 25 years), and five studies assessed from childhood to adulthood (over 25 years). Most of the studies reviewed that addressed changes from adolescence to adulthood encompassed the social competence area. However, there were few studies in the behavior problem section, supporting the idea of the scarcity of studies on behavior problems [51]. This Discussion section is based on all the studies assessed in the screening section but not selected due to receiving a lower score, in addition to other reviews and studies that make up the empirical body of behavior problems and social competence in FXS.

The prevalence of behavior problems observed in this review is in general agreement with previous findings for different behavior problems. This is the case for the prevalence of attention and ADHD-related problems [114], and clinical range [115], although even higher

scores were found in boys (77%) in other studies [116]; for the prevalence of aggression and severity rates [117,118], and self-injurious behavior [118–121], although higher prevalence has been found in studies with functional analyses [122]; and for the prevalence of thought problems in the clinical range [116]. Low percentages in the clinical range for delinquent behavior align with studies finding scores for this behavior in the normal range [123]. Depression scores reported here are consistent with other studies [39], although higher percentages in the clinical range in younger girls have been found [124]. Furthermore, higher percentages of withdrawn behaviors in the clinical range were found in other studies with boys (38.8%) [116] and girls (37%) [115]. Moreover, social problems in the clinical range reported in this review are below the 75% found in boys [116], are similar to a sample of girls in the same age range [115] and are higher than the 29% reported in older girls [125]. The prevalence of social avoidance reported corresponds to the well-established phenotypic characteristics [126]. Externalizing, internalizing, and total problems in the clinical range show a high variance in the studies reviewed and concur with other studies [116].

Regarding trajectories of behavior problems, the decreases in aggressive behaviors during adolescent stages may resemble those seen in the TD population and concur with results that have found an improvement in aggressive behaviors after adolescence in boys with FXS, which were drug dependent [127,128]. Interestingly, decreases in aggressive behavior depended on ASD symptomatology, decreasing less over the years in individuals with ASD comorbidity than in individuals without ASD comorbidity [78]. To our knowledge, this is the first finding signaling how autism symptomatology could mediate aggressive behavior, although higher aggressive behaviors have been reported in comorbid individuals with FXS+ASD [111]. Furthermore, decreasing trajectories in behavior problems over time affected by ASD symptomatology have been found [51].

The decreases in attention problems found in this review differ from the results of previous reviews and studies that have found stability in attention problems for individuals with FXS' entire life [75,114,129]. A cross-sectional study partially supported these results, finding a negative association between age and inattention scores in females aged between 4 and 66 years [130]. The EXPLAIN study also found lower mean decreasing ADHD scores across participants, with individuals over 18 years old exhibiting the lowest scores [131]. Different trajectories of attention problems depending on ASD symptomatology and maternal characteristics have also been found [78]. This result is supported by the strong association between ADHD symptomatology and ASD symptoms and might expand results from studies that have found developmental improvements in cognitive attention in samples of boys aged between 4 and 7 and 4 and 10 years [128,132,133].

Contrary to previous studies reporting decreases in hyperactivity behavior [75,128,130,134,135], attention/hyperactivity and over-activity were stable over time in the studies reviewed based on samples aged between 3 and 30 years and 6 and 54 years [77,88]. A closer look at the results of one of them shows lower scores for attention/hyperactivity from primary school to adolescence, although the finding may not be significant [77]. Furthermore, the study does not report results in primary school or in young adulthood. The other study found stability over eight years for FXS-only individuals and those with comorbid ASD [88]. However, this study used a different measure to assess hyperactivity.

Regarding trajectories of social competence, mixed results were found for socialization scores in the studies reviewed, such as declines in socialization during infancy which then stabilized in adolescence [91], a trajectory of restraining improvements or decreases in the middle of childhood (aged 4–8 years overall), with the differences between individuals with FXS only and those with FXS+ASD also decreasing [93,94], and steady increases from 1 to 10 years old [92]. Supporting the finding of increases during infancy, improvements in socialization scores in boys aged 9–15 years over three assessment points have also been reported, with a higher increase from 11/13 to 13/15 years than from 9/11 to 11/13 years [134]. Three trajectories based on past research on socialization in FXS have been proposed, including declines over time, positive trajectories which then decline or

stabilize, and increasing trajectories over time, suggesting that they could depend on gender, age, the measures used, or the number of time assessment points [136]. Based on the results of this review, ASD symptomatology should also be considered since it has been found to influence socialization growth at 24 months [99], while autism symptomatology mediated the increase in social skills in boys aged between 3 and 14 years [34]. Autism comorbidity was controlled in all but one of the studies reviewed [91], but in a categorical way. All three of the studies reviewed included both males and females with FXS in their samples. Therefore, further investigation should be conducted to discern the socialization profile in individuals with FXS from childhood to adolescence controlled by ASD symptomatology. Furthermore, the studies reviewed do not provide information on transitions in socialization from adolescence to adulthood.

Regarding internalizing symptoms, and in contrast to other studies which found stability, one study found higher symptoms in adolescence than in childhood for females with FXS [84]. These results agree with those found in this review regarding social anxiety, which was mainly stable in all the studies except for two, with one pointing out increasing social anxiety problems in adolescent stages in boys, and the other decreasing social avoidance over the years [90,96]. However, in one of the studies, the association with age was not significant when receptive language was accounted for [96]. Moreover, the other study included a wide age range of individuals between 2 and 46 years [90]. Furthermore, a positive association was found between social anxiety and autism symptoms [90]. Higher scores in generalized anxiety with increasing age have also been reported up to 15 years old [89]. Nonetheless, stability in anxiety scores was reported for both males and females [128]. Further exploration into anxiety and internalizing symptoms during adolescence is therefore needed to consider variables that might affect social anxiety such as ASD symptomatology.

In terms of comparisons between samples, a worse profile for behavior problems is generally reported for individuals with FXS than for TD individuals, as would be expected, while some behaviors do not differ between the groups, including somatic complaints and delinquent behavior in boys and girls [22,66]. These behavior problems are reported in a lower prevalence in this review and do not pertain to the behavioral phenotype of individuals with FXS [31]. The lack of differences in aggressive behaviors between individuals with FXS and those with TD with bad attentional abilities [101] is supported by studies in the general population reporting that inattention scores predict elevated aggressive-disruptive behaviors [137]. In addition, other studies found that individuals with FXS are less aggressive than individuals with other IDs, such as Angelman and Smith–Magenis syndromes [138]. Furthermore, some factors have been identified as increasing the risk for aggressive behaviors, such as impulsivity and hyperactivity [18,138].

Compared to individuals with DS, differences were found in attention and hyperactivity, stereotyped behaviors, repetitive behaviors, insistence on sameness, and impulsivity, which were more prevalent in FXS individuals [101,102]. These results are supported by others that also found higher rates of inattentive behavior and hyperactivity, fewer stereotypical behaviors in individuals with DS than in individuals with FXS, and greater behavior problems for individuals with FXS than for DS individuals [139–141].

Compared to individuals with other IDs, differences were rarely found in behavior problems, apart from those specific and characteristic of the specific syndrome, such as autistic-related behaviors such as eye avoidance and self-absorbed behaviors [79], the prevalence of stereotypy and frequency of self-injury [80], and general activity level and repetitive behaviors [79,102]. However, other studies have reported lower aggressive behaviors than in individuals without a defined etiology and individuals with other IDs [142,143]. Fewer externalizing behaviors than in individuals with Williams–Beuren have also been found [144], as well as an equal prevalence of repetitive behaviors between FXS and Prader–Willi [142]. Therefore, a general inference could not be made due to the specificity of the syndromes.

Compared to individuals with ASD, individuals with FXS showed no differences in more significant behavior problems in terms of activity level, manic/hyperactive behaviors, and distractibility [35,73,105], in agreement with studies reporting higher levels of activation in individuals with FXS than in those with ASD [145].

Regarding social competence, and as expected considering their behavioral phenotype, individuals with FXS showed lower socialization scores that developed at lower rates and exhibited higher social avoidance and withdrawal behaviors than TD individuals. Higher social avoidance, fewer social interaction gestures, and delayed communication repair have also been found [68,146,147]. Furthermore, a low prevalence of depression for individuals with FXS has been seen, resembling the prevalence in the general population [63,148]. Higher anxiety scores for boys with FXS than for the CA- or MA-matched TD group were reported in two studies [77,101], while not in others [66]. This discrepancy could be explained by differences in the comparison groups, such as whether or not they accounted for CA or MA, whether they included individuals with siblings, or differences in the age ranges used. Furthermore, other studies have found a higher prevalence of anxiety in a sample with FXS than in the general population [38].

With regard to comparisons with DS individuals, lower socialization skills, more eye gaze avoidance, and higher social anxiety have been found for FXS individuals [96,97,104,106]. These results are supported and explained by the high levels of sociability of individuals with DS and the lower difficulties in social functioning [140,149].

Compared to individuals with other IDs, the only findings were that individuals with FXS were more avoidant and exhibited less withdrawal and less eye contact [90,104]. Supporting these findings, more avoidant behavior in girls with FXS and requiring more time to initiate interaction than individuals with Turner syndrome have been found [125], in addition to higher eye gaze avoidance than individuals with other IDs [150].

Compared to individuals with ASD, a better profile of social competence appears, along with higher anxiety levels for individuals with FXS [73,105,110]. This profile is supported by other studies which found higher personal-social profiles for individuals with FXS than individuals with ASD [151–154]. This may be expected considering that the primary diagnosis of ASD in the Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5; American Psychiatric Association [152]) points to specific impairments in social interactions along with other behaviors [155]. Moreover, the higher levels of anxiety are consistent with the explanation for the social deficits in individuals with FXS in contrast to individuals with ASD [48]. In FXS, social deficits are driven by high levels of anxiety and hyperarousal, while in individuals with ASD, they are driven by a lack of interest [48]. A higher social preference in individuals with FXS than in individuals with ASD has also been reported [156].

Although not unitary, most of the studies reviewed found higher behavior problems for individuals with comorbid FXS+ASD than for FXS-only individuals in different age bands (early childhood, adolescence, and adulthood), except for one that did not find any differences between samples [63]. However, in this study, the assessment of comorbidities was carried out by asking parents if their offspring had ever been treated or diagnosed for a comorbid condition such as autism, not by using a validated measure. This worse profile of behavior problems mainly comprised behaviors that could be included under externalizing behaviors [157], such as hyperactivity, aggression or irritability, and repetitive behaviors, although greater attention problems have also been reported in individuals with comorbid ASD. Other studies support this worsening profile, showing generally greater problems in males with FXS+ASD than in those with FXS only [158], in addition to increasing rates of repetitive behaviors in individuals with FXS with comorbid ASD in comparison to those with FXS only [159]. Furthermore, higher rates of challenging behavior were exhibited for comorbid individuals with FXS+ASD compared to those with FXS only [160]. Differences in attention problems and hyperactivity between both samples could be supported by the causal relation between ADHD and ASD symptoms in a sample with ASD [78,132].

The few studies addressing behavior problems in individuals with FXS+ASD compared to autistic-only individuals showed discrepancies in their results. Studies showed a worse profile for comorbid FXS+ASD in adolescent/young adult samples, while for infant samples, it was the autism group that showed higher impairments in behavior problems [35,46,47]. Since ASD behaviors usually vary over time [161], a single conclusion could not be inferred. However, the results of two studies reviewed resembled each other, showing a similar worse profile of behavior problems such as total problems, aggressive, thought, and attention for the FXS+ASD group [35,46]. Further research on these comparisons is needed to further define the behavioral phenotype of FXS.

Regarding social competence, the studies reviewed achieved a higher agreement in terms of implications of FXS+ASD comorbidity, including higher impairment in socialization scores and withdrawn/lethargy behavior [26,35,46,92–94,105,112]. These results agree with those of some studies suggesting that social impairments could be the greatest predictors of comorbidity [162]. Other studies have found higher withdrawn behaviors in comorbid FXS+ASD individuals than in FXS-only individuals [126], while others have found no differences in mood swings/depression when comparing groups with FXS and those with FXS+ASD [27].

Comparisons between studies focusing on individuals with comorbid FXS+ASD and those with ASD only in social competence showed contradictory results, and thus an inference could not be drawn. Further investigation should be conducted in this area to delineate differences between the two syndromes, although some studies have reported that FXS+ASD individuals are more similar to ASD individuals than FXS individuals in social competence [48].

Parental characteristics such as criticism, maternal warmth, and the number of positive comments were associated with behavior problems in individuals with FXS [35,84]. Although maternal warmth was not associated with behavior problems [78], it is essential to highlight that the measures used in the studies reviewed were different. A clear interaction of maternal flexibility with behavior problems in their offspring was found, although in an unexpected way for social anxiety [78]. Besides parental characteristics such as positive comments, closeness in the relationship, mother–offspring interaction, and maternal responsivity have been associated with social competence factors [84,93,95]. Other studies have also reported characteristics of mothers such as expressed emotion to be related to behavior problems and social competence [141]. It seems that parental characteristics influence behavior and social competence problems, but there is scant research on parental characteristics, and thus further research should be conducted to elucidate the true implication.

Furthermore, parental mental health has been associated with behavior problems and social competence, including parental psychopathology, maternal depressive symptoms, and maternal psychological distress [66,86,95], although the last variable was not associated with behavior problems [100]. Although not unitary, these results, along with previous studies [163], point out that the mothers' interactions with their offspring might be influenced by their psychological situation, which also impacts the behavioral traits of their offspring. Further efforts should be made to discern parental mental health status and the implications for their offspring with FXS.

Regarding characteristics of the home situation, and reinforcing the positive results for living outside the parental home due to spending more time socializing [110], one study conducted under the COVID-19 lockdown found increasing behavior problems reported by mothers in that period [164].

Several limitations should be considered regarding misinterpretation or overlooked information. First, only one reviewer assessed the eligibility criteria, and second, two papers were not fully retrieved even after requesting them from the authors. Third, the search string, although broad, might not have retrieved all the relevant papers for the review, and the search was only conducted in three databases. Fourth, specific information related to autism symptoms, such as the information provided by autism questionnaires,

was not included in this review because it was not relevant to its objective. Lastly, three studies reviewed specified that some mothers reporting their children's information had the full mutation condition. Although not usually considered in studies, the mother's condition might be relevant because it may affect the way the child is raised and the reported information provided by them about their offspring.

5. Conclusions

The researched profile of behavior problems in the last 20 years concurs with the prevalence of previous works replicating results from past research. However, considering behavior trajectories, recent longitudinal studies may have discovered buried developmental changes thanks to higher methodological control. Regarding the prevalence of social competence problems, the studies also provided the expected results, which were similar to those from other studies. However, fewer studies reported information about prevalence due to the nature of the construct and the specificity of some measures. Trajectories for social competence have also been affected by recent studies, which have highlighted the need to continue with longitudinal research in this specific area and focus mainly on the childhood to adolescent and adulthood stages [165]. Similar findings on the behavior problems and social competence of individuals with FXS and TD individuals reflect specific areas in which FXS individuals behave the same way as TD individuals, driven by a lower prevalence of these problems in individuals with FXS, thus further profiling the phenotype characteristics of individuals with FXS. Specific comparisons with individuals with DS are also in line with previous works, signaling a better behavior problem profile and social competence for these individuals. Regarding comparisons with ASD individuals, both a higher activation and higher social competence were seen for individuals with FXS, concurring with the previous literature.

When addressing the phenotype of FXS, ASD comorbidity is still a controversial issue [19]. However, recent studies such as those reviewed here shed light on this area, which could benefit future interventions with comorbid FXS+ASD individuals. Notably, the addition of ASD comorbidity to the FXS profile seems to implicate higher behavior problems that are mainly related to the externalizing profile, and worse social competence for the comorbid individuals. Regarding comparisons between individuals with FXS with comorbid ASD and individuals with ASD, inferences could not be drawn due to the scarcity of research. However, it seems that these comparisons could help define the comorbid profile to a greater extent than only just relying on comparisons with individuals with FXS. Last, environmental variables coming from parental characteristics have been reported to influence behavior problems and social competence in their offspring. However, only 5 of the studies among the 38 reviewed, all of which included parent-reported information on behavior problems and social competence in individuals with FXS, reported the mother's condition. Thus, greater effort should be made in terms of the methodology, with increased control of the variables that influence the conditions, such as ASD comorbidity or symptomatology and parental characteristics, to fully understand the phenotype of individuals with FXS.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/genes13020280/s1, Table S1: Summarized information from all studies reviewed [85,166–237].

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Appendix A

Table A1. Matrix for assessing quality of studies.

Research Paper Assessed for:	Total Score:
1. Control group	0 = No control group 1 = Comparisons between non-genetically distinct groups or utilized standardized assessment tools 2 = Genetically distinct control group
2. Controls by autism comorbidity	0 = No 1 = Yes, statistically 2 = Yes, removing those with comorbid ASD
3. Sample size	0 = Fewer than 15 participants 1 = 15 or more participants 2 = 30 or more participants
4. Recruitment	0 = Participants selected by clinician(s) 1 = Participants recruited either through charity or medical clinic 2 = Multiple methods, multiple clinics, or multiple charities are used for recruitment
5. Syndrome diagnosis	0 = Based on reports from the parents 1 = Diagnosis based on physical features or sibling diagnosis 2 = Diagnosis based on appropriate genetic test (PCR or blood test)
6. Methodology	0 = No validated measures are used 1 = Use validated and/or standardized assessment tools 2 = Validated and/or standardized measures are used alongside new measures, observations, or other methodologies
7. Considerations for development	0 = Participants are compared as a whole 1 = The study considers age as a variable for at least one aspect of behavior or social competence 2 = Age is considered as a variable in relation to behavior and social competence
8. Appropriate statistics/comparisons	0 = Data not analyzed 1 = Descriptive statistics are used 2 = Appropriate comparative/correlative statistics are reported

Adapted from Cross and Hare (2013) [49]. Discrepancies found and solutions provided: In the "Control group" section, if a study added a control group for only part of the study fitting with the topic researched in this review, a score of 1 or 2 was given to it depending on the characteristics of the control group; In the category "Controls by autism symptomatology", if a study measured the ASD symptomatology to describe it or correlate it with variables such as social competence, behavior problems, or developmental trajectories, it was given a score of 0. A score of 1 was given if the study used the measures of ASD symptomatology, controlling for it in models or using it in regressions as control variables; In the "Sample size" category, only the samples with FXS were included in the number of participants. If a study included 47 individuals with FXS, but, for example, 20 of them had comorbid FXS+ASD, only 27 individuals were included in the FXS sample, thus scoring 1 point; In the "Recruitment" category, if a study reported that its sample came from another study and included the reference of that study, the original sample study was searched, and the score given to the study would depend on its recruitment characteristics. However, if a study reported that its sample came from another study with no more information about the original sample study, a score of 0 was given; In the "Considerations for development" category, a score of 2 was given if a study assessed age statistically and included it in models or regressions. If a study only assessed age differences between the samples and did not include it in the models, 1 point was given to it.

Table A2. Behavior problem and comorbidity prevalence or borderline/clinical concern in the studies reviewed.

Behavior Problem/ Comorbid Condition	Study	Gender	Age	Prevalence %	Borderline/ Clinical Concern %
Attention	Hessl et al. (2001) [66]	Boys	6–17 years		62
		Girls			47.5
	Hatton et al., 2002 [22]	Boys	4–12 years		56
		Boys and girls	6 years		66
	DaWalt et al., 2021 [78]		12 years		46.67
			18 years		44.44
			18 years		20
	Talisa et al., 2014 [63]	Boys	3–11 years	74.3	
			>11 years	85.5	
ADHD	Von-Gontard et al., 2002 [87]	Boys	5.7–16.10 years		73.5
Attention and hyperactivity	Côte et al., 2020 [77]	Boys and girls	3–30 years		15
Hyperactivity/ impulsivity	Talisa et al., 2014 [63]	Boys	3–11 years	58.9	
			>11 years	68.9	
Self-injurious behavior	Talisa et al., 2014 [63]	Boys	3–11 years	35.7	
			>11 years	44.7	
	Hall et al., 2016 [80]	Boys	11–18 years	70.6	
Depression	Talisa et al., 2014 [63]	Boys	3–11 years		1.2
			>11 years		16
Thought	Talisa et al., 2014 [63]	Boys	6–17 years		54.4
	Hessl et al.,2001 [66]	Girls	6–17 years		25
		Boys			57
	Hatton et al., 2002 [22]	Boys	4–12 years		57
Social problems	Hatton et al., 2002 [22]	Boys	4–12 years		26
	Hessl et al.,2001 [66]	Girls	6–17 years		40
		Boys			41.8
Withdrawn	Hessl et al., 2001 [66]	Boys	6–17 years		21.5
		Girls			17.5
	Hatton et al., 2002 [22]	Boys	4–12 years		17
Aggressive	Hessl et al.,2001 [66]	Boys	6–17 years		12.7
		Girls			12.5
	Hatton et al., 2002 [22]	Boys and girls	6 years		33
	Talisa et al., 2014 [63]	Boys	3–11 years	29.2	
			>11 years	41.7	
	DaWalt et al., 2021 [78]	Boys and girls	6 years		16.67
			12 years		26.67
			18 years		6.25
	Hall et al., 2016 [80]	Boys	11–18 years	82.4%	
Anxious/depressed	DaWalt et al., 2021 [78]	Boys and girls	6 years		8.33
			12 years		33.33
			18 years		18.7
			18 years		20
Delinquent behaviors	Hessl et al.,2001 [66]	Boys	6–17 years		2.5
		Girls			5
Total behavior problems	Hessl et al.,2001 [66]	Boys	6–17 years		44
		Girls			47.5
	Hatton et al., 2002 [22]	Boys and girls	6 years		44
	Von-Gontard et al., 2002 [87]	Boys	5.7–16.10 years		89.8
Externalizing	Hessl et al.,2001 [66]	Boys	6–17 years		26.6
		Girls			25
	Hatton et al., 2002 [22]	Boys and girls	6 years		19
	Von-Gontard et al., 2002 [87]	Boys	5.7–16.10 years		67.3
Internalizing	Hessl et al.,2001 [66]	Boys	6–17 years		34.2
		Girls			40
	Hatton et al., 2002 [22]	Boys and girls	6 years		17
	Von-Gontard et al., 2002 [87]	Boys	5.7–16.10 years		63.3
Stereotypy	Hall et al., 2016 [80]	Boys	11–18 years	90.6	
Property destruction	Hall et al., 2016 [80]	Boys	11–18 years	62.4	

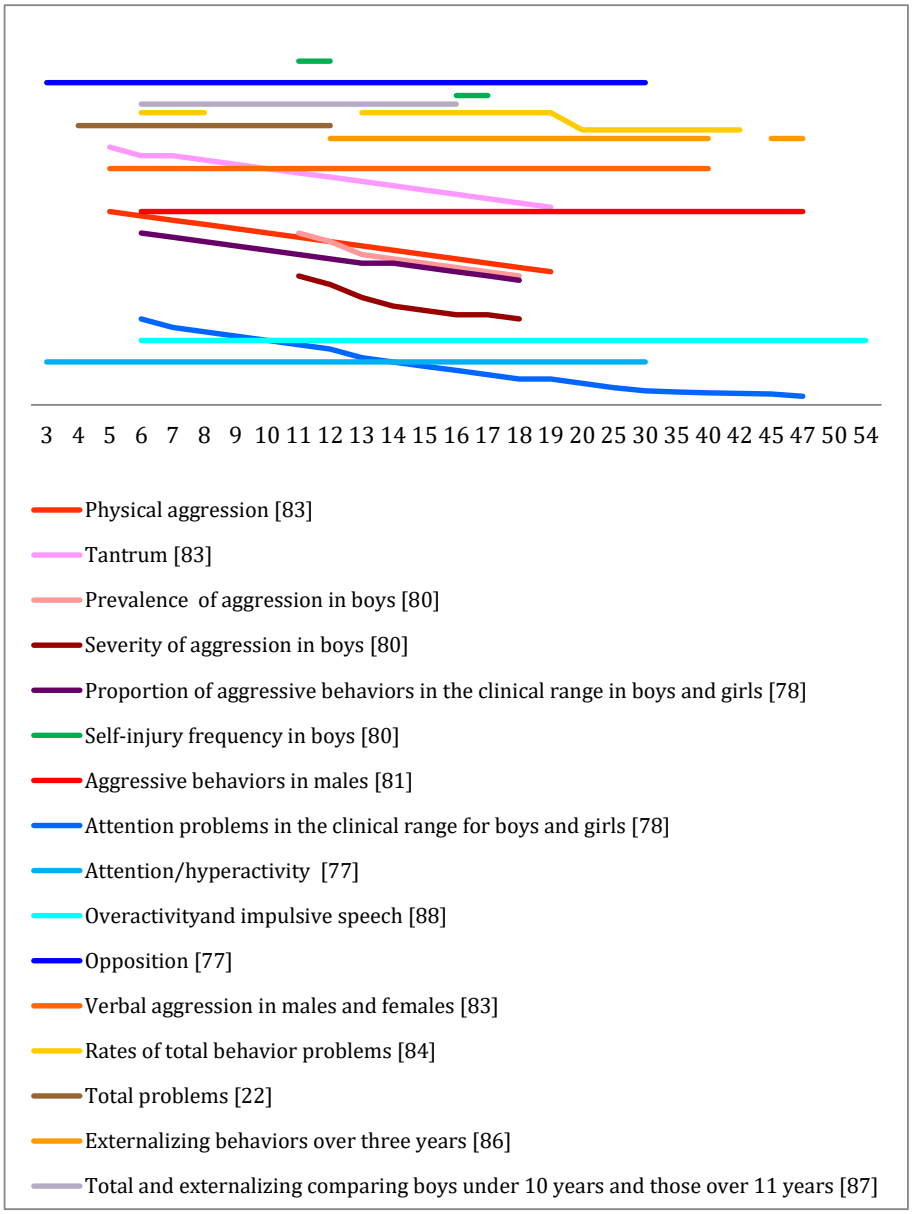

Figure A1. Trajectories of behavior problems over the years reported by the studies reviewed. This graph provides descriptive information of the trajectories reported in the studies reviewed [22,77,78,80,81,83,84,86–88]. The Y-axis has been removed because of the use of different measures and comparisons not being possible. Higher or lower lines do not represent greater problem behaviors or a higher frequency of behavior problems, nor does the slope. Each line should be compared with itself. For example, in this graph, tantrum scores compared with physical aggression are not higher, nor do they decrease faster over the years. One finding from the graph is that tantrum scores decreased from 5 to 19 years in [83].

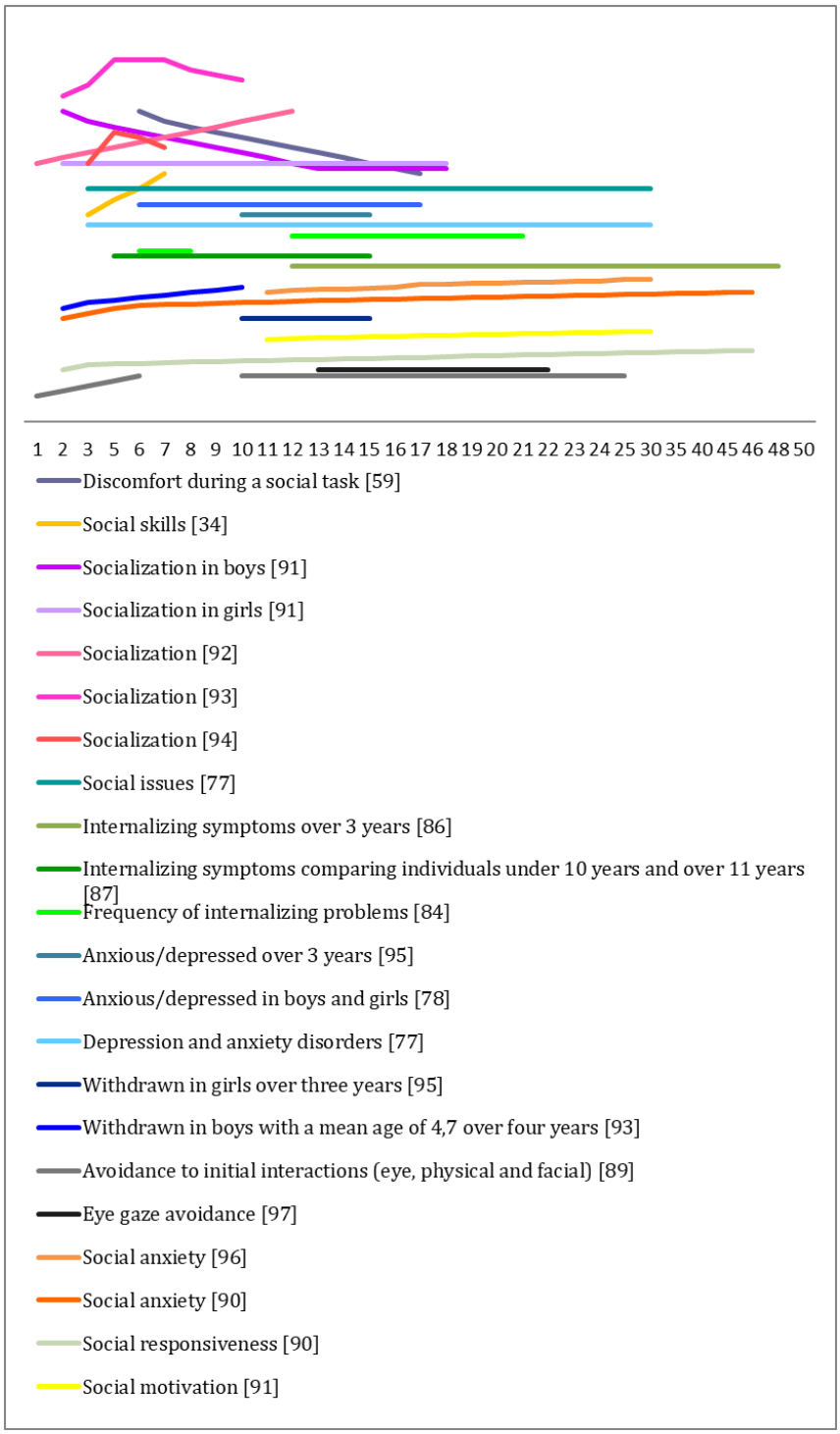

Figure A2. Trajectories of social competence from the studies reviewed. This graph provides descriptive information of the trajectories reported in the studies reviewed [34,59,77,78,84,86,87,89–97]. The Y-axis has been removed because of the use of different measures and comparisons not being possible. Higher or lower lines do not represent greater problem behaviors or a higher frequency of behavior problems, nor does the slope. Each line should be compared with itself. For example, in this graph, social anxiety and social skills increase over the years, but scores for social skills are not higher than those of social anxiety, nor do social skills increase faster over the years. One finding from the graph is that social skills increased from 3 to 6 years in [34].

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Supplementary Table S1

Authors/ year	Study aims	Control group	ASD control (scale used)	Sample size (n=)/gender/age	Recruitment	Diagnosis	Methodology/Assessment tools	Developmental factors	Statistics	Findings
Bailey et al., 2000 [105]	Examine differences between boys with FXS and those with ASD in general indicators of development, functional abilities, and behavior.	FXS ASD FXS+ASD TD (reference group)	ECI/SG - The Child Autism Rating Scale (CARS) [166]	FXS (n=31) Boys 36-95 months Then it ads 13 boys with FXS+ASD	FOS	GT	S/VM -Behavioral Style Questionnaire (BSQ) [167]. -The Batelle Developmental Inventory (BDI)[168].	CA	DS EC Y*	Significant differences were found between boys with FXS and boys with Aut in the personal-social domain, with the formers performing better in this domain. Boys with Aut also scored significantly higher in the behavior domain, reflecting more impairment. Compared to the reference sample, both the FXS and the Aut group scored significantly more withdrawing, and boys with FXS were significantly more active than the reference group. Besides, the group with FXS was significantly more active than the Aut group. In the personal-social domain, boys with comorbid ASD and FXS showed higher impairments than boys with FXS only but lower impairments than those with Aut only. Similarly, the group

										with FXS+Aut was more impaired than the FXS only in behavior measures.
Score=13		2	2	2	0	2	1	2	2	
Kau et al., 2000 [104]	Examine the differences between individuals with FXS and those with DD in four behavior problem areas: social avoidance, hyperactivity or attention problems, difficulties with changes, and irritability.	FXS DD	No	FXS (n=41) Boys 3-6 years	SC Chs	GT	S/VM -The Child Behavior Checklist (CBCL) [169, 170]. -The Aberrant Behavior Checklist-Community (ABC-C) [171, 172]. -The Temperament Survey [173]. -The Vineland Adaptive Behavior Scale (VABS) [174].	AM IQM	EC Y*	Boys with FXS showed significantly higher scores on social avoidance behavior but fewer scores on withdrawal behavior. Differences were not found between both groups on attention problems, hyperactivity, or general activity. However, high levels of attention problems were found in both samples. Differences did not appear in the flexibility/rigidity, somatic complaints, anxiety/depression, or irritability scales. However, the boys with FXS showed a significantly higher level of general activity than the DD group when considering maternal characteristics.
Score=13		2	0	2	2	2	1	2	2	
Hessl et al., 2001 [66]	Examine the association between genetic variables and environmental variables in	FXS TD (siblings)	No	FXS (n=120) 80 boys/40 girls 6-17 years	Ch NW M R MC	GT	S/VM -CBCL [85]. -The SCL-90-R [190]. -The HOME [175].	SA	DS WR Y*	Internalizing and externalizing problems in boys with FXS were predicted by the effectiveness of educational/therapeutic services and psychological issues in their parents. The quality of the

	behavior problems of individuals with FXS compared to their TD siblings.						-The special Curriculum Opportunity Rating Scale (SCORS) -The Autism Behavior Checklist (ABC) [176].			conditions at home predicted autism symptomatology. In girls, FMRP percentage influenced social withdrawal scores and anxious/depressed behavior.
Score=13		2	0	2	2	2	1	2	2	
Cornish et al., 2001 [101]	Examine the behavior profile on attention and hyperactivity between individuals with FXS, DS, and TD individuals.	FXS DS TD	None	FXS (n=25) Boys 8-15 years	Ch	GT	S/VM -Comprehensive Teacher Rating Scale (ACTeRS)[177]. -CBCL [85].	VIQ-matched CA-matched	CE Y*	Compared to the DS group, the FXS group showed significantly lower scores on attention and higher scores on hyperactivity. Significantly higher scores on attention problems and anxiety were found for the FXS than in individuals with DS. Similar hyperactivity and attention problems were found between TD (EC or EM paired) individuals with inadequate attention and FXS individuals. In contrast, those with DS scored better but well below those with TD with good attention scores.
Score=11		2	0	1	1	2	1	2	2	
Hatton et al., 2002 [22]	Explore the trajectory of behavior problems	None	No	FXS (n=59) 4-12 years boy	MC	GT	S/VM -CBCL [85,178]. -The BSQ [167].	LS (3 years)	DS WC WR	Regarding the clinical concern of problem behaviors, attention, thought, and social problems

	in boys with FXS over three years. Determine the most challenging behavior problems, and discern which variables might predict the behavioral outcomes.						-The CARS [166].			were the ones with the higher percentage. Stability on behavior problems was found all over the three years. Higher autistic symptomatology was significantly associated with greater behavior problems. Higher education of mothers was significantly associated with higher rates on behavior problems as attention, thought, and total scales.
Score=11		0	0	2	2	2	1	2	2	
Rogers et al., 2001 [26]	Examine the behavioral phenotype of young children with FXS compared to young children with AD and DD. Specifically, this study focuses on ASD symptomatology and developmental, including socialization.	FXS AD DD	SG -The Autism Diagnostic Interview -Revised (ADI-R) [179]. -The Autism Diagnostic Observation Schedule (ADOS) [180].	FXS (n=24) 21-48 months	MAP C NW M	GT	S/VM -The VABS [174].	AS	DS CFVSF+ ASD CE Y*	The group with FXS+ASD and the AD group differed from the DD group on social scales with the groups with ASD having higher impairments. The FXS group only did not differ on any adaptive scale from the DD group including socialization.

			-The Diagnostic and Statistical Manual of Mental Disorders -IV [181].							
Score=14		2	2	1	2	2	1	2	2	
Steinhausen et al., 2002 [79]	Examine the behavioral phenotype of four syndromes: Fetal Alcohol Syndrome (FAS), Prader-Willi syndrome (PWS), Tuberous Sclerosis (TS), and FXS.	FAS PWS FXS TS	No	FXS (n=49) Boys 5.7-16.10 years	Ch, SC	NM	S/VM -The Developmental Behavior Checklist (DBC) [182, 183].	SA	DS EC Y*	Boys with FXS and those with Fetal Alcohol syndrome showed relatively high frequencies of behavior problems. The FXS scores were the second higher. The most frequently reported behavior problems for boys with FXS were overexcited/impulsive, abusive/swear, irritable, and attention-seeking. Significant differences were found for the six subscales of the DBC, with boys with FXS scoring highest on self-absorbed, communication disturbances, anxious, and autistic relating behaviors. At the same time, individuals with FAS scored higher than those with FXS for disruptive behavior and antisocial. The boys with FXS

										scored significantly higher than those individuals with PWS and Tuberous Sclerosis on disruptive behavior and higher than those with tuberous sclerosis on antisocial behaviors.
Score=11		2	0	2	2	0	1	2	2	
Von-Gontard et al., 2002 [87]	Examine behavior problems and the emotional impact in boys' families with FXS and Spinal Muscular Atrophy.	FXS SMA TD	No	FXS (n=49) Boys 5.7-16.10 years	Ch, MC	NM	S/VM -The CBCL [85]. - The 'Kinder-DIPS' [184]. - F-SOZU questionnaire [185]. - Questionnaire on Resources and Stress [186,187]. - Family Crisis Orientated Personal Evaluation Scale (F-COPES) [188].	SA	DS WR EC Y*	Compared to SMA and TD children, boys with FXS showed more significant behavior problems, particularly externalizing. 73.5% of the subjects with FXS had a comorbid ADHD diagnosis.
Score=11		2	0	2	2	0	1	2	2	
Hatton et al., 2003 [92]	Examine the trajectory of adaptive behavior, including socialization in individuals with	FXS FXS+ASD	SG -The CARS [166].	FXS (n=45) 10 girls/35 boys 12-143 months	MC	GT	S/VM - The VABS [174].	LS (8 years)	DS CFVSF+ASD Y*	Individuals without ASD comorbidity and higher FMRP protein expression levels showed higher scores on socialization and all over subscales. Increases in

	FXS considering age, gender, ethnicity, maternal education, FMRP expression, and ASD symptomatology.									socialization scores over the assessment points were highest for girls with low ASD symptoms, followed by boys with low ASD symptoms, and then the lowest scores and increases were found for the comorbid FXS+ASD boys. Besides, the lowest scores for comorbid FXS+ASD boys were found for the socialization scale.
Score=14		1	2	2	2	2	1	2	2	
Kau et al., 2004 [46]	Examine the specific characteristics of individuals with FXS in their social behavior profile.	FXS FXS+PDD FXS+Aut DLD+Aut IA	SG -ADI-R [179].	FXS (n=23) FXS+PDD (n=18) Boys Mean age 56.4 months	FOS	GT	S/VM -The CBCL [85,169]. -The VABS [174].	*SG	DS CFVSF+ASD EC Y*	The group with comorbid FXS+Aut showed significantly higher scores in problem behavior, with internalizing behaviors contributing to this difference compared to FXS only individuals. Higher scores on withdrawn, attention problems, lethargy/social, and stereotypic behavior were also found for the comorbid group. The highest differences in adaptive domains were found for socialization with comorbid FXS+Aut individuals scoring significantly lower. Comparison with IA boys showed that the comorbid group exhibited a milder profile in autism symptomatology with

										a better performance in reciprocal social interaction, although in behavior problems, the comorbid FXS+Aut group was similar to the DLD+Aut group.
Score=11		2	2	1	0	2	1	1	2	
Kaufman n et al., 2004 [48]	Examine the social behavior profile of individuals with FXS across the ASD comorbidity spectrum from individuals with FXS only through individuals with FXS+PDD to individuals with FXS+ASD. Identify predictors of ASD symptomatology and differences in behavior problems exhibited along the spectrum.	FXS FXS+PDD FXS+Aut	SG -The ADI-R [179].	FXS (n=32) Boys Mean age 4.71 years FXS+PDD (n=10) FXS+Aut (n=14)	FOS	GT	S/VM -The CBCL [85, 169]. -The ABC-C [171]. -The VABS [174].	NM	DS CFVSF+ASD Y*	An increasing impairment in behavior problems was found for the ASD comorbidity spectrum, with individuals with FXS only being the least impaired and those with comorbid ASD being the most impaired. Items that reflect complex social interaction could discern individuals with FXS+PPD and FXS+ASD from the cohort of individuals with FXS only.
Score=10		1	2	2	0	2	1	0	2	
Budimiro vic et al., 2006 [112]	Discern the behavioral characteristics that better contribute to	FXS FXS+ASD	SG -DSM-IV [181].	Cross-sectional assessment FXS (n=32) Boys	FOS	GT	S/VM -The VABS [174].	SA LS	DS CFVSF+ASD Y*	Delayed socialization and social withdrawal correlated with FXS+ASD. Adaptive socialization was the strongest

	the comorbid diagnosis of FXS+ASD			3-8 years Longitudinal FXS (n=19) 3-8 years			-The CBCL [85, 169].			predictor of ASD comorbidity in FXS although withdrawal also predicted it. Items representing social avoidance are the main predictors of ASD inside of scales assessing withdrawal. Adaptive socialization skills were associated with verbal reasoning abilities and thus with FXS+ASD comorbidity. Models combining withdrawal and adaptive socialization could distinguish FXS+ASD groups.
Score=12		1	2	2	0	2	1	2	2	
Hessl et al., 2006 [9]	Examine the association between cortisol reactivity and social behavior profile in individuals with FXS compared to TD individuals.	FXS TD	No	FXS (n=90) 32 girls and 58 boys 6-17 years	NM	GT	S/VM -The ABC [189]. -The CBCL [85]. - The HOME [175]. -The SCL-90-R [190]. -ABC [176] OM -A social task observed and rated	SA	DS WR EC Y*	In comparison to the TD group, boys and girls with FXS had inferior gaze, vocal quality, increased discomfort and task avoidance. Increased cortisol reactivity during the social task was associated with autism symptoms (sensory and social relating). Cortisol decreases were associated with more gaze avoidance and cortisol increases with more eye contact in FXS.
Score= 11		2	0	2	0	2	1	2	2	
Sullivan et al., 2006 [237]	Examine the profile of ADHD symptoms in individuals with	FXS TD	No	FXS (n=63) 7-13 years 6 girls 57 boys	FOS	GT*	S/VM -The CBCL [85, 169, 85].	MA	DS WR Y*	Parents and professors rated between 54-59% of individuals with FXS as meeting diagnostic criteria for ADHD and its

	FXS by describing it, comparing it with a sample of TD individuals, and finding predictors that might influence these behavior problems.						-The Childhood Symptom Inventory-4: Parent Checklist (CSI-PC) [191]. -The Adolescent Symptom Inventory-4: Parent Checklist (ASI-PC) [191]. -The Childhood Symptom Inventory-4: Teacher Checklist (CSI-TC) [191]. -The ASI-4: Teacher Checklist (ASI-TC) [191]. -The CARS [166]			subtypes. Scores of ADHD symptoms in the FXS sample were significantly higher than those of the general population and the MA-matched TD peers. Differences in assessments of individuals with FXS between parents and professors were found.
Score=11		2	0	2	0	2	1	2	2	
Hall et al., 2006 [100]	Examine the mutual influences of behavior problems in offspring and family functioning as maternal distress comparing individuals with	FXS TD (siblings)	No	FXS (n=150) 56 girls and 94 boys Mean age 10.9 years	Chs IW	GT	S/VM -The CBCL [85]. -The Teachers Report Form (TRF) [85]. -The SCL-90-R [190]. -The Family Environment	AS	WR EME	Children's behavior problems influenced maternal distress, but maternal distress did not impact behavior problems in their offspring with either TD or FXS. Family environment was not associated with behavior problems in individuals with FXS, although it was associated

	FXS to those with TD.						Scale (FES) [192].			with behavior problems in individuals with TD.
Score=13		2	0	2	2	2	1	2	2	
Murphy et al., 2007 [97]	Examining the influence of social-information processing demands on eye-gaze avoidance in individuals with FXS, DS or TD.	FXS DS TD	ECI -DSM-IV [181]. -The ABC [176].	FXS (n=15) Mean age 16.5 years 13-22 years	R NW M	GT	CT* -Experimental eye-gaze task	SA	WR EC Y*	Individuals with FXS were significantly more eye-gaze avoidance during tasks, although differences were not found regarding proportions of eye contact avoidance between social or non-social tasks. Depending on task difficulty, differences were not found between groups. Age did not influence levels of eye avoidance during tasks.
Score=12		2	2	1	2	2	1	2	2	
Hatton et al., 2009 [98]	Describe the phenotype of girls with FXS examining developmental trajectories and the influence of autistic behavior.	No	S -CARS [166]	FXS (n=15) Girls 6months-9 years A subsample of 11 girls was also added for some statistics	MC	GT	S/VM -The BDI [168]. Personal-social domain	LS 9 years	DS WR	Higher scores on autistic symptomatology were significantly associated with worse outcomes in the personal-social domain over the assessment points.
Score=11		0	1	1	2	2	1	2	2	
Hernandez et al., 2009 [94]	Examine the stability of ASD comorbidity in FXS and find social behaviors and skills	FXS FXS+ASD FXS+PDD	SG -DSM-IV [181]. -ADI-R [179].	FXS (n=32) Boys FXS+ASD (n=24) Of those FXS+PDD	FOS	GT	S/VM -The CBCL [85, 168]. -The ABC-C [171].	LS (3 years)	WR CFVSF+ASD Y*	The diagnostic of ASD remains relatively stable over the years. Socialization scores and peer relationships differentiated between individuals with FXS

	that could predict ASD comorbidity and severity.	FXS+ AUT	-ADOS-G [180].	(n=10), FXS+AUT (n=14) Mean age at T1 56.6 months			-The VABS [174].			only and those with FXS+ASD (PDD and AUT groups) and correlated with autism severity scores. Over the three years of assessment, scores of the FXS only in socialization skills worsened in comparison to those of the FXS+ASD individuals, which improved.
Score=12		1	2	2	0	2	1	2	2	
Roberts et al., 2009 [107]	Examine the development of social approach behaviors over time, its association with cortisol levels, and its relation with autism symptomatology in individuals with FXS.	FXS FXS+AS DTD	SG -The CARS [166].	FXS (n=33) Boys Mean age 3.99 years	Chs MC Rese arch proje ct	GT	S/VM -The Social Approach Scale (SAS) -The VABS [174].	AS	DS CFVSF+ ASD EC Y*	Differences between boys with FXS only and those with comorbid FXS+ASD were found in cortisol levels, elevated for the comorbid group, and poorer scores on the social approach scale. Higher ASD severity was associated with lower levels of cortisol change between the first hour of assessment and the last one.
Score=15		2	2	2	2	2	1	2	2	
Langthor ne et al., 2012 [82]	Explore the functions of problem behaviors in individuals with FXS and SMS in comparison to a control group of NSID.	FXS SMS NSID	No	FXS (n=34) 5-21 years	Ch	DPG T	S/VM -The ABC-C [189]. -The Questions About Behavioral Functions (QABF) [193].	MA MAB	DS WC WR Y*	Behavior problems for individuals with FXS are less likely to be displayed as attention-maintained behaviors than escape or tangible-maintained. Most individuals with FXS presented 2 or 3 topographical classes of

							-The VABS [194].			problem behaviors (attention, tangible, escape, physical discomfort, or self-stimulation), while only 2.9% exhibited one class. .
Score=13		2	0	2	1	2	1	2	2	
Greenberg et al., 2012 [84]	Examine the relationship between family environment and the behavioral phenotype in individuals with FXS through childhood, adolescence, and adulthood.	* FXS ASD	No	FXS (n=167) 24 females/143 males 6-42 years	Chs MC	DPGT	S/VM -The Five Minute Speech Sample (FMSS) [195]. -CBCL [196]. -Adult Behavior Checklist (ABCL) [197].	SG	DS WR	Maternal criticism was related to externalizing symptoms across all age groups with FXS and criticism with total problems for adolescents with FXS. Higher maternal warmth and more positive remarks were negatively associated with externalizing and total problems in children and adults with FXS. Maternal levels of negative and positive environmental factors did not differ among individuals with FXS or ASD, nor did the effect of these variables on behavior problems in their offspring.
Score=13		2	0	2	2	2	1	2	2	
Smith et al., 2012 [35]	Determine if having a comorbid ASD diagnosis is different regarding the behavioral phenotype of	FXS FXS+ASD ASD	SG -Social Communication Questionnaire	FXS (n=106) 19 girls 87 males Mean age 21.62 years FXS+ASD (n=30)	Chs MC	CDP	S/VM -Scales of Independent Behavior-Revised (SIB-R) [199].	AS	DS CEY*	Comorbid individuals with FXS+ASD displayed greater impairments in social reciprocity and higher scores on challenging behaviors than individuals of the FXS only

	individuals with FXS only or ASD only.		(SCQ) [198].				- The CBCL [196].			group. Repetitive and challenging behavior levels were also higher than the ones of those with ASD only.
Score=15		2	2	2	2	2	1	2	2	
Wolff et al., 2012 [47]	Examine behavioral differences between individuals with FXS+Aut and individuals with IA in social impairments and restricted, repetitive behaviors.	FXS+ASD FXS IA	SG -The ADOS [200].	FXS+ASD (n=23) FXS (n=27) Boys 3-5 years	MCs R	GT	S/VM -The Repetitive Behavior Scales-Revised (RBS-R) [201].	AS	DS $EC_{(FXS+Aut\ vs\ IA)}$ $Y^{*}_{(FXS+Aut\ vs\ IA)}$	Differences were not found in stereotypy, self-injury, and sameness rates between boys with FXS+Aut and boys with Aut only, while compulsive and ritual behaviors levels were lower for the FXS+Aut group. Gaze integration, Quality of Social Overtures, Social smile, Facial expression, and joint attention were less impaired in the comorbid FXS+Aut group. The radar graph of the repetitive behavior scale shows a less impaired picture for individuals with FXS only.
Score=13		2	2	1	2	2	1	2	1	
Klaiman et al., 2014 [91]	Examine the trajectories of adaptive behavior in individuals with FXS compared to individuals with TD.	FXS TD	No	FXS (n=275) 89 females/189 males 2-18 years	MC Ch	GT	S/VM -The VABS [174].	LS (12 years)	DS WC EC Y*	In comparison to other adaptive behaviors, socialization scores seem to be an area of strength in boys, with FXS decreasing the least over the years. Compared to TD boys, socialization scores are lower for both girls and boys with FXS.

Score=13		2	0	2	2	2	1	2	2	
Russo-Ponsaran et al., 2014 [108]	Explore the social information processing skills of girls with FXS compared to girls with TD MA-matched on a social task, determine the functioning and explore if autistic symptomatology is associated with performance on social information processing.	FXS TD	*SG -The SCQ [202]. -The ADOS [203].	FXS (n=11) 7-18 years girls	SC	DPG T	IQ	VMA	DS WC Y*	Girls with FXS were found to reach lower scores in social information processing at the early stages (as identifying problems) than TD girls. They also scored at a lower level for the latter stages as generating competent goals or competent first solutions. Autism symptomatology was associated with competent goal generation.
Score=12		2	2	0	1	2	1	2	2	
Thurman et al., 2014 [73]	Determine the profile of psychiatric symptoms in a sample of boys with FXS and compare its profile with the profile of individuals with ASD.	FXS ASD	S -The ADOS [180].	FXS (n=41) 4-10 years Boys	FOS	DPG T	S/VM -The Anxiety Depression and Mood Scale (ADAMS) [204].	CA	DS WC Y*	Hyperactive/manic behaviors and general anxiety were significantly more common in the group with FXS. Social avoidance and general anxiety were associated in boys with FXS more robustly than in the group with ASD.
Score=12		2	1	2	0	2	1	2	2	
Talisa et al., 2014	Examine differences between	FXS	SG IQ	FXS (n=177) 3-11 years	MCh	PR	IQ	SG	DS WR	High percentages of attention problems,

[63]	comorbid syndrome as ASD or Anxiety or a combination in the FXS FM phenotype and see if profiles differ from FXS only individuals. Compare differences between age groups.	FXS+ASD FXS+Anx FXS+ASD+Anx		Boys FXS+ASD, FXS+Anx and FXS+ASD+Anx 3-11 years 112 individuals with FXS, FXS+ASD, FXS+Anx and FXS+ASD+Anx >11 years						hyperactivity/impulsivity, autism and anxiety were found in the sample in both children and adolescents/adults. The sample with comorbid FXS+ASD+Anx showed the highest prevalence of attention problems, hyperactivity/impulsivity, self-injurious behavior and aggressiveness. While in groups of FXS without anxiety (with or without ASD) this scores were lower. Depression and seizures differences were only found in the adolescent/adult sample.
Score=11		1	2	2	2	0	0	2	2	
Rice et al., 2015 [83]	Examine the developmental trajectories of aggression.	FXS DS PWS	None	FXS (n=63) <19 years >19 years	NM	States *that syndrome origins were established through medi	S/VM - The DBC [205]	LS SG	WR	Verbal aggression scores were not significantly associated with age for any group. Physical aggression scores declined over the years for DS, FXS, and WS until 19 years. After this age, physical aggression is not associated with age for FXS or DS.

						cal and genetic history, and in case of not being sure, other methods were followed.				
Score=11		2	0	2	0	2	1	2	2	
Hall et al., 2016 [80]	Examine the prevalence, frequency, and severity of problem behaviors in adolescent boys with FXS.	Mixed etiology ID FXS	No	FXS (n=85) Boys 11-18 years	Chs, social media	NM	S/VM -The Functional Analysis Screen Tool (FAST) [206].	CA SA	DS EC Y*	Boys with FXS showed significantly more frequently self-injurious behavior, more prevalent stereotyped behavior, and aggression was less severe than for the group of boys with mixed-etiology ID. Aggression scores and property destruction correlated with each other in both syndromes. In the group

										with FXS frequency of self-injury decreased with age.
Score=11		2	0	2	2	0	1	2	2	
Smith et al., 2016 [86]	Describe developmental trajectories of behavior problems, psychological symptoms, and ASD symptomatology in individuals with FXS.	None	No	FXS (n=147) 12-48 years at T1 27 females/120 males	MC Chs	DPG T	S/VM - SIB-R [199]. -The CBCL [196]. -The Center for Epidemiological Studies Depression Scale (CES-D)[207]. -The FMSS [195] -The SCQ [198].	LS	WR	Regarding behavior trajectories, increasing age was significantly associated with reduced internalizing symptomatology. Fewer behavior problems appeared in females and of older age. Regarding environmental variables that could affect behavior problems within families, warmth increases were associated with decreases in behavior problems. The higher criticism levels mothers showed between families, the more severe behavior problems individuals with FXS exhibited. Besides, higher levels of maternal depressive symptoms and criticism were associated with higher externalizing behaviors between families. Females at older ages exhibited significantly fewer autism symptoms. Higher warmth between families was also associated with fewer autism symptoms.

Score=11		0	0	2	2	2	1	2	2	
Oakes et al., (2016) [42]	Examine the repetitive behaviors profile of individuals with FXS considering inter-correlations and predictive factors as anxiety, nonverbal cognition, and ASD symptoms that could influence this kind of behavior problems.	No	S -The ADOS [180].	FXS (n=39) Boys 6-10 years	R, WS, NWP, flyers at parent meetings	GT	S/VM -The RBS-R [201]. -The ADAMS [204].	As a group	DS WR	The most problematic behaviors were restricted interests (with fascination/preoccupation with a subject or activity and strongly attached to an object as the most frequently reported items in the moderate to severe problems) and sensory-motor behaviors (with hand/finger stereotypies and sensory difficulties being the most frequently reported as severe). Self-injury behavior problems were the less severe problems. Anxiety scores correlated positively and significantly with restricted interests, compulsive behavior, and ritualistic/sameness. And ASD social-affective symptomatology was positively associated with restricted interests.
Score=10		**0**	**1**	**2**	**2**	**2**	**1**	**0**	**2**	
Zhu et al., 2016 [106]	Examine the adaptive behavior of individuals with FXS, comparing it to individuals with DS and TD individuals	FXS DS TD	ECI	FXS (n=18) Boys 40-167 months	SCS	GT	S/VM -The Infants-Junior Middle School Students' Social life Abilities Scale [208].	MA-matched CA-matched	DS EC Y*	Socialization scores were significantly lower for the boys with FXS. Compared to TD boys matched by CA, socialization scores of boys with FXS were significantly lower, while when comparing boys with FXS to

	matched by CA and MA.									those with TD MA-matched, differences in socialization were not found.
Score=14		2	2	1	2	2	1	2	2	
Caravella et al., 2017 [99]	Examine the developmental trajectories on adaptive behavior comparing infants with FXS, TD, and siblings of individuals with ASD.	FXS TD Infant siblings of children diagnosed with autism (ASIBS)	S/ SG -The Autism Observation Scale for Infants (AOSI) [209]. -The ADOS-2 [210].	FXS (n=25) Boys 6-24 months Of those 11 were comorbid with ASD	R, Chs Social media groups, MC	GT	S/VM -The VABS-II [211].	LS	WR CFVSF+ ASD CE Y*	Compared to the ASIBS and individuals with TD, infants with FXS showed lower socialization scores at nine months. These differences become greater until 24 months, the last study time point. Girls with FXS showed higher socialization abilities than boys at nine months, with girls gaining skills faster. Differences in communication between individuals with only FXS and those with comorbid ASD were found.
Score=13		2	1	0	2	2	1	2	2	
Kaufmann et al., 2017 [111]	Determine how ASD comorbidity influences the behavioral phenotype of individuals with FXS.	FXS FXS+ASD	SG -The SCQ [202]. -The DSM-5 [147]. -The DSM-IV [181].	FXS (n=713) 155 females/ 558 males 0-24 years FXS+ASD (n=237) 0-23 years	MC	GT	S/VM -The ABC [189].	SG	CFVSF+ ASD Y*	Higher proportions of behavior problems were found in individuals with comorbid ASD, including attention problems, hyperactivity, hypersensitivity/over-activity, irritability/aggressive behavior, and perseverative/obsessive-compulsive behaviors. While fewer differences were found for anxiety, only differentiating

										older samples with the comorbid sample showed greater anxiety problems. No differences were found for mood swings/depression.
Score=14		1	2	2	2	2	1	2	2	
Reisinger and Roberts, 2017 [34]	Explore the relationship between social skills and chronological age in boys with FXS compared to boys with TD. And discern how autism and anxiety symptoms are related to social skills when controlled by adaptive behavior.	FXS TD	No	FXS 64 boys 3-7 years (cross-sectional comparisons) 102 boys 3-14 years (assessing predictors of social skills)	R, Chs, MC and ongoing studies	GT	S/VM -The CBCL [85,196]. -The preschool and elementary version of the Social Skills Rating System (SSRS) [212, 213]. -The VABS [174]. -The CARS [166].	CA	EC Y*	With age, individuals with FXS and those with TD increased their scores in social skills, although the group with FXS reached significantly lower levels of social skills. Individuals with low levels of ASD symptomatology showed more significant improvements in their social skills as they got older compared to those with a medium level who reached their higher social skills at younger ages showing small increases after that, or those with high levels of ASD who, besides scored lower at earlier stages showed minimal improvements in social skills. In the case of anxiety, boys with FXS with high levels of anxiety showed decreases in self-control as they got older compared to those with medium and low levels

										who showed an increase with age.
Score=13		2	0	2	2	2	1	2	2	
Richards et al., 2017 [102]	Examine the behavioral phenotype of Phelan-McDermid syndrome compared to individuals with FXS, ASD, and DS.	PMDS DS ASD FXS	No	FXS (n=30) Boys 6-39 years	Ch	CDP	S/VM -The Activity Questionnaire (TAQ) [214]. -The Repetitive Behaviour Questionnaire (RBQ) [215]. - SCQ-L [216].	CA	DS EC Y*	Boys with FXS scored significantly lower in over-activity, impulsivity, and total activity scale than those with ASD and significantly higher in the same variables than those with DS. Similarly, boys with FXS scored significantly lower than those with ASD on the insistence on sameness and stereotyped behavior, scoring lower than those with PMD and significantly higher than those with DS. Boys with FXS did not differ from the other groups on compulsive behaviors.
Score=12		2	0	2	1	2	1	2	2	
Martin et al., 2017 [113]	Examine the ability to indicate a communication breakdown in individuals with FXS, DS, and ASD.	FXS FXS+ASD ASD DS TD	SG -The ADOS [217].	FXS (n=38) 27 girls/11 boys 5.6-16.3 years	R, Ch, MC	NM	OM* Noncomprehension signaling task	S	EC CFVSF+ASD Y*	Boys with comorbid FXS+ASD and boys in the DS group made significantly fewer signals of non-comprehension overall than boys with ASD and TD. Boys with FXS+ASD indeed produced fewer signals of non-comprehension than those with FXS only. Depending on the context, the number of non-

										comprehension signals varied with comorbid FXS+ASD boys signaling fewer than FXS only boys in unfamiliar and ambiguous conditions. Girls with FXS+ASD and girls with DS produced fewer signals of non-comprehension than TD girls. In ambiguous and incompatible conditions, girls with FXS+ASD and DS made fewer signals than TD girls.
Score=12		2	2	2	2	0	1	2	2	
Tonnsen et al., 2017 [109]	Observe trajectories of stranger anxiety in individuals with FXS and TD longitudinally and establish comparisons with parent ratings of anxiety, withdrawal, and autism symptoms.	FXS TD	S -The CARS [166].	FXS (n=46) 12 girls/34 boys Mean age 38.85 months	Other studies Chs	DPGT	S/VM -The CBCL [218]. -The Laboratory Temperament Assessment Batery (Lab-TAB) [219].	LSS	ECY*	Over the years, distress vocalizations remained stable while there was an increase in escape behavior for individuals with FXS and TD. Individuals with FXS exhibited fewer facial expressions of fear altogether, tending to increase over the years. In the group with FXS, lower mental age was associated with higher ASD symptoms, escape behaviors, and distress vocalizations. The higher the withdrawal scores, the higher the autistic and anxiety symptoms the group showed. Medium and elevated withdrawal scores were

										associated with stability in distress vocalizations over the years, while inferior levels of withdrawal were related to decreases in distress vocalizations.
Score=14		2	1	2	2	2	1	2	2	
Warren et al., 2017 [93]	Examine the relationship between parenting and the development of adaptive behavior.	FXS FXS+ASD	SG S -The CARS [166].	FXS (n=55) 11 girls/44 boys Between 2.84-9.38 years on average at T1 Of those 18 were classified as comorbid FXS+ASD	R, advertisements at conventions, networking with community	NM	OM -Observation of maternal interactions with their offspring.	LS	WR CFVSF+ASD	There was an increase in socialization scores for individuals with FXS. Those increases were higher for the group without ASD comorbidity and lower for those with ASD comorbidity. Between 80 and 100 months, rates of increase in socialization scores slowed, with many children declining at these stages. Maternal responsivity has a positive influence on socialization scores. Maternal behavior management did not show any influence on adaptive trajectories.
Score=12		1	2	2	2	0	1	2	2	
Crawford et al., 2018 [88]	Examine differences between individuals with and without elevated levels of autism in impulsive	FXS+ASD FXS-ASD	SG -The SCQ [202].	-FXS-ASD (n=37) -FXS+ASD (n=32)	Ch	NM	S/VM -TAQ [214, 220]. -The RBQ [215].	LS SG 8 years	WR	Over time, individuals with FXS with low autism symptoms decreased in their levels of impulsivity and repetitive behaviors. Individuals of the FXS+ASD group scored higher

	and repetitive behaviors. Examine developmental trajectories and links between overactivity and impulsivity with repetitive behaviors.			Mean age at T1=16.32/ 18.43 years T3= 23.76/25.45 years All boys						on the overactivity scale at T1 and T2 and on the impulsivity scale at T3. Over the 8 years overactivity and impulsive scores did not change in both groups. Overactivity and impulsivity scores were not associated with repetitive behaviors in any group.
Score=11		1	2	2	1	0	1	2	2	
Del Hoyo-Soriano et al. (2018) [95]		None	No	-16 FXS Females 10-15 years old	NWM IWR	DPGT GT	S/VM -The SCL-90-R [190]. -The CBCL [196].	LS 3-years	DS WR	The level of withdrawal and anxious/depressed levels was associated with the ratio of affected total chromosomes but not with FMRP levels. Severity of mother symptoms and reciprocated closeness of the mother with withdrawn behavior with higher reciprocated closeness being associated with lower withdrawn in the offspring and higher symptoms in the mother were positively associated with higher withdrawn scores. A trend was found for higher reciprocated closeness and lower anxious depressed behavior in offspring. Scores in both withdrawn and

										anxious/depressed were stable over the 3 years.
Score=10		0	0	1	2	2	1	2	2	
Crawford et al., 2019 [96]	The authors examined the socio-behavioral phenotypes of individuals with FXS, RTS, CdLS, and DS, considering adults' familiarity and interaction environments for social anxiety and social motivation scores.	FXS RTS CdLS DS	No	FXS (n=20) Boys Mean age: 23.68 years >= 11 years.	SC	CDP	IQ -Social Task -The Social Anxiety and Motivation Rating Scale (SAMS). -The SCQ [202].	SA	Y*	Boys with FXS exhibited higher social anxiety than individuals with DS but comparable levels of social motivation. Increasing age was associated with decreasing social anxiety in the FXS group. The higher the social anxiety, the lower the social motivation scores for individuals with FXS.
Score=10		2	0	1	1	2	1	1	2	
Crawford et al., 2019 [81]	Over eight years, examine the prevalence, frequency, and associated risk markers of self-injurious behaviors in individuals with FXS.	No	No	FXS (n=79) Boys 6-47 years at T1	SC	CDP (pediatrician or geneticist)	S/VM -The Challenging Behavior Questionnaire [221]. -TAQ [214]. -The SCQ [202].	LS (8 years)	DS WR	Persistence rates for self-injurious and aggressive behaviors were 77% and 69%. Repetitive behavior scores at T1 predicted continuing self-injurious behavior, while impulsivity predicted persistent aggressive behavior. Over-activity, impulsivity, and age were associated with continuous aggressive behavior.

Score=10		0	0	2	1	2	1	2	2	
Chromik et al., 2019 [236]	Examine the relation between variables associated with ADHD and social functioning in a cohort sample and in a longitudinal sample to find predictors of functioning.	No	No	FXS (n=73) 15-25 years 40 boys, 33 girls	R PA IW	GT	S/VM -The Attention Deficit/Hyperactivity Disorder-Test [222]. -The ABC-C [223]. -The CBCL [85]. -The VABS [174]. -The ADOS [180].	LS	WR	Some ADHD symptoms could predict social functioning on the second time assessment eight years later from the first. In case of females, higher hyperactivity scores at T1 predicted higher social problems. For males, higher socialization scores predicted higher socialization scores and higher hyperactivity contributed to lower socialization scores at T2. In the cohort sample, ADHD symptoms and hyperactivity were associated with social problems and socialization scores.
Score=11		0	0	2	2	2	1	2	2	
Roberts et al., 2019 [89]	Examine the appearance of social anxiety and the developmental trajectory over time in individuals with FXS.	FXS TD	No	FXS (n=191) Boys 4-72 months 10-25 years	R, past studi essoc ial medi a, colle ague s, Ch	GT	-The Social Avoidance Scale (SAS) [107,126,].	CA	DS EC Y* OR	81% of boys with FXS exhibited social avoidance appearing at early infancy, worsening through childhood, and stabilizing in adolescents and adults (until 25 years).

Score=13		2	0	2	2	2	1	2	2	
DaWalt et al., 2019 [110]	Explore the differences in friendships, social participation, recreational activities, and family networks between individuals with FXS and those with AD in adolescence and adulthood.	FXS AD	ECI -The ADI-R [179].	FXS (n=81) 12-21 years >22 years	MC Ch	DPP C	S/VM MQ -Social participation based on the National Survey of Families and Households [224]. -The ADI-R [179]. -Zarit Burden Interview [225].	SG S	WR EC Y*	In comparison to individuals with AD, those with FXS had more friends and impacted less the family's social development. In both comparison groups, there was a difference between the adolescent stage and the adult with adolescents being less with friends and neighbors and spending more time exercising than adults.
Score=15		2	2	2	2	2	1	2	2	
Ellis et al., 2020 [90]	Describe the sociability profiles of individuals with FXS, CdLS and RTS taking into consideration both autism and developmental trajectories	FXS CdLS RTS	No	FXS (n=36) Boys Mean age 15.24 years 2-46 years	SC Ch	CDP	S/VM -The Child sociability Rating Scale [226-228-235]. - The ADOS-2 [210].	AS	CE Y*	In comparison with CdLS, individuals with FXS showed significantly lower scores on eye contact and less attention to persons but more object attention. An association between social affect and social anxiety in individuals with FXS was found. Regarding developmental trajectories for the FXS group, the higher the age, the higher scores on social responsiveness and social communication skills, and higher scores on anxiety.

Score=12		2	0	2	2	2	1	1	2	
Britton et al., 2020 [103]	Examine the forms and functions of aggressive behavior in boys with FXS as well as the maintainer conditions.	FXS IDD	No	FXS (n=41) Boys 11-18 years	Chs	PR	S/VM -FAST [206].	CA	DS EC Y*	Compared to boys with IDD, boys with FXS were significantly more prone to exhibit specific forms of aggressive behaviors as scratching others or biting others. Both groups had similar reinforcements as maintainers of the behaviors.
Score=11		2	0	2	2	0	1	2	2	
Côte et al., 2020 [77]	Examine the specific behavioral problems associated with adaptive functioning in individuals with TS, DS, FXS, and TD.	TS DS FXS TD	No	FXS (n=23) 3-30 years 8 females/15 males	MC, Social media	NM	S/VM -The RBS-R [229, 230] -ABC-C [189]. -Social Responsiveness Scale [231,232]. -The CBCL [218,233]. -Brief Symptom Inventory [234]. -Adaptive Behavior Assessment-II [235].	SA/SG	DS EC Y*	Compared to the TD group, all clinical groups showed less adaptive behavior, including the social composite, more social issues, higher global scores on autistic questionnaires, and higher scores on lethargy. Specifically, the group with FXS exhibited significantly more irritability, stereotypic behavior, and inappropriate speech than TD individuals. Besides, the groups with FXS and TS showed significantly higher hyperactivity scores, and the FXS and DS group showed greater problems on the SRS questionnaire compared to TD individuals. The FXS and TS group also showed more

										symptoms on the Attention and hyperactivity scale than the TD group. Furthermore, the FXS group showed higher anxiety scores than the TD group, a trend for more serious oppositional problems was also found in the FXS group.
Score=10		2	0	1	2	0	1	2	2	
DaWalt et al., 2021 [78]	Describe developmental trajectories of attention problems, depression/anxiety, and aggressive behavior in individuals with FXS and examine if autism symptoms and parenting features could predict outcomes in these behavioral variables.	No	SG -The CARS [166].	FXS (n=55) 6-18 years Boys and girls	FOS	GT	S/VM -The CBCL [196]. -Videotaped session to assess mother-child interactions	LS	DS WR	Developmental trajectories of both attention and aggressive problems declined slightly from 6 to 18 years. However, anxious/depressed scores remained stable over the years. Maternal flexibility and autism had impacts on the trajectory of attention problems. Autism comorbidity was associated with fewer declines in attention and aggressive behavior. Higher maternal flexibility was associated with higher declines in attention problems and increases in depression/anxiety scores for their offspring.
Score=11		0	2	2	0	2	1	2	2	

Key for table

NM= Not mentioned

Control group:

-SQ= standardized questionnaire on typically developing children; TD= Typically Developing; FXS+ASD= Fragil X Syndrome and Autism Spectrum Disorder; SMS= Smith Magenis syndrome; DS= Down syndrome; PDD= Pervasive Developmental Disorder; PW= Prader-Willi; WS= Williams syndrome; NSID= Non-specific ID; IDD= Intellectual and Developmental Disability; FAS= Fetal Alcohol Syndrome; DD=Developmental Delay

ASD control:

- S= Statistically; SG= Stablishing Groups; ECI= Excluding comorbid individuals

Recruitment:

-SC= Single clinic or diagnostic centre; MC= multiple clinics or diagnostic centers; Ch= single charity or parent support group; MCh= multiple charities or parent support groups; FOS= Participants recruited from other study; NWM=Newsleters or magazines; IW=Internet websites; R=Registries of families or databases, parent list servers; PA= Public announcements; MAPC= Mail advertisement to past clients; S= Schools;

Syndrome diagnosis:

-PR= Parent Reports; GT=Genetic tests; DPGT= Document Proof of Genetic Testing; CDP= Confirmed Diagnoses by Professional; DPPC= Document Proof of Professional Confirmation

Methodology:

CE=Clinical examination; IQ=Idiosyncratic questionnaire designed to the study; I=Interview; S/VM= Standarized/Validated measures; MM=Multiple methods; CT= Computarized task; MQ= Modified Questionnaire

Developmental factors:

LS= Longitudinal study; MA= Mental Age matched; VMA= Verbal Mental Age matched; NVIQM= Non-verbal IQ matched; VIQM= Verbal IQ matched; EVAM= Expressive vocabulary ability; AS= Accounted by statistical analysis; SG= Stablish groups to compare between ages; MAB=Matched by Adaptive Behavior

Statistics:

DS= Descriptive Statistics/percentages; WC= within syndrome comparative statistics; WR= within syndrome correlations; CFVSF+ASD= Comparisons between groups with FXS and groups with FXS+ASD; CE= Comparative statistics between syndrome and genetically distinct control group. Y/N (*) = sig. diff. found from genetically distinct control / repeated measures/ groups with FXS and groups with FXS+ASD Y/N ES = Effect size reported OR = Odds ratio reported. EME= Estructural model equations.

* A discrepancy was found in this study

Estudio 3

Behaviour problems and social competence in Down syndrome: A structured review

Behaviour Problems and Social Competence in Down Syndrome: A structured review

Olga Cregenzán-Royo, Carme Brun-Gasca y Albert Fornieles-Deu

Abstract

Background: Understanding Down Syndrome (DS) phenotypes regarding behaviour and social problems is essential to help individuals reach social inclusion and achieve their highest competence. This structured review focuses on behaviour and social problems of the last 20 years of research. Method: Three databases were examined, and a backward review carried out, leading to 26 and 18 studies, respectively, meeting the inclusion criteria, for 44 papers included in the final sample. Results: Overall, higher behaviour and social problems were found for people with DS than typically developing individuals. Less behaviour and social problems were found compared with individuals with other intellectual disabilities. Similar to results from typically developing populations, higher internalizing and externalizing problems were found for girls and boys. Social competence might improve after adolescence. Environmental factors influenced behaviour problems and social competence. Conclusions: Future research should consider environmental and gender differences and use gold-standard measures to define both profiles.

Keywords: Down syndrome, Behaviour problems, Challenging behaviour, Social skills, Social competence, Environmental influences, Phenotype.

Introduction

Intellectual disability (ID) is characterized by significant limitations in both intellectual functioning and adaptive behaviour, including conceptual, social, and practical skills, and originating before the age of 18 (American Association on Intellectual and Developmental Disabilities; AAIDD, 2020). According to the meta-analysis conducted by Maulik et al. (2011), the estimated prevalence is 10.37/1000 population. Down Syndrome (DS) is the leading identifiable cause of ID, accounting to around 15-20% of the ID population (University of Hertfordshire, 2020). In the United States, there are 1/700 babies born with DS (National Down Syndrome Society; NDSS, 2021).

DS is usually caused by an error in cell division occasioning an embryo with three copies of chromosome 21 (NDSS, 2021). Generally, the average Intelligence Quotient (IQ) for people with DS stands in the mildly-to-moderately low range (Centers for Disease Control and Prevention, 2021). As a consequence, individuals with DS might exhibit increased behaviour problems and they are also at greater risk of having impaired social functioning than their Typically Developing (TD) peers (Patel et al., 2018; Næss et al., 2017)

Behaviour problems

Behaviour problems, which are frequent in children with ID regardless of the underlying aetiology are disabling and create problems in everyday life (Ageranioti-Bélanger et al., 2012). They could be defined as culturally atypical behaviours that either jeopardize the physical safety of the person or others in their environment or limit

the usual functioning of the individual in the environment, for example the access to ordinary community facilities (Emmerson, 1995). Instead of considering them as concrete disorders, behaviour problems could be understood as quantifiable deviations from the norm (Edelbrock and Costello, 1988). The occurrence of behaviour problems, which might become chronic and continue through adulthood, could disturb learning processes and interaction with others, affecting the quality of life of individuals with ID (Ngashangva and Dutt, 2015). In addition, family functioning, parenting stress, and well-being of the child with IDs might be affected by behaviour problems in individuals with DS (Stores et al., 1998; Cuskelly and Dadds, 1992; Cunningham, 2007). In 1979, Achenbach and Elderbrock considered that behaviour problems could be grouped in two categories: internalizing and externalizing behaviours. Over the years, and under the construct of behaviour problems, 8 DSM oriented scales have been included in the Child Behaviour Checklist (CBCL; Achenbach, 1991; Achenbach and Rescorla, 2001) to assess behaviour problems: affective problems, anxiety problems, somatic problems, attention-deficit/hyperactivity problems, oppositional defiant problems, and conduct problems. This classification has guided other well-known tools to assess behaviour problems and their conceptualization. In this review, we consider behaviour problems based on this classification since in view of behaviour problems both affecting the person with DS and the family environment they are a major research concern. Although a behavioural phenotype has been characterized for individuals with DS over the years, there remain individual differences between individuals with DS (Karmiloff-Smith et al., 2016), thus different studies pointed out different behaviour phenotypes for individuals with DS. By way of example, Coe et al. (1999) showed that individuals with DS have higher attention deficit, non-compliance, thought disorder, and social withdrawal than TD individuals, and Chapman and Hesketh (2000) found delays in non-

verbal cognitive development, and specific deficits in speech, language production, and auditory short-term memory, but fewer adaptive behaviour problems than individuals with other IDs. Walz and Benson (2002) found good social skills and low ratings of behaviour problems, including hyperactivity, and Dykens (2007) pointed out the existence of externalizing behaviours such as stubbornness, oppositional, inattention, speech problems, difficulties concentrating, attention-seeking, and impulsivity.

Social competence

Social functioning is a wide construct that defines an individual's exchanges with their environment and the ability to accomplish their role in situations like work, social interactions, and relationships with partners and family (Bosc, 2000). Socially competent behaviour refers to meeting the demands of a particular social situation and involves the effective coordination of multiple social-cognitive and emotion processes and contextual factors (Iarocci et al., 2008). Social competence and social skills are interrelated but not identical constructs that were clearly differentiated by McFall (1982; in Gresham, 1992), who explained that social skills are certain behaviours that an individual exhibits in particular situations to be competent in social tasks. Social competence is also an evaluative term and is an assessment of how proficiently a person has performed a social task. Moreover, social competence is pertinent to understanding developmental adaptation over time, achieved through experience in everyday life situations at home and in educational settings, including working groups and when playing games, where group members communicate, negotiate, do things together, help each other, and so on. Social competence becomes particularly significant in people with DS, who strive for social inclusion and participation (Iarocci et al., 2008; Jędrzejowska, 2020).

For a long time, people with DS have been described as having adequate social behaviours, although some studies have concluded that in comparison with TD peers individuals with DS might be at greater risk of having impaired social competence (Næss et al., 2017). Given that the definition of ID includes significant limitations in social abilities, and because global delays in the skill components of social competence are also common (Kasari and Bauminger, 1998; in Hardiman et al., 2009), it is not surprising that individuals with DS might have impairments in this area compared with TD individuals. However, scarce social competence research has focused on people with ID (Rosner et al., 2004) and little attention has been paid to how the cognitive sequelae of DS may affect social cognition and social adaptation in the DS population (Iarocci et al., 2008).

Environmental factors

As Grieco et al. (2015) stated, specific behavioural phenotypes associated with DS might help professionals and parents to better understand individuals with DS, as well as enlighten treatments and instructional methods for helping the DS population to reach their highest level of independence and to optimize their functioning and quality of life. Although behavioural phenotypes are related with the likelihood of exhibiting particular behavioural patterns and are not exclusive of one syndrome (Dykens, 1995; Fidler, 2005). Nevertheless, aside from defining the behavioural phenotype, there must be a focus on the environment because the context might influence proximal processes and developmental outcomes in individuals in terms of both the resources available and their stability and consistency over time (Bronfenbrenner and Ceci, 1994). In this line, individual factors may interact with environmental aspects in the child's family, peer group, school, community, and culture to determine variability in development (Iarocci

et al., 2008), and there may be variations in children's social traits that are attributable to the family, neighbourhood and school influence (Karra, 2013). Hence, social and living environments might shape the behaviour of children with ID (Ngashangva and Dutt, 2015). In fact, life events have an impact on behaviour problems in individuals with DS and behaviour problems might lead to parental stress (Coe et al., 1999; Hastings, 2002). Therefore, the study of phenotype-environment interactions in DS might help our understanding of the aetiology of behaviour problems (Tunnicliffe and Oliver, 2011).

Current study

Given that numerous studies have been conducted on behaviour problems and several studies on social competence have emerged over the last 20 years, a compilation of the results of the research on both variables in DS is needed. In addition, collecting data in this area is crucial given that social competence and behaviour problems might be influenced by the environment. The main aim of the present review, therefore, is to summarize the findings of the studies carried out with individuals with DS over the last 20 years, considering phenotypic and environmental influences for behaviour and social problems. Specifically, we researched four questions:

1. What behaviour problems have been researched in individuals with DS in the last 20 years?
2. What social competence problems have been researched in individuals with DS in the last 20 years?
3. What differences have been found in behaviour problems and social competence when comparing individuals with DS with TD individuals and individuals with other IDs?

4. How might environmental factors affect behaviour and social problems in individuals with DS?

Method

A comprehensive search strategy including the search terms (Down Syndrome OR trisomy 21 OR Down's Syndrome) AND (social skills OR social interaction OR social behavior OR social competence OR problem behavior OR disruptive behavior OR challenging behavior) was applied to three databases: Web of Science, Psycinfo, and PubMed. The search, was conducted on 1 December 2019. The terms were selected by taking MesH terms from PubMed and testing them on the other databases. This search strategy produced a total of 160 papers.

The criteria used for studies to be included in the review were as follows. First, the study had to empirically address behaviour problems or social competence in people with DS. Second, studies that focused on other variables could be selected if they included behaviour or social problems in their results. And third, eligible studies had to be published from 2000 onwards in English or Spanish, and only if they were full text papers. The exclusion criteria were studies which were not original research, those that focused on participants other than people with DS (which was not applied if the study assessed different groups), comorbidity of the participants with DS with autism (unless it was a control group), and DS plus dementia control groups. After checking for duplicates, 97 papers were selected. The titles and abstracts were then screened, leading to a final selection of 37 papers. Last, only full texts were included, bringing the total number of eligible studies down to 26. In September 2021, 45 studies were identified through a backward review of the bibliographies included in the 26 studies. After reviewing full texts, a further 18 studies were selected and included in the review.

Consequently the review compiled a total number of 44 studies (see figure 1 below for the complete flowchart).

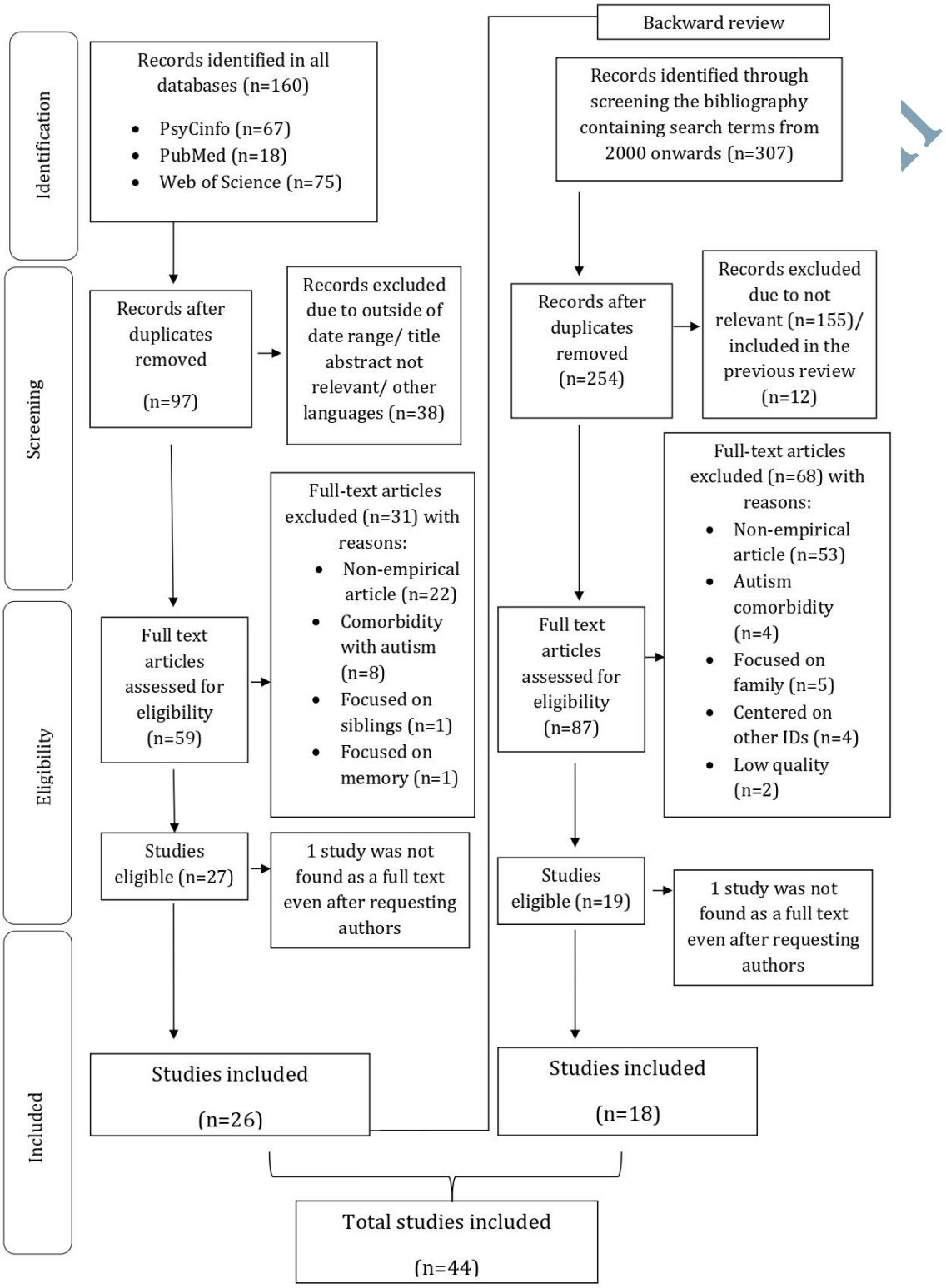

Figure 1. Flowchart. Adapted from Page et al. (2021)

Results

Key summary data for each of the studies included in the review are shown in Table 1, studies found in the backward review are included in grey in the table.

Behaviour problems

Behaviour problems described in individuals with DS

Three of the studies that characterized the DS sample found certain behaviour problems more frequently than others. First, the study by Patti and Tsiouris (2006) found that non-compliance was the principal challenging behaviour across the entire age range of participants, followed by physical aggression and disruptive behaviours. More than 50% of adults exhibited disruptive behaviour, with between 33% and 54% exhibiting physical aggression. Meanwhile, other problems such as property destruction, tantrum behaviours, difficulty with transitions, or elopement happened in a moderate-to-low frequency. Average scores for both aggression and attention were the highest across ages from 4 to 19 years in the study by Dykens et al. (2002) with aggression scoring higher. In the study by Foley et al. (2015), disruptive/antisocial behaviors were the most reported behaviour problems at the average age of 13.9 years-old age. Meanwhile, at ages 21.3 and 23.5 anxiety was the most commonly reported behaviour problems.

Comparisons between individuals with DS and TD individuals

The studies generally reported negative results for individuals with DS, who showed more behaviour problems than the TD samples (Bhatia et al., 2005; Gau et al., 2008; van Gameren-Oosterom et al., 2011; Yahia et al., 2014; Kelmanson, 2016; Van Gameren-Oosterom et al., 2013_b). By way of example, Bhatia et al. (2005) found that 55% of the sample of individuals with DS showed behaviour problems compared to

12% of the TD sample. The percentage of individuals with DS scoring above the clinical or borderline range on at least 1 scale of the CBCL was over 51%, a figure that was more than double the percentage of the normative sample in Van Gameren-Oosterom et al. (2013_b). Channel et al. (2015) found that individuals with DS scored higher for autistic mannerisms than normative samples. Even when compared to TD MA-matched individuals, children with DS showed higher scores in behaviour problems and scored significantly higher in hyperactivity (Guralnick et al., 2011_b). Interestingly, Yahia et al. (2014) found that oppositional defiant and conduct disorders were less prevalent in cases with DS, despite non-significant differences and Gau et al. (2008) found no differences in aggressive behaviours between individuals with DS and TD siblings or TD individuals

The most frequently reported behaviour problems among individuals with DS when compared with TD individuals or normative samples was attention problems, which was mentioned in 6 of the 11 studies with TD comparison groups (Bhatia et al., 2005; Gau et al., 2008; van Gameren-Oosterom et al., 2011; Kelmanson, 2016; Van Gameren-Oosterom et al., 2013_b ; Yahia et al., 2014). This behaviour problem was reported in 12.5% of the sample in Bhatia et al. (2005). It was also the most mentioned behaviour problem reported by parents in Kelmanson (2016), and one of the most severe behaviour problems in Gau et al. (2008). Individuals with DS scored significantly higher in attention problems and had very large effects compared to TD individuals in van Gameren-Oosterom et al. (2011), and Van Gameren-Oosterom et al. (2013_b). Furthermore, individuals with DS showed a higher prevalence for Attention Deficit Hyperactivity Disorder (ADHD) of different types in Yahia et al. (2014). It is important to highlight that thought problems were also significantly higher for individuals with DS and showed a large difference compared to TD individuals in Van Gameren-

Oosterom et al. (2013_b) and were one of the most severe problems in Gau et al. (2008). Other behaviour problems reported included bedtime resistance, sleep anxiety, night walking, affective and somatic problems (Kelmanson, 2016), delinquency, somatic complaints (Gau, et al., 2008), easily angered, mood swings, disobedience, and/or could not be corrected and finding changes difficult (Van Gameren-Oosterom et al., 2013_a).

Comparisons between individuals with DS and individuals with other IDs

Generally, adults and children with DS seemed to show less behaviour problems than individuals with other IDs. In Esbensen et al. (2008), adults with DS were advantaged in their lack of behaviour problems and externalized behaviours. Young adults with DS presented the lowest levels of behaviour problems in overactivity, aggression, and self-injury, in comparison with individuals with mixed ID, cerebral palsy, and autism, and had significantly lower behaviour problems in comparison with individuals with mixed ID (Blacher and McIntyre, 2006). Besides, adults with DS showed significantly lower levels of aggressive/disruptive behaviour in Straccia et al. (2014). Furthermore, in Esbensen et al. (2010) adults with DS showed less behaviour problems than adults with autism spectrum disorder. Children with DS also showed less behaviour problems than individuals with ID without an identified condition, with significant scores in irritability (Chadwick et al., 2000). In the same line, Hattier et al. (2012) found in young children, that the group with DS scored lower than children with seizures/seizures disorder in tantrum/conduct behaviour, although the group with DS did not differ from the one with cerebral palsy. Furthermore, in the study conducted by Einfeld et al. (2006) individuals with DS aged between 4-18 years showed lower scores in behaviour problems (disruptive behaviours, attention deficit hyperactivity, abusive with others, tantrums, kicks, throws) than individuals with ID, Fragile X Syndrome, Williams Syndrome, autism and Prader-Willi, among other syndromes. And in the study by Cregenzán-Royo

et al. (2018), the group with DS aged between 4-17 years showed less externalizing, and total problems in comparison with the FXS group. Additionally, Nevill and Benson (2018) found that scores in irritability, and hyperactivity were significantly lower in young individuals and adults with DS than in validation samples of individuals with other IDs. Besides, in the study by Lundqvist (2013) the proportion of individuals with DS aged between 18-87 years who showed self-injurious behaviour, stereotyped behaviour and aggressive/destructive behaviour was lower than the proportion for individuals with Prader-Willi, Fragile X Syndrome, autism and epilepsy, but compared to individuals with cerebral palsy individuals with DS exhibited more stereotyped and aggressive/destructive behaviours along with less self-injurious behaviours. In fact, having DS was found to be a protective marker for having self-injurious behaviour or stereotyped behaviour in Lundqvist (2013). Besides, the study by Last, Tyrer et al. (2006) reported that aggression was up to three times less likely to be reported by parents of individuals with DS in comparison to the parents of individuals with epilepsy and autism.

Factors associated with behaviour problems

The degree of ID was related to behaviour problems in five studies, with higher behaviour problems significantly related to increasing severity of ID in adolescents (Van Gameren-Oosterom et al., 2013_b). Adolescents and adults with DS with severe/profound ID and mosaic mutation presented higher behaviour problems than those with mild severity (Makary et al., 2014). Additionally, fewer behaviour problems were initially exhibited if the adult with DS had a less severe ID in Esbensen et al. (2008). Intelligence scores were significant predictors of attention-deficit/hyperactivity problems in a sample of children and adolescents (Kelmanson, 2016), with children and adolescents with severe and moderate ID showing high percentages of ADHD-

impulsive and combined (inattentive-impulsive) compared to no cases in mild and borderline ID in Yahia et al. (2014). Channel et al. (2015) also found that children's and adolescent's nonverbal cognitive ability was associated with elevated symptoms of autistic mannerisms. Last, a higher level of ID was identified as a risk marker for both self-injurious behaviour and stereotyped behaviour among individuals with ID in Lundqvist (2013).

Tonguing, understood as a behaviour registered when observers see tongue protrusion in individuals with DS (not including licking lips while eating or smiling), and verbal ability might be protective factors related to behaviour problems. Evidence concerning the former came from Barret and Fidler (2008), who found that individuals with DS and reported negative mood who did not engage in tonguing were more likely to display externalizing behaviours and stress-inducing characteristics than those who did engage in tonguing. Regarding the latter, verbal expression ability was positively associated with both behaviour problems and aggressive/disruptive behaviours in Straccia et al. (2014). Besides, Nevill and Benson (2018) reported that nonverbal participants were higher in stereotypy, than verbal participants. Furthermore, a low expressive language age observed 2 years before the study suppressed the children's expressive language development and increased behaviour problems in Huang et al. (2007). Last, Channel et al. (2015) found that lower receptive language ability was associated with higher symptomatology for autistic mannerisms.

Considering possible risk factors for behaviour problems, both childhood psychopathology and functioning were associated with severe behaviour disorders in adult life (McCarthy, 2008). Additionally, routinized behaviours and compulsive-like behaviours were associated with worries an fears (Glenn et al. 2015). Regarding sleep, parent-reported sleep duration was related to reported inattention in their children with

DS, and a shorter sleep period, measured by actigraphy, was related to higher parent ratings of both inattention and hyperactivity/impulsivity (Esbensen et al., 2018). In the same line, adults with DS who showed behavioural sleep disturbances in the study by Esbensen (2016) had more generalized behaviour problems than individuals with DS without behavioural sleep disturbances. Kelmanson (2016) also found that total sleep disturbance scores were significant predictors of attention-deficit/hyperactivity problems.

Environmental factors related to behaviour problems.

Some studies pointed out how variables from the environment are related to behaviour problems in individuals with DS. Nevill and Benson (2018) found that excluding positive experiences, all stressors (anticipation, changes, unpleasant events, pleasant events, social/environmental and ritual-related stress and fear) correlated with irritability, hyperactivity, manic/hyperactive, and obsessive-compulsive behaviour. Negative recent life events were positively correlated with irritability, hyperactivity, lethargy, and stereotypy, and the number of recent negative life events has been associated with all caregiver-reported symptoms of psychopathology and challenging behaviour, except for inappropriate speech. Furthermore, anticipation and social/environmental and fear stress have correlated moderately with lethargy and stereotypy, while ritual-related stress has been moderately related to lethargy. Regarding placement, participants living with their family scored significantly higher in obsessive/compulsive behaviour than those living in residential care. Additionally, Esbensen et al. (2008) found that not living at home, having worse family relations and experiencing parental death during the study period were associated with higher measures of behaviour problems (generalized and externalized).

Concerning parental care, Huang et al. (2007) found that in Taiwan, maternal instructions (understood as maternal orders) suppressed their children's language development and increased behaviour problems, while in Japan maternal responses did not influence their offspring's behaviour problems. Higher behaviour problem scores have been reported for Taiwanese children with DS than Japanese children with DS. Furthermore, Cregenzán-Royo et al. (2018) found that expressed emotion in mothers of individuals with DS was significantly related to externalizing, and total behaviour problems in their offspring and impulsiveness in mothers was associated with aggressive behaviours, ADHD problems, and opposite defiant problems. Additionally, Esbensen et al. (2008) found that fewer behaviour problems were exhibited initially if the adult with ID had better family relations. However, McCarthy (2008) found that family environment, as measured by parental mental health, quality of parental marriage, and social class, did not predict severe behaviour disorder in adult life. Interestingly, taking into consideration cultural aspects, Huang (2009) found that Japanese children with and without DS had negative scores on behaviour and rebelliousness, whereas the scores of Taiwanese children with and without DS were positive. Furthermore, regarding impulsive behaviour, only Japanese children with DS had negative scores, while non-disabled Japanese children and Taiwanese children with and without DS had positive scores.

Age patterns in behaviour problems.

Regarding whether behaviour problems such as temper tantrums and physical aggression change over time, three studies found that they decreased with aging in DS samples, declining before 19 years old in a sample of individuals aged 4-40 years (Rice et al., 2015). Generalized and externalized maladaptive indices in a sample of individuals between 17-57 years with longitudinal follow-up for 9 years (Esbensen et

al., 2008), and scores on the disruptive/antisocial behaviour subscale decreased over time in a sample between 4-49 years (Foley et al., 2015). In a sample of individuals aged between 20-71 years, Patti and Tsiouris (2006) found that some behaviour problems like physical aggression and disruptive behaviours decreased significantly after the age of 50, as did inappropriate sexual behaviours and self-injurious behaviour. There was a trend in the number of adults that did not present challenging behaviour with age, while behaviour rituals remained constant across age groups (Patti and Tsiouris, 2006). Four studies have indicated that some behaviour problems remained stable over time or even increased. In this regard, the rate of severe behaviour disorder and verbal aggression, showed no evidence of diminishing with age and verbal aggression was not associated with age after 19 years, (McCarthy, 2008; Rice et al., 2015). In the same line, Straccia et al. (2014) found a trend between aging and autistic symptoms in adults with DS aged between 25-42 years. Furthermore, the study by Glenn et al. (2015) found that routinized and compulsive-like behaviours remained stable for both chronological age (CA) or verbal mental age in adults with DS.

Regarding adolescence, Dykens et al. (2002) found that adolescents with DS aged between 10-13 years showed significantly higher aggressive and delinquent behaviour than those aged between 4-6 years. Interestingly, Fidler et al. (2006_a) found that the onset of behaviour problems in individuals with DS emerged later in life, with individuals with DS showing less behaviour problems at 30 months than their counterparts with mixed ID aetiologies, reaching the level of behaviour problems of individuals with mixed ID and even scoring higher at the age of 45 months. However, Makary et al. (2014) did not find any significant associations between age and the range or severity of any behavioural item.

Gender differences in behaviour problems

Regarding gender differences, five studies showed lower behaviour problems in females, with girls and young females exhibiting fewer behaviour problems like disruptive/antisocial behaviours than boys (Foley et al., 2015), as well as lower externalizing problems although not significant (van Gameren-Oosterom et al., 2011) and lower externalizing, thought and attention problems, delinquent behaviour, and aggressive behaviour (Van Gammeren-Oosterom et al., 2013_b). Adult females also scored lower than boys in hyperactivity, presenting a lower vulnerability to externalizing challenging behaviour (Nevill and Benson, 2018). And boys with DS scored higher in stereotyped behaviours (Van Gammeren-Oosterom et al., 2013_a). Conversely, Esbensen et al. (2008) found that adult females had higher behaviour problems at initial point although gender did not predict changes in behavioural problems. Neither gender was a predictor of behaviour problems in Kelmanson (2016). Last, some studies found no differences regarding gender for challenging behaviour (Hattier et al., 2012), verbal or physical aggression (Rice et al., 2015), externalizing or total problems (Cregenzán-Royo et al., 2018).

Social competence

Social competence problems described in individuals with DS

Regarding problems in social competence in the descriptions of the samples with DS of the studies reviewed, Van Gameren-Oosterom et al. (2013_a) found that 90% of adolescents with DS experienced significant problems in social functioning, 75% showed trouble understanding conversations and 67% had some trouble processing information. In the same line, Van Gameren-Oosterom et al. (2013_b) found that the highest scores associated with problems in social competence among adolescents with DS were observed on the social subscale and thought problems subscales. Additionally,

in individuals with DS aged between 16-87 years the highest scores were shown in social avoidance in the study by Nevill and Benson (2018).

Comparisons between individuals with DS and TD individuals

The studies comparing the groups with DS through the TD groups and CA-matched TD groups, revealed lower social competence scores for the former. In that line, Bhatia et al. (2005) found in children with DS that 37.5% of their sample showed unsocialized conduct disturbances, with individuals with DS scoring significantly higher than the control group. Furthermore, the eight-year-old individuals with DS in the sample in van Gameren-Oosterom et al. (2011) had the highest effect size on the social problems subscale and scored significantly lower than children from normative data on the social functioning scale. In Van Gammeren-Oosterom et al. (2013_a), 90% of adolescents with DS showed greater problems in social functioning than individuals without DS, with differences between groups being significant for total social problems and large effect sizes for orientation to problems and understanding social information. In the same line, Gau et al. (2008), also found in children and adolescents with DS aged between 2-14 years higher social and withdrawal problems than the TD sample and their siblings, and individuals with DS aged between 10-21 years, showed higher scores indicative of more problems on social cognition, social communication and social awareness than normative samples in the study by Channel et al. (2015). Concerning social competence, Guralnick et al. (2009) found that during play interactions individuals with DS had a smaller network size of playmates, played for shorter periods of time, played less amicably were less involved in play, had less control of the play, needed more frequent assistance from their mothers when playing, required more help to continue being involved in the game and in understanding how to play. In a second study, Guralnick et al. (2011_b) supported some of these findings. Although they did not find differences on

network size of playmates, they did find that individuals with DS played on average less time, less frequently, were less involved in play, showed less excitement during play, required more support for playing coming from the teachers particularly to help them getting started, remaining involved in play, understanding social rules and understanding how to play. Additionally, individuals with DS scored lower in social skills and were less prosocial and more asocial. In another study of Guralnick et al. (2011_a) the authors found that the DS group was less advanced in terms of peer interactions, engaging with playmates at a less advanced level, playing less alone, were less in transition, observed their playmates more often, participated less in a group, conversed with peers less and showed a lower level of constructive play. Notably, three studies found a possible strength in children and adolescents with DS, reporting less severe anxiety/depression symptoms than for normative samples (Van Gameren-Oosterom, et al., 2013_b), with significant differences in two of them (Gau et al., 2008; van Gameren-Oosterom et al., 2011).

The four studies that matched individuals with DS with TD individuals by Mental Age (MA), verbal age or receptive vocabulary tasks found fewer differences between groups than in studies with CA-matched groups. Guralnick et al. (2011_a) found that the peer interactions of individuals in the DS group only differed from the MA-matched group of younger TD children in less peer conversation with children with individuals with DS behaving the same way as the MA-matched groups in terms of play and friendship, with the only difference being more onlooking behaviour with friends. Additionally, Hippolyte et al. (2010) found relatively good social reasoning skills in the group with DS, the results finding no differences in global scores for a task related to understanding the appropriateness of the social behaviour of others, although the group with DS identified significantly fewer inappropriate situations than the control group. In the

same line, Guralnick et al. (2009) found that children with DS did not differ significantly from the MA-matched group on average or frequency of playtime and amicably play, or on the needs for assistance when playing, or to remain involved in play and understanding social rules. Similarly, Guralnick et al. (2011_b) found no differences in frequency of play with peers, level of involvement and average play time. However, differences between individuals with DS and TD MA-matched were found. Guralnick et al. (2009) found that the DS group needed more help to understand how to play, were less involved in the play interaction, and exerted less control during play. Furthermore, Guralnick et al. (2011_b) found that children with DS exhibited less excitement during play and required more support from teachers to getting play started, remain involved and understanding social rules and how to play. Individuals with DS also scored lower in social skills and were less prosocial and more asocial.

Comparisons between individuals with DS and individuals with other IDs

Several studies found that the DS group scored higher on social competence, showing the highest overall social competence scores and having more positively rated behaviour with others than individuals with Williams Syndrome or Prader-Willi (Rosner et al., 2004). They also scored higher on social behaviour, and on the social attitude, respect for social rules, and the socioemotional behaviour subscales, and had lower levels of self-absorbed and depressive behaviours than adults with other IDs (Straccia et al., 2014). Adults with DS showed less severe asocial problems (Esbensen et al., 2008), and individuals aged between 5-20 years have been found to have lower levels of social problems and anxiety/withdrawn behaviours than individuals with other IDs (Fidler et al., 2005). Additionally, young adults with DS presented the lowest levels of avoidant behaviour in comparison with individuals with mixed ID, cerebral palsy, and autism (Blacher and McIntyre, 2006) and in the study by Chadwick et al. (2000), the

individuals with DS showed the highest score in socialization and scored the lowest in lethargy/social withdrawal in comparison to individuals with autism, rare syndromes and non-condition identified IDs, although the differences were not significant. Individuals with DS aged between 4-18 years also showed lower scores for self-absorbed, anxiety and depression than individuals with ID, Fragile X Syndrome, Williams Syndrome, autism and Prader-Willi, among other syndromes (Einfeld et al., 2006) and less internalizing behaviours than individuals with FXS were also found in Cregenzán-Royo et al. (2018). Furthermore, the study by Esbensen et al. (2010) pointed out that in comparison to adults with autism spectrum disorder, adults with DS had more frequent social contact with friends. Last children aged between 2-3 years with DS showed significantly higher scores on socialization skills in Fidler et al. (2006_b). Additionally, Nevill and Benson (2018) found that young and adults with DS reached significantly lower scores for mental health symptoms including depressed mood and general anxiety than in validation samples of individuals with other IDs. However, the study by Guralnick (2002) did not find any differences between children with DS and other children with IDs regarding peer involvement (social network size, average time spent with playmates, frequency of play) and in Esbensen et al. (2008), adults with DS were similar in terms of internalized maladaptive behaviours to individuals with other IDs.

Factors associated with social competence

Some risk factors may have been identified. Verbal ability has negatively predicted social avoidance (Nevill and Benson, 2018) and high scores in verbal ability were associated with lower scores for respect on social rules (Straccia et al., 2014). In the same line, Channel et al. (2015) found that lower receptive language ability correlated with higher symptomatology in areas like social cognition, social communication, social

awareness, and social motivation, and nonverbal IQ was associated with elevated social cognition problems. Moreover, Hippolyte et al. (2010) reported that receptive vocabulary, selective attention, and social relating skills were the best predictors of the performance of adults with DS on a social task and Nevill and Benson (2018) reported that nonverbal participants scored higher in general anxiety than verbal participants. Additionally, Matthews et al. (2018) found that individuals with DS with more current health issues were significantly more likely to have less communication and social skills. Fidler et al. (2005) found a significant negative association between smiling frequency and anxiety/depression scores in 5 to 20 year-old individuals with DS and "tonguing" was associated with internalizing behaviours (Barret and Fidler, 2008). Last, Esbensen (2016) found that adults with DS with behavioural sleep disturbances had more asocial behaviors (socially offensive and uncooperative) than individuals without these disturbances and Rosner et al. (2004) found that social competence correlated negatively with externalized and total behaviour problems.

Environmental factors related to social competence.

Three studies found environmental factors associated with social competence. Nevill and Benson (2018) reported that participants with DS living with their family scored significantly higher on inappropriate speech and social avoidance than participants in residential care. Participants not registered on a day placement or without a job or vocational placement scored higher on depressive symptom scales. Furthermore, all stressors except positive experiences (anticipation, changes, unpleasant events, pleasant events, social/environmental and ritual-related stress and fear) correlated with depressed mood, and general anxiety. Negative recent events also correlated with depressed mood and general anxiety and stressors like anticipation, social/environmental, fear stress, and ritual-related stress correlated moderately with social avoidance scores. Social

avoidance was positively predicted by social/environmental stressors and negatively predicted by anticipation-related stressors. Additionally, Esbensen et al., (2008) found that living outside home was associated with higher socially offensive behaviour and uncooperativeness, and experiencing parental death during the study period was associated with higher internalized and asocial problems. Last Cregenzán-Royo et al. (2018) found that expressed emotion in mothers was associated with internalizing behaviours and impulsiveness in mothers was associated with anxious/depressed and social problems in their offspring with DS.

Age patterns in social competence.

A pattern of lower social competence skills seems to appear in both adolescent and mature samples, together with periods of higher social competence between adolescent and aging samples. More specifically, Dykens et al. (2002) found higher social problems in children 10-13-years-old than in those aged 4-6 and 7-9 years and significantly more internalizing behaviours in individuals with DS aged between 10-13 and 14-19 years than in young children aged 4-6 years. Moreover, increasing scores in social problems, anxiety and depression scores have been found in a sample aged between 5-20 years (Fidler et al., 2005). For adults, social skills and frequency of social activities were found to significantly decrease after the age of 40 in a sample aged between 20-69 years (Matthews et al., 2018), along with decreases in the social composites, and a pattern of stability in the asocial maladaptive index (socially offensive behaviour and uncooperative behaviour) in aging samples aged between 20-56 years and 17-57 years (Makary et al., 2015; Esbensen et al., 2008). In the same line, the 10-year longitudinal study in the social/communication area conducted by Hawkins et al. (2003) with individuals aged between 31-56 years found that scores remained relatively constant until the age of 45, after which a gradual decline started, accelerating

as the years passed. However the anxiety behaviour subscale decreased over time in a sample between 4-49 years (Foley et al., 2015) and internalized behaviours decreased over time in individuals aged between 17-57 years (Esbensen et al., 2008). And aging was positively correlated with behavioural signs of depression in adults with DS aged between 25-42 years in Straccia et al. (2014).

A trend of higher scores on social competence after adolescence has also appeared, with lower social relating behaviours for those aged 16-20 years, increasing at older ages between 26-31 years in the study by Rosner et al. (2004). In the same line, the study conducted by Foley et al. (2015) on social competence (self-absorbed behaviours and communication disturbances) also showed a statistically significant improvement when aging in a sample aged between 2-24 years. Furthermore, the study by Dressler et al. (2010) found increasing socialization scores (interpersonal, play-leisure and coping) across the different age groups (0-10, 10-20 and 20-30 years) reaching a peak in the group between 20-30 years after which, a slight decline was identified although it was not significant. More specifically, in play those aged between 20-30 years scored significantly higher than those between 10-20 years. Coping was a strength both in individuals aged between 20-30 years and 30-40 years, while interpersonal relation was an area of strength with more individuals scoring above average levels and no differences across age groups. Furthermore socialization was higher among those aged above 30 years than in those aged between 0-10 years. However, Patti and Tsiouris (2006) found that social avoidance increased in frequency from low-to-moderate from the twenties to the sixties, decreasing again after the age of 60. Interestingly, the study by Fidler et al. (2006_a) suggests a peak in internalizing problems between 30-45 months in individuals with DS.

Gender differences in social competence.

Four studies found differences in social competence among girls and boys. Van Gameren-Oosterom et al. (2013_a) found that boys with DS had more problems in total social functioning than girls, and in the subscale orientation to problems. Moreover, Foley et al. (2015) found that on average, females aged between 2-24 years scored consistently lower than males across all subscales (self-absorbed, anxiety, communication disturbance, social relating, and depressive), with females' having significantly less self-absorbed behaviours. Dykens et al. (2002) found that females between 14-19 years presented higher scores on the withdrawn domain than males of the same age group. And girls scored higher in internalizing problems, although the difference was not significant in van Gameren-Oosterom et al. (2011). Meanwhile, three studies found no differences on the social problems subscale, although there were more boys in the clinical range on this subscale (Van Gameren-Oosterom et al., 2013_b) in social competence domain scores (Rosner et al., 2004) or in internalizing behaviors (Cregenzán-Royo et al., 2018).

Discussion

We aimed to summarize the information relevant to behaviour problems and social competence among individuals with DS gathered the last 20 years to see the advances made. Overall, the results from the different papers pointed to a general negative profile of behaviour problems and social competence for individuals with DS when compared with TD individuals. When the studies controlled for MA, the results were far less severe for the groups with DS, especially in social problems although differences between groups still remained. Additionally, a positive profile was found for participants with DS, showing less anxiety/depression symptoms than the normative samples in three studies. In addition, when the studies controlled for MA, the results were far less severe for the groups with DS, and specifically in social problems.

Although, this interpretation should be taken with caution due to scarce data on the incidence and prevalence of anxiety symptoms in the DS population (Afife-Ersoy et al., 2018). And since anxiety symptoms could be masked by other behaviour problems such as aggression or hyperactivity as well as being a reflection of other problems such as auditory or visual impairments (Garvía, 2014). Generally, less behaviour and social competence problems were also found when individuals with DS were compared with other ID individuals. Strikingly, only 15 of the studies selected (34%) focused on social competence. Therefore, while the importance of socially competent behaviours for optimal everyday functioning is recognized by some authors such as Rosner et al. (2004), few studies were found to address this variable in individuals with DS. The studies largely differed in their criteria for both participant inclusion and exclusion (e.g., moderate ID, comorbid health issues, including individuals with mosaicism, excluding individuals with hearing impairments, and so on), with qualitative and quantitative differences among samples, and in the measures used to collect the data. Consequently, statistics could not be conducted to develop numerically based results.

As expected, the main behaviour problems are in line with previous findings such as those of Coe et al. (1999), who found that children with DS had more behaviour problems, and in particular attention deficit, non-compliance, thought disorder, and social withdrawal. The most frequently reported behaviour problems among the studies reviewed were related to attention deficits, with a high prevalence in two of them. These results are supported by Ekstein et al. (2011), who also found a high prevalence of ADHD among DS samples, at 43.9%. Consequently, interventions in this area should continue since ADHD may affect other behaviour problems, having also been related to social competence. Another feature that should be considered is verbal expression since the paths associating this with behaviour problems have been supported by other

studies, including Patel et al. (2018), who found that behaviour problems in DS significantly correlated with age and expressive language abilities. Therefore, given that it seems to mediate with some behaviour problems, improving this variable or implementing other ways to communicate might reduce behaviour problems in individuals with DS.

To our knowledge, this is the first review to summarize information about gender, finding this variable to be involved in some cases of behaviour problems with DS, meaning that results in this area should be taken with caution. Notably, the vast majority of the studies considered included larger samples of males than females. Moreover, not all the studies assessed gender differences and some of them only made a first demographic analysis of gender among the two study groups, discarding this variable from the analysis if no differences were found. Among the studies that found gender differences, the trend was towards higher internalizing behaviours for females and higher externalizing problems for males. These results are similar to those of Hicks et al. (2008) in TD twin populations, where externalizing disorders increased at a greater rate among men than among women. In the same line, Rescorla et al. (2007) who compared the CBCL in 31 societies showed that among the TD population between 6-16 years most societies showed higher internalizing problems for girls and higher externalizing problems for boys. In the study by Van Gameren-Oosterom et al. (2013_b) the authors also found a gender difference for the normative sample, with boys without DS showing more externalizing problems than girls. In the same line, Lund (1985) found less behaviour problems and less social interaction problems in females with DS than in males.

Given the relevant information found about gender in the results reviewed, a closer look at this variable is required to discern whether there are two different phenotypes

when addressing behaviour problems. The scarce studies addressing gender and social competence again had larger samples for males and seem to indicate no gender differences or less social competence problems in girls, although caution with this interpretation is needed. These results are consistent with the study by Rescorla et al. (2007), who did not find gender differences in social problems in the TD population across age.

Regarding developmental outcomes, the studies that found associations between behaviour problems and age showed that some behaviour problems such as externalizing behaviours decreased after adolescence, except for verbal aggression which remained stable, while the pattern of internalizing behaviours seems to be more variable. These findings are in line with Grieco et al. (2015), who found a shift from externalizing to internalizing behaviours as individuals got older. The findings of Straccia et al. (2014) showed increasing depression and autistic symptoms when aging, which could be interpreted as an evidence of early onset cognitive impairment. However, there is a consensus coming from both longitudinal and cross-sectional studies that there is a cognitive preservation in individuals with DS until age of 40 in functional skills (Collacott and Cooper, 1997), self-help skills, and communication (Rasmussen and Sobsey, 1994). Additionally, Devenny et al. (1992) found that adults with DS did not show declines in orientation, concentration, coordination, visual attention, and auditory memory over 5 years, while they did show cognitive declines over 50 years, in addition to declines in speed psychomotor tests and memory tasks (Devenny et al., 1996). Individuals with DS were found to be more advantaged from their counterparts with other ID who showed an earlier decline in Zigman et al. (1987). In fact, the findings of Foley et al. (2015) showing less disruptive/antisocial behaviours support the suggestions of Devenny et al. (1996) which stated that during the fourth or

fifth decades adults with DS with lower levels of ID might be at a lower risk for dementia. Contrarily, we would expect more behaviour problems. More research is needed in this area in order to discern which variables might influence the decreases, stability of or increases in behaviour problems in individuals with DS since the study by Makary et al. (2014), which establishes a high methodological control (controlling by gender, age, level of ID, type of mutation and medical conditions) did not found any association between behavioural problems and age. Thus differences found by others could be related with differences in methodological control also affecting the trajectories of behaviour problems. Discerning this could help environmental interventions to be implemented to try to reduce these problems, helping people with DS to better fit into society. Notably, in the aging section the results of the studies did not concur, because of the use of different variables, so this information should be interpreted with caution and more research is required to confirm these results. Regarding social competence, the studies reviewed seemed to reveal an age-related development. Results from this area showed a trend towards lower social competence scores in adolescent stages than in childhood stages, tending to improve and then worsen again in subsequent stages. This pattern might be similar to that of the TD individuals, since Monahan and Steinberg (2011) found that during adolescence TD individuals had lower social competence skills, becoming even less competent and their particular difficulties becoming more pronounced. In the same line, in a wide cohort of individuals with DS, Nærland et al. (2017) found that peer problems were more common among adolescents than among junior school children. The study conducted by Rosner et al. (2004) also showed that there was an increase in social problems related to the adolescent stage, after which there is a decline, followed by another increase as the 40-year-old mark approached. Therefore, in the social competence area it could be

inferred that early cognitive impairment may have played a role in the results for the over-40's since three of the studies which included older samples pointed to a stability or decreases in social competence in older stages. Some studies in the general population have identified abnormal social functioning as a risk marker for dementia (Henry, et al., 2012). However, in this review we found few studies in this area, with those we did find comparing individuals of different ages, with some of them assessing participants across wide age groups, so again the results should be interpreted carefully. In fact, there was an exception to this pattern of improving social competence after adolescence. Patti and Tsiouris (2006) found that social avoidance scores increased with age from the twenties to the sixties. This was the only finding in this direction. An explanation for this result could be that social avoidance can be measured as a psychiatric sign so it could be related with depression or mood disorders which, as reported in the present review, also seemed to worsen with age (Fidler et al., 2005). In fact, in other IDs such as FXS, social avoidance has been found to increase from childhood to adulthood, tending to stabilize in younger adulthood (Roberts et al., 2019). Nevertheless, longitudinal studies should be conducted to discern the implications of age in social problems to discern if this area can detect the onset of cognitive impairment.

Among the studies that reviewed environmental factors, most of which with the notable exception of Nevill and Benson (2018) and Esbensen et al. (2008) focused on behaviour problems, there were some interesting results pointing to how different factors such as parental care, placement and stressors might affect behaviour problems. However, the results are not univocal and a single conclusion cannot be inferred. A closer look is recommended by the authors of this review since an influence of environmental variables is shown. Additionally, Feeley and Jones (2008) found that characteristics

associated with the behaviour phenotype, such as illness, sleep disorders and the way in which people from the environment interact with the behaviours of the person with DS, contributed to the occurrence of challenging behaviour. Furthermore, as may be inferred from the studies conducted by Huang et al. (2007) and Huang (2009), it seems that cultural variables might interfere with results, making them contradictory or incomprehensible. Thus, they cannot be interpreted without taking the particularities of these populations into consideration.

Last, it was noticed that researchers need to make a far greater effort regarding measures to assess both behaviour problems and social competence. This is particularly the case for studies of behaviour problems because of the 35 studies reporting assessments for this variable just 11 used the CBCL (Achenbach, 1991) in its different versions and 6 the Developmental Behaviour Checklist (DBC; Einfeld and Tongue, 1992; Einfeld and Tongue, 2002). In the case of studies addressing aspects of social competence, the variability in measures is huge with every study except 4 using different measures. Furthermore, the four studies that used the same measure used the Vineland Adaptive Behavior Scale (VABS; Sparrow et al., 1984), which is not a specific measure for social competence despite containing a socialization scale. We believe that since social competence has not yet been clearly defined it was difficult for the authors to identify their studies using the construct social competence and measures for social competence. In fact, of the 15 studies addressing this variable, only 1 included social competence as a term in the title, 3 included social skills, 2 peer social networks, 1 social behaviour, 1 social reasoning skills, 1 involvement with peers and 1 social relating behaviours. The rest of the studies that included results that could fit into social competence did not use any term related with it and therefore did not assess this variable as their main objective.

Review limitations

The review findings should be interpreted in the light of possible limitations. Although we aimed to carry out a comprehensive search of the three databases, some studies might not have been found because of the terms used in the search strategy. Moreover, because of our inclusion criteria of only full-length articles available in English or Spanish and published between 2000 and 2019, some relevant articles published earlier or in other languages might have been lost. In addition, this review excluded case studies, interventions, other reviews, and grey literature such as book chapters and dissertations, and this literature could have impacted on the results. Furthermore, we could not retrieve all the identified papers because one study could not be found even after requesting it from the authors. Although all the papers were read twice by the same researcher and the results compiled in a document with a time lapse of a month between the first and second reading, some information presented in this review might have been misinterpreted or overlooked. In the same line, in terms of the backward review some limitations should be taken into consideration regarding misinterpretation or overlooked information, and again one paper was not retrieved even after requesting it to the authors. Moreover, when reviewing the reference section of the selected papers, articles that did not include the term Down syndrome on the title were screened, although this was not the case for the database search because Down syndrome had to appear on the title. Therefore, papers that focussed on general ID but had specific information for DS in their full text were excluding in the database search but included in the backward search. Last, in this review we excluded the articles that stated that individuals with autism comorbidity were included in their sample due to this having been found to influence both social development (Fidler, 2005) and behaviour problems, including conduct problems and hyperactivity (Warner et al., 2014). However, individuals with

DS and comorbid autism or autism spectrum disorder might have been included in the samples because most of the studies did not control for autism comorbidity in their studies.

Conclusions

This review not only compiles evidence on the intrinsic variables that affect behaviour problems and social competence in individuals with DS, but it also sheds light on environmental variables that should be considered when researching on DS samples. Gender seems to play a role in the DS phenotypes and so needs further exploration. In addition, and given that the studies reviewed revealed several influences, external factors that might affect behaviours in individuals with DS should be taken into consideration when developing interventions to reduce behaviour problems and increase adaptive behaviours. As a result of the findings, we concur with Dykens and Hodapp (2007), who recommend including the roles of gender, development across the lifespan, and environmental factors when studying the behavioural phenotype of individuals with DS. Some protective and risk factors might have been identified by the studies assessed and so, as stated in Dykens (2007), it is essential to disentangle complicated biopsycho-social risk and protective factors that might increase or reduce psychopathology, and future research could address protective factors that might reduce problems among the population with DS. However, further description of the samples is needed in order to correctly address the phenotype of individuals with DS without comorbidities. Last, studies on individuals with DS should use gold standard measures such as CBCL, developed for TD people but counting with a large evidence of use in ID samples, or DBC (Einfeld and Tongue, 1992; Einfeld and Tongue, 2002), which has been developed specifically to assess individuals with ID (Einfeld et al., 2006), to make comparison between studies possible given that just 11 articles of the 44 used the CBCL and only 6

the DBC, making statistic comparison impossible. Additionally, more studies concerning social competence should be conducted to find the true implications of this variable in the DS phenotype. The construct also needs to be clearly defined and efforts made to find a measure that could capture the behaviours that are representative of it.

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Table 1. Key information of the studies reviewed

Study	Type		Sample	Ages	BP measures	SC measures
	Cross sectional	Longitudinal				
(Chadwick et al., 2000)	X		- 139 children with ID - 15 children of those had DS.	- 4-11 years.	- The Aberrant Behaviour Checklist-Community Version (Marshburn and Aman, 1992).	- Vineland Scales of Adaptive Behaviour (Sparrow et al., 1984).
(Dykens et al. 2002)	X		-211 individuals with DS.	- 4-19 years.	- Child Behaviour Checklist (CBCL; Achenbach, 1991).	
(Guralnick, 2002)	X		- 21 individuals with DS. - 21 children with mixed ID.	-2-5 years.	- CBCL (Achenbach and Edelbrock, 1983).	- VABS (Sparrow et al., 1984).
(Hawkins et al., 2003)		X	- 58 individuals with DS.	- 31-56 years. - 41-57 years.		The Inventory for Client and Agency Planning (ICAP; Bruininks et al., 1986)
(Rosner et al., 2004)	X		- 65 individuals with DS. - 58 individuals with WS. - 54 individuals with PW.	- 4-49 years.	- CBCL (Achenbach, 1991).	- CBCL (Achenbach, 1991).
(Bhatia et al., 2005)	X		- 40 children with DS. - 60 siblings. - 40 TD children CA-matched.	-6 months - above 6 years.	(Klastin and Jackson, 1995).	
(Fidler et al., 2005)	X		- 42 individuals with DS. - 25 individuals with mixed ID.	- mean age 11.34 years. - mean age 12.02 years.	- Reiss Profiles (Reiss and Havercamp, 1998). - CBCL (Achenbach, 1991).	
(Blacher & McIntyre, 2006)	X		Anglo participants: - 63 individuals with mixed ID. - 52 inviduals with. CP.	-16-26 years	- Scales of Independent Behavior-Revised (SIB-R; Bruininks et	

			- 23 individuals with DS. - 12 individuals with ASD. Latino participants: - 50 individuals with mixed ID. - 35 individuals with CP. - 36 individuals with DS. - 11 individuals with ASD.		al., 1996) - Reiss Screen for Maladaptive Behavior (Reiss, 1994)	
(Enfield et al., 2006)	X		- 74 individuals with DS. - 111 individuals with autism. - 64 individuals with WS. - 67 individuals with FXS. - 59 individuals with PW. - 249 with ID due to other causes.	- 4-18 years.	-The Developmental Behaviour Checklist (DBC; Einfeld and Tongue, 1992).	
(Fidler et al., 2006$_a$)		X	- 24 children with DS. - 33 ID children with mixed/non-specific aetiologies.	-12 - 45 months.	- Bayley Scales of Infant Development (Bayley, 1993). - Revised Infant Temperament Questionnaire (Carey and McDevitt, 1978). - CBCL (Achenbach, 1991).	
(Fidler et al., 2006$_b$)	X		- 18 toddlers with DS. -19 individuals with mixed ID (MA). - 24 MA TD children.	-2-3 years. -2-3 years. -1-2 years.		- VABS (Sparrow et al., 1984)
(Patti and Tsiouris, 2006)	X		- 104 adults with DS. - 102 adults with DS.	- 20-49 years. - 50-71 years.	-The Behavior Problem Inventory (BPI; Rojhan, 1986). -The psychiatric Signs Profile (Tsiouris et al., 1998).	
(Tyrer et al., 2006)	X		- 3065 adults with ID. - 502 of those with ID had DS.	- under 20 years-over 70 years	- Interviews	
(HUANG et al., 2007)	X		- 16 Taiwanese children with DS. -16 Japanese children with DS.	- 56.75 months on average. - 59.44 months on average.	- Eyberg Child Behavior Inventory (ECBI; Eiberg, 1992). - ECBI translated to Taiwanese.	
(Esbensen et al., 2008)		X	- 150 adults with DS. - 240 adults with other ID causes.	- 17-57 years. - 19-68 years.	- ICAP (Bruininks et al., 1986).	
(Barrett & Fidler, 2008)	X		- 40 individuals with DS. - 20 individuals with ID of mixed aetiology.	- 4-25 years.	- CBCL (Achenbach, 1991).	
(Mccarthy, 2008)		X	- 50 individuals with DS.	- 6-17 years. - 22-33 years.	- A behavioural inventory.	

(Gau et al., 2008)	X	- 45 children with DS. – 36 siblings. - 50 control families.	- 2-14 years. - 3-18 years. - 3-15 years.	- Maudsley Personality Inventory. - Brief Symptom Rating Scale (Lee et al., 1990). - CBCL (Achenbach, 1991).	
(Guralnick et al., 2009)	X	- 27 inidividuals with DS. - 27 CA TD individuals. - 27 MA TD individuals.	- mean age 5.62 years. - mean age 5.61 years. - mean age 3.21 years.		-Social Contact Questionnaire (Guralnick, 1997; Guralnick, 2002).
(Huang, 2009)	X	- 16 Taiwanese children with DS. - 17 Taiwanese children without ID. - 16 Japanese children with DS. - 15 Japanese children without ID.	- 43-69 months. - 17-25 months. - 44-74 months - 16-24 months.	- Chinese and Japanese versions of the ECBI (Eiberg, 1992).	
(Dressler et al., 2010)	X	- 75 individuals with DS.	- 4-52 years.		- VABS (Sparrow et al., 2003)
(Esbensen et al., 2010)	X	- 70 adults with autism and ID. - 70 age-matched adults with DS.	- 22-53 years. - 24-52 years.	- SIB-R (Bruininks 1996).	
(Hippolyte et al., 2010)	X	- 34 adults with DS. - 34 TD adults matched by receptive vocabulary.	- 18-52 years. - 4-11 years.	- Developmental Behaviour Checklist (DBC-A; Mohr et al., 2005).	- The Social Resolution Task (Barisnikov et al., 2005).
(Guralnick et al., 2011_a)	X	- 27 children with DS. - 27 TD CA-matched. - 27 TD MA-matched.	- 54-83 months.	- CBCL (Achenbach and Rescorla, 2000).	
(Guralnick et al., $2011_{b)}$	X	- 27 inidividuals with DS. - 27 CA TD individuals. - 27 MA TD individuals.	- 54-83 months.	- Preeschool Caregiver and school-age Teacher Report Forms (C-TRF; Achenbach and Rescorla, 2000; TRF; Achenbach and Rescorla, 2001)	- Social Skills Rating System (Gresham and Elliott, 1990). -Child Behavior Scales (Ladd and Profilet, 1996). -Teacher Social Network Questionnaire (Guralnick, 1997; Guralnick, 2002).
(Van Gameren-Oosterom et al., 2011)	X	- 285 children with DS. - 238 individuals of the normative data.	- 8 years.	- CBCL (Achenbach, 1991).	
(Hattier et al., 2012)	X	- 27 children with DS. - 18 children with cerebral palsy. - 29 children with history of seizures.	- 17-35 months	- Baby and Infant Screen for Children with aUtIsm Traits-Part 2 (Matson et al., 2007).	
(Lundqvist, 2013)	X	- 915 individuals with ID. - 113 of those had DS.	-18-87 years.	- BPI (Rojahn et al., 2001).	

(Van Gameren-Oosterom et al., 2013_a)	X		- 322 individuals with DS.	- 16-19 years.		- Social competence rating scale. - Children's Social Behavior Questionnaire (Hartman et al., 2007).
(Van Gameren-Oosterom, et al., 2013_b)	X		- 322 individuals with DS. - 2076 individuals from a normative sample	- 16-19 years. - 15-18 years.	- CBCL (Achenbach, 1991; Verhulst et al., 1996).	
(Makary et al., 2014)	X		- 25 adults with DS.	-16-42 years.	- DBC-Adult version (DBC-A; Mohr et al., 2011_a).	
		X	- 28 adults with DS.	- 20-52 years.		
(Straccia et al., 2014)	X		- 34 DS adults. - 34 adults with nonspecific ID.	- 25-42 years - 22-57 years.	- The Reiss Screen for Maladaptive Behavior (Reiss, 1988). - DBC-A (Mohr et al., 2005).	- Social Behavior Quesionnaire (Barisnikov and Straccia, 2012).
(Yahia et al., 2014)	X		- 100 individuals with DS. - 100 siblings.	- 6-26 years.	- Disruptive Behavior Disorder Rating Scale (Silva et al., 2005).	
(Channel et al., 2015)	X		- 46 individuals with DS without ASD. - Normative sample of the scale.	-10-21 years.		- The Social Responsiveness Scale (SRS; Constantino and Gruber, 2005).
(Foley et al., 2015)		X	- 319 individuals with DS.	- 3-24 years.	- DBC (Einfeld and Tonge, 1995). - DBC-A-R (Mohr et al., 2011_b).	
(Glenn et al., 2015)	X		- 125 adults with DS. - 206 individuals with DS.	-18-43 years. -4.5-43 years.	- The childhood routines inventory (Evans et al., 1997).	
(Makary et al., 2015)		X	- 20 adults with DS.	- 20-56 years.	- DBC-A (Mohr et al., 2011_a).	
	X		- 33 adults with DS.	- 16-42 years.		
(Rice et al., 2015)		X	- 72 DS individuals. - 63 FXS individuals. - 62 WS individuals. - 51 individuals with PW.	- 4-40 years	- DBC-A (Mohr et al., 2005). - DBC (Enfield and Tonge, 1994).	
(Esbensen, 2016)	X		-75 adults with DS.	-37-65 years.	- SIB-R (Bruininks, 1996)	
(Kelmanson, 2016)	X		- 34 children with DS. - 34 TD children CA-matched.	- 9–15 years.	- CBCL 6-18 (Achenbach and Rescorla, 2007). - The Child Sleep Habit Questionnaire (CSHQ; Owens et al., 2000).	
(Nevill & Benson,	X		- 80 adults with DS. - 265 individuals with ID of	- 16-68 years.	- Aberrant Behaviour Checklist Community	

2018)		a validation sample.	- 10-79 years.	(Aman et al., 1985). - Anxiety, Depression and Mood Scale (Esbensen et al., 2003).	
(Cregenzán-Royo et al., 2018)	X	- 21 DS participants - 40 FXS participants	- 4-17 years - 7-25 years.	- CBCL (Achenbach and Rescorla, 2000; Achenbach and Rescorla, 2001).	
(Esbensen et al., 2018)	X	- 30 children with DS and their parents	- 6-17 years	- Micro-Mini Motionlogger Actigraph - CSHQ (Owens et al., 2000) - A companion sleep diary. - Parent and teacher versions of the Nisonger Child Behaviour Rating Form (Aman et al., 1996). - Vanderbilt ADHD Rating Scales, parent and teacher Forms (Wolraich et al., 2003).	
(Matthews et al., 2018)	X	- 188 individuals with DS.	- 20-69 years.		An ad-hoc survey.

Note: BP= Behaviour Problems; SC= Social Competence; DS= Down Syndrome; TD= Typically Developing; ID= Intellectual Disabilities; CP= Cerebral Palsy; WS= Williams syndrome; PW= Prader Willi syndrome; FXS= Fragile X Syndrome; ASD= Autism Spectrum Disorder; CA= Chronological Age; MA= Mental Age.

Capítulo 3

3.1. Discusión

La presente tesis se ha desarrollado a través de tres estudios que buscaban recopilar, sintetizar y extender la información existente sobre problemas de comportamiento y competencia social en individuos con SD y SXF teniendo en cuenta a su vez una perspectiva de desarrollo.

El primer artículo publicado encajaría con el objetivo de extender la información existente, siendo una investigación empírica realizada con 40 individuos con SXF y 21 con SD a través de la información reportada por las madres. De este artículo se desprende que tanto la emoción expresada como la impulsividad en las madres de individuos con SXF o SD se relacionan con los problemas de comportamiento en sus descendientes. Lo cual apoya los resultados de un estudio previo sobre emoción expresada (Greenberg et al., 2012) que también encontró relaciones entre variables de emoción expresada y problemas de comportamiento, aunque utilizaba un instrumento diferente para evaluar tal característica en las madres de individuos con SXF. Por lo que respecta a la impulsividad, en las dos revisiones realizadas no se han encontrado estudios que asocien dicha variable en los progenitores con problemas de comportamiento o competencia social en individuos con SXF o SD por lo tanto, según parece, esta variable no ha sido explorada con anterioridad en lo que respecta a problemas de comportamiento en la descendencia con SXF o SD. Aunque y salvando las distancias, el estudio de Kau et al. (2000) demuestra como utilizando la actividad de las madres como variable de control, los problemas de comportamiento en los individuos con SXF son mayores o menores en comparación con individuos con DI de etiología desconocida. Si bien, exactamente la variable actividad no es impulsividad, puede estar asociada con la misma, reflejando la parte conductual de dicha variable. También, el artículo 1 señala a su vez el perfil más severo de problemas de comportamiento en los individuos con SXF en comparación con los individuos con SD lo cual concuerda con los resultados encontrados en los estudios revisados en el artículo 2 de la presente tesis.

El artículo número 2, recopila y sintetiza la información referida a problemas de comportamiento y de competencia social en individuos con SXF. Señalando como problemas de comportamiento más frecuentemente reportados los de déficit de

atención. En general, los individuos con SXF presentaban mayores problemas de comportamiento y competencia social que en población de DT, con la excepción de problemas que no tienen una parte tan central en el fenotipo de SXF como las quejas somáticas o los comportamientos delictivos. De hecho, los resultados sobre quejas somáticas fueron los únicos que no resultaron significativos en el artículo 1 y por ello, como se indica en el mismo, se eliminaron de la tabla de resultados. Del mismo modo, los problemas de atención, de delincuencia y de comportamientos agresivos no difirieron frente a aquellos individuos de DT con deficientes habilidades atencionales (Cornish et al., 2001). En competencia social, uno de los estudios no identificó diferencias en cuanto a síntomas ansioso-depresivos (Hessl et al., 2001) aunque otro sí lo hizo (Cornish et al., 2001) y las reacciones ante desconocidos en edades tempranas fueron similares en Tonnsen et al. (2017). En comparación con individuos con SD, se encuentra un perfil más grave tanto en problemas de comportamiento como en competencia social para los individuos con SXF aunque no se encuentran diferencias en motivación lo cual apoya la idea referida por Hagerman (1996) de que los déficits sociales en SXF provienen del exceso de activación y no de la indiferencia social. Asimismo, apoya los resultados encontrados en el artículo 1, en el cual los individuos con SXF tienen más problemas de comportamiento que los individuos con SD (incluida la variable problemas sociales de la CBCL). En comparación con otras DI son menos las diferencias encontradas, aunque la evitación social, evitación ocular o los comportamientos de retraimiento como rasgo prominente del fenotipo conductual del SXF continúan siendo mayores que en otros individuos y también se reportan diferencias en estereotipias, autolesiones, comportamientos de irritabilidad, de sobreexcitación, hiperactividad general y algunos comportamientos más relacionados con el autismo. En comparación con individuos con TEA, los estudios revisados o no encuentran diferencias o muestran mayores problemas de comportamiento para los individuos con SXF y un mejor perfil de competencia social acompañado de mayor sintomatología ansiosa aunque son pocos los estudios que arrojan datos a este respecto.

Por lo que respecta a los diferentes fenotipos conductuales en SXF, los estudios revisados reportan un peor perfil para aquellos sujetos con SXF y autismo comórbido tanto en problemas de comportamiento como en competencia social en

comparación con los individuos que únicamente presentan SXF. En particular, los estudios muestran "*quorum"* con respecto a un mayor retraimiento social en aquellos individuos con SXF y autismo comórbido así como señalan que los individuos comórbidos alcanzan menores puntuaciones en los perfiles de socialización en etapas de la infancia. Solamente un estudio reporta datos sobre la adolescencia manteniendo estos mismos hallazgos (Smith et al., 2012). Sin embargo, los estudios no coinciden en las comparaciones entre individuos con SXF y autismo comórbido y aquellos con autismo exclusivamente mostrando diferentes perfiles de problemas de comportamiento y competencia social.

En cuanto a la perspectiva de desarrollo, si bien todos los estudios revisados en el artículo 2 no coinciden, parece que los problemas de atención según algunos de los estudios revisados se reducen a lo largo de la vida, al igual que las conductas agresivas que como se ha señalado, puede que dependan de la sintomatología autista. Por lo tanto, un mayor control metodológico se requiere en los estudios para discernir dichas trayectorias. Las escalas generales de problemas de comportamiento parecen mantenerse estables a lo largo de la vida de los sujetos con SXF (total, externalizantes). Por lo que respecta a los problemas de competencia social, respecto a las trayectorias de socialización todavía es necesario investigar más tratando de discernir cual es el perfil de las mismas dado que los diferentes estudios revisados arrojan distintos patrones. Del mismo modo, se hace necesario profundizar en las trayectorias de sintomatología ansiosa/depresiva para conocer si se agudizan o no durante las etapas de la adolescencia temprana, del mismo modo que la sintomatología internalizante. Cabe destacar que tanto la sintomatología autista como la ansiedad fueron variables de interacción en la competencia social en individuos con SXF afectando las trayectorias de desarrollo a lo largo de los años.

Finalmente, por lo que respecta a factores ambientales, se han identificado tanto características de las madres como factores de salud mental en los progenitores que se relacionan con problemas de comportamiento y competencia social. Algunos factores relacionados con las características del hogar se relacionaron con la competencia social en los individuos con SXF y la variable flexibilidad en las madres junto con la sintomatología autista se relacionó con los problemas de

atención dando lugar a diferentes combinaciones y grados de afectación en el estudio de DaWalt et al. (2021).

En cuanto al estudio 3, que todavía no ha sido publicado, la revisión de estudios realizada coincide con el artículo 2 en los problemas de comportamiento más frecuentemente reportados en este caso en individuos con SD. Siendo éstos los problemas de atención y relacionados en estudios que los comparaban con individuos de DT. Por lo general, los individuos con SD mostraban mayores problemas de comportamiento que los individuos de DT con la excepción de algunos problemas concretos como la agresión o los comportamientos de oposición/ desafiantes (Yahia et al., 2014; Gau et al., 2008). Del mismo modo, los individuos con SD presentaban mayores problemas de competencia social y aunque cuando se les emparejaba por edad mental las diferencias en competencia social se reducían, los individuos con SD continuaban mostrando una menor competencia social. Tres estudios reportaron una fortaleza para los individuos con SD en cuanto a sintomatología ansiosa/depresiva (Van Gameren-Oosterom et al., 2013_b; Gau et al., 2008; Van Gameren-Oosterom et al., 2011). Dicha fortaleza podría tener que ver con los hallazgos de otros estudios que encontraron en individuos con DI una tendencia a exhibir mayores síntomas depresivos y ansiosos en función de la capacidad intelectual, con aquellos individuos con mayor capacidad intelectual presentando más síntomas de este tipo (Einfeld y Tonge, 1996; Gillberg et al., 1986). De modo que las puntuaciones en dicha sintomatología podrían estar asociadas con el grado de DI. En cuanto a las comparaciones con individuos con otras DI, los individuos con SD mostraban menores problemas de comportamiento y una mejor competencia social. Si bien, los individuos con SD no se diferenciaban de individuos con otras DI en cuanto a la implicación con sus compañeros y tampoco lo hacían en comportamientos internalizantes (Guralnick, 2002; Esbensen et al., 2008).

Si bien de la revisión del estudio 3 se excluyeron aquellos individuos comórbidos con autismo (n=8), es esperable que, al igual que ocurre en los artículos de SXF, individuos con SD y autismo comórbido formen parte de las muestras revisadas. En particular, en el caso de SD al menos en lo que respecta a problemas de comportamiento y competencia social, es extraño que los estudios controlen por

sintomatología autista o por como ésta interfiere. Asimismo, son menos los estudios que reportan dicha variable en sus resultados en comparación con las muestras de SXF, lo cual llama la atención teniendo en cuenta la elevada comorbilidad entre el SD y el TEA y dado que los estudios que controlan dicha variable estableciendo grupos señalan en individuos con SD comórbido con TEA una conducta estereotípica significativamente mayor, una mayor hiperactividad, mayores comportamientos autolesivos y un uso repetitivo del lenguaje mayor que en el grupo que solamente presentaba SD (Moss et al., 2012). De manera similar, Carter et al. (2007) encontraron problemas de comportamiento más severos en individuos con SD y TEA que en individuos con SD únicamente y Capone et al. (2005) encontraron también mayores comportamientos estereotipados, letargo e hiperactividad en aquellos con SD y TEA comórbido. También Dressler et al. (2011), encontraron menores niveles de socialización en individuos con SD y TEA comórbidos en comparación con individuos con SD únicamente. Por lo que un mayor nivel de control se hace necesario en futuros estudios en individuos con SD para delimitar de manera correcta los problemas de comportamiento.

En cuanto a las trayectorias de desarrollo en individuos con SD, parece que en problemas de corte externalizante se produce una mejoría conforme los individuos se desarrollan y especialmente tras la adolescencia, de una manera similar, pasadas las etapas de adolescencia o en estudios que abarcan un gran rango de edad se reporta la disminución de sintomatología internalizante y/o otros síntomas psicológicos como la ansiedad. Sin embargo eso no ocurre en cuanto a la sintomatología depresiva y/o autista que parece incrementarse tras la adolescencia en uno de los estudios (Straccia et al., 2014). En cuanto a la competencia social, en los estudios revisados se aprecia una tendencia hacia un peor desempeño durante la etapa de la adolescencia, así como en síntomas internalizantes y ansiedad. Si bien, el desempeño en competencia social luego mejora en la adultez temprana llegando a alcanzar el mejor desempeño en torno a los 30 años de edad para en posteriores edades empeorar nuevamente. Una vez alcanzada la adultez, no parece que los problemas de comportamiento señalen signos de deterioro cognitivo, que sin embargo sí parecen apreciarse en las variables de competencia social. De ese modo, la mayor parte de los estudios revisados sobre competencia social parecen reportar un declive general en dichas

habilidades a partir de los 40 años de edad. Dichos hallazgos podrían señalar y ser claves en cuanto a la identificación temprana del deterioro cognitivo en individuos con SD, dado que hay estudios que han señalado a la comunicación social deficiente como un signo temprano de disfunción frontal en individuos con SD (Head et al., 2012). Además, Cipriani et al. (2018) señalan el retraimiento social como uno de los signos de alerta para el inicio de la enfermedad de Alzheimer en individuos con SD.

Por lo que respecta a los factores que afectan a los problemas de comportamiento en individuos con SD se encontraron algunos factores de riesgo como el grado de DI, la conducta de "tonguing", es decir las conductas de sacar la lengua fuera de la boca, la expresión verbal y el sueño, entre otros. Por lo que respecta a la competencia social, tanto la habilidad verbal como la conducta de "tonguing" y el sueño influían en la competencia social de los individuos. En cuanto a los factores ambientales, tanto los estresores como las características del hogar y el lugar de residencia además de algunas variables relacionadas con las madres como las instrucciones maternas o el entorno familiar se relacionaban tanto con los problemas de comportamiento como con la competencia social.

Finalmente, se encontraron relaciones entre el género de los individuos con SD y los problemas de comportamiento y competencia social similares a los hallados en población de DT. Aunque también se encontraron estudios que no reportaban diferencias. A diferencia de los individuos con SXF en los que la variable género se suele tener en cuenta en la realización de los estudios debido a sus implicaciones fenotípicas, en el caso de los estudios de individuos con SD es en pocas ocasiones considerada.

3.2. Conclusión

Los tres estudios realizados ponen de manifiesto las interacciones señaladas en la figura 3 señalando la importancia que tienen los factores ambientales en los problemas de comportamiento y de competencia social en individuos con SD y SXF. De ambas revisiones realizadas se desprende que pese al cambio de paradigma (Luckasson et al., 2002) y al mayor peso otorgado por las definiciones actuales de DI a los factores ambientales, son pocos los estudios, al menos centrados en problemas de comportamiento y competencia social, que se centran en controlar o evaluar variables ambientales, pese a que los que sí lo hacen, encuentran resultados que relacionan los problemas de comportamiento y de competencia social de los individuos con DI con características de las madres como el criticismo (Smith et al., 2016; Greenberg et al., 2012), la emoción expresada (Cregenzán-Royo et al., 2018; Greenberg et al., 2012), el afecto (Greenberg et al., 2012), la flexibilidad cognitiva (DaWalt et al., 2021), las relaciones familiares (Esbensen et al., 2008), los estresores (Nevill y Benson, 2018), el lugar de residencia (Esbensen et al., 2008), la salud mental de los progenitores (Hessl et al., 2001; Smith et al., 2016; Soriano et al., 2018) y los factores culturales (Huang et al., 2007; Huang et al., 2009). De hecho, algunos estudios revisados no fueron incluidos finalmente en las revisiones debido a que se centraban en la influencia de los problemas de comportamiento de los descendientes en los progenitores, sin tener en cuenta la posible influencia bidireccional de los mismos y siendo que en múltiples momentos el contexto es el que dificulta la adquisición de comportamientos adecuados y promueve el desarrollo de comportamientos desajustados (Verdugo y Gutiérrez, 2009).

Al mismo tiempo, se desprende de las dos revisiones realizadas la importancia que tiene el desarrollo en los problemas de comportamiento y la necesidad de realizar mayor investigación sobre las trayectorias de los problemas de comportamiento teniendo en cuenta variables de control procedentes del ambiente. Pudiendo ser éste el motivo por el cual todavía se hace difícil describir las trayectorias específicas de evolución de los problemas de comportamiento y la competencia social en ambos síndromes, encontrando resultados en ocasiones contradictorios. Otros factores explicativos para las diferencias en las trayectorias podrían deberse

a la presencia de comorbilidades, las diferencias individuales o a las diferencias metodológicas que presentan los diferentes estudios. Como ejemplo, el estudio de DaWalt et al. (2021), que muestra las diferentes trayectorias en problemas de atención atendiendo a dos variables, flexibilidad en las madres y sintomatología autista, denota cómo un factor ambiental puede cambiar el desarrollo en las trayectorias de un problema de comportamiento.

La escasez de control sobre variables ambientales y en concreto familiares en los estudios se hace especialmente alarmante en el caso de los individuos con SXF teniendo en cuenta las diferencias individuales y el fenotipo conductual que pueden expresar las madres en función de si tienen la mutación completa o la premutación. Puesto que las personas con la premutación por lo general no tienen el mismo fenotipo conductual que las personas con mutación completa (Boyle y Kaufmann, 2010). Mostrando un fenotipo que aunque es generalmente menos severo que el de los varones con la mutación completa incluye problemas asociados con dificultades de aprendizaje, dificultades socioemocionales y también problemas de salud mental (Hagerman et al., 2017). Sin embargo, y pese a que las madres son las principales informantes de los estudios, se han encontrado pocos estudios que controlen si éstas poseen la premutación o la mutación completa, pudiendo tener dicha variable una gran influencia tanto en las respuestas otorgadas, como en el entorno de crianza de los individuos con SXF y dificultando el esclarecimiento de los fenotipos conductuales dentro del síndrome.

Particularmente en la revisión realizada sobre SD se ha encontrado un menor número de estudios referidos a variables de competencia social en comparación con estudios centrados en problemas de comportamiento. Son varias las explicaciones que pueden dar lugar a este resultado. Pude ser que debido a la estrategia de búsqueda utilizada se hayan encontrado un menor número de estudios que no son representativos de la producción real. Otro factor a considerar es la complejidad del constructo competencia social y la configuración de éste a lo largo del tiempo en la definición de la DI pudiendo explicar que no se hayan encontrado más resultados relevantes que sí se ajustan al constructo. O que durante la revisión de los mismos se hubieran omitido artículos relevantes. También pudiera ser que debido a la creencia establecida referida a unas buenas

habilidades sociales en el síndrome, se haya realizado menos investigación al respecto dado que en la revisión realizada con SXF no encontramos esta dificultad. Aunque hay que señalar que en la cadena de términos utilizados en la búsqueda de la revisión del artículo 2, se incluyeron más términos relacionados con la competencia social. El riesgo de que un menor número de estudios se lleven a cabo teniendo en cuenta la competencia social de los individuos con SD, pasa por la posibilidad de que haya variables y factores en los que sea posible intervenir y que sean susceptibles de fomentar una mejora en los mismos y debido a la menor investigación no se estén detectando. De cualquier modo, los estudios revisados indican como era esperable teniendo en cuenta los rasgos de su fenotipo conductual, que la competencia social es un área de fortaleza en los individuos con SD y que en comparación con individuos con otras DI les posiciona en un lugar privilegiado. Si bien, en comparación con individuos de desarrollo típico, los individuos con SD presentan mayores dificultades que además se han visto asociadas con la capacidad de comprensión verbal (Izuzquiza-Gasset, 2003). Lo cual apoya los hallazgos de los estudios de la revisión sobre SD que señalan una relación entre la habilidad verbal y la competencia social en individuos con SD.

Es importante señalar que la competencia social tiene una gran importancia tanto en individuos con DI como en la sociedad humana en general, entendiendo que el ser humano es un ser social. Pero en concreto, en individuos con DI puede resaltarse la importancia de dicha variable dado que las personas con DI pueden presentar dificultades laborales que pueden ser en parte suplidas por una vida social satisfactoria (Sigman et al., 1999). Sin embargo, la mayoría de los estudios todavía no utilizan medidas específicas que puedan evaluar la competencia social como constructo en sus diferentes aristas. Ello dificulta el avance en las investigaciones debido a que hay áreas que no quedan adecuadamente evaluadas con instrumentos que por ejemplo se centran en habilidades adaptativas como la Vineland Adaptive Behavior Scale (VABS; Sparrow et al., 1984) centrada en relaciones interpersonales, juego y tiempo libre y habilidades de manejo social, o que se centran en un área muy específica y concreta como por ejemplo las relaciones con los iguales como la Teacher Social Network Questionnaire (Guralnick, 1997; Guralnick, 2002) siendo más útil contar con un instrumento que pudiera recoger varias áreas de competencia social al mismo tiempo. De hecho, ya

en 1983, Waters y Sroufe señalaban las dificultades de conceptualización de la competencia social que habían llevado en ocasiones a la definición específica de capacidades o habilidades perdiendo el potencial integrativo del concepto como tal o a la utilización del constructo desde la molaridad dificultando la evaluación del mismo.

Por lo que respecta a problemas de comportamiento, los estudios revisados y el estudio empírico realizado en la presente tesis ponen de manifiesto ese mejor perfil en el caso de individuos con SD frente a los individuos con SXF. Asimismo, muestran un claro perfil de los individuos con SD presentando por lo general menos problemas de comportamiento y competencia social que aquellos individuos con otras discapacidades intelectuales. Mientras en el caso de los individuos con SXF se observa por lo general una mayor similitud en ambas variables con el resto de individuos con DI con la excepción de aquellos comportamientos prominentes en su fenotipo conductual particular.

En cuanto a la comorbilidad con el autismo, en el caso de SXF algunos autores sugieren que aquellos individuos con SXF y TEA comórbido presentarían una mayor similitud en cuanto a comportamientos internalizantes y externalizantes con los individuos con autismo que con los individuos con SXF, debido a que encuentran un mayor número de diferencias con el grupo de individuos con SXF solamente (Smith et al., 2012). Sin embargo, y dado que son pocos los estudios que comparan individuos con SXF y autismo comórbido con individuos con autismo exclusivamente, se requiere un mayor énfasis por discernir aquellos aspectos que caracterizan la comorbilidad. Y en ese sentido, la comparación con grupos de autismo puede acercarnos más a la comprensión del fenotipo conductual de aquellos individuos con SXF y autismo comórbidos. Por contra, son pocos los estudios que se centran en controlar la comorbilidad a la hora de realizar estudios sobre competencia social o problemas de comportamiento en SD pese a que se ha observado que la comorbilidad con el autismo afecta a ambas variables. De modo que algunos de los resultados de individuos con SD pueden ser fruto de dicha comorbilidad que no está siendo controlada. En individuos con SD y TEA comórbido algunos autores sugieren una mayor similitud en comportamiento

adaptativo con individuos con SD solamente que con aquellos con autismo solamente (Dressler et al., 2011).

3.3 Limitaciones de los estudios

Como se ha indicado en los tres estudios, los resultados de los mismos deben ser considerados a la luz de posibles limitaciones. En cuanto al estudio empírico (artículo 1), aunque en el mismo se tuvieron en cuenta las características de la madre asegurando que tuvieran la premutación, al ser un estudio online, no se realizaron pruebas confirmatorias de dicha condición. Además, aunque se preguntó por la comorbilidad con autismo en los individuos con SXF, tampoco se comprobó con un diagnóstico clínico por lo que los resultados pueden no reflejar con exactitud aspectos fenotípicos del síndrome debido a la comorbilidad con TEA, lo mismo sucede en el caso de los resultados de individuos con SD. Por lo que respecta a las revisiones, la revisión realizada sobre individuos con SXF (artículo 2), si bien cuenta con una cadena amplia de términos de búsqueda y con un sistema de clasificación de los estudios en función de su calidad metodológica, dada la escasez de control en los estudios sobre problemas de comportamiento, no fue posible establecer diferencias en función de la comorbilidad con autismo, lo cual habría resultado enriquecedor. Por lo que respecta a la revisión realizada sobre individuos con SD (estudio 3), debido a la cadena de búsqueda puede no haber recogido todos los estudios relevantes sobre el tema y algunos de los resultados pueden haber sido omitidos por el propio proceso de revisión.

3.4. Puntos fuertes de los estudios

Los tres estudios realizados también cuentan con fortalezas a señalar:

El estudio empírico (artículo 1) cuenta con la fortaleza de haber recopilado muestras de individuos con SXF de diferentes países, lo cual amplia la generalización de los resultados a diferentes contextos culturales. Si bien, los países en los que se recopiló información eran todos hispanohablantes, se contó también con la ayuda de psicólogos nativos para asegurar la comprensión de los ítems del cuestionario online. Por añadido, el hecho de evaluar la impulsividad en madres no solo mediante un cuestionario, sino también mediante una tarea, refuerza los resultados encontrados que relacionaban la impulsividad de las madres con problemas de comportamiento en la descendencia, aunque como se muestra en la tabla del estudio, cuando solo se consideraban varones en la muestra de SXF no aparecían las asociaciones con la escala de impulsividad. Y en concreto en la muestra de SD las asociaciones solamente se encontraron con las medidas in situ.

En cuanto a las dos revisiones realizadas, ambas se aproximan a los problemas de comportamiento y de competencia social abarcando un largo periodo de tiempo, 20 años. Además, en lugar de realizar una búsqueda de los factores ambientales que pueden afectar a los mismos e incluirlos en la estrategia de búsqueda, se decidió buscar directamente aquellos estudios que abordaran directamente problemas de comportamiento y competencia social reportados en ambos síndromes, para de ahí extraer la información del entorno que pudiese estar relacionada con dichos problemas. Teniendo en cuenta las dificultades que presenta el término competencia social por su definición particular, se decidió incorporar todos aquellos estudios que reportaran variables relacionadas con la misma, independientemente de la etiqueta o el término utilizado por los autores de los estudios, dado que la exclusión de estudios se realizó tras la lectura de los resúmenes de los mismos.

En particular, en el caso del artículo 2 además de tratarse de una revisión sistemática y por lo tanto contar con un método definido y replicable para hallar los resultados de la revisión, cuenta con una herramienta de evaluación de los

estudios asegurando una mayor calidad metodológica en aquellos estudios revisados y por lo tanto en los resultados hallados.

Por lo que respecta al estudio 3, además de contar con la búsqueda en la base de datos que al ser más escueta puede arrojar menos estudios de los existentes, se decidió realizar una búsqueda hacia atrás para aumentar el número de estudios y asegurar la inclusión de un mayor número de estudios representativos. Esto, además hizo que no solo aquellos resultados de estudios que incorporaran el término SD en el título fueran incorporados sino que también aquellos estudios que arrojaran información sobre el SD dentro de estudios de DI fueran incorporados. A través de esta estrategia, se aumenta la representatividad de los resultados aunados en la revisión.

3.5. Futuras líneas de investigación

De acuerdo con las ideas de Karmiloff-Smith et al. (2016), existe una necesidad de dividir cada grupo de comparación en grupos más pequeños debido a las diferencias individuales que se encuentran entre las diferentes personas con SD, incluyendo factores ambientales y comorbilidades, aumentando de ese modo el control metodológico y por lo tanto pudiéndonos aproximar y precisar en mayor medida a la relación entre genotipo y fenotipo. Esta interpretación se puede extrapolar del mismo modo a los individuos con Síndrome de X Frágil haciendo necesario controlar en mayor medida tanto comorbilidades como factores ambientales para obtener unos resultados más precisos sobre su fenotipo conductual. De modo que, futuras investigaciones podrían establecer un nivel más elevado de rigor metodológico que permitiera discernir realmente el fenotipo conductual de los individuos con SXF teniendo en cuenta sus comorbilidades y aquellos factores ambientales que se ha reportado que influyen sobre los problemas de comportamiento y la competencia social de los mismos. Del mismo modo, sería interesante observar si en el caso de los individuos con SXF, dependiendo del genotipo materno hay diferencias en problemas de comportamiento y competencia social en individuos con SXF.

De acuerdo con Smith et al. (2012), la etapa de la adolescencia y la transición a la adultez son etapas en las que se han centrado pocos estudios, hasta la fecha. En el artículo 2 de la presente tesis se reporta que la mayor parte de los estudios revisados que se centran en dicha etapa son estudios de competencia social. Mientras en los estudios revisados sobre SD en el estudio 3, son menos los estudios hallados que vierten resultados en esta franja de edad en problemas de comportamiento que en competencia social. De modo que, futuras líneas de investigación podrían centrarse en dicha etapa que además posee sus peculiaridades particulares por ser una etapa de transición muy importante en el desarrollo.

Asimismo, la exploración del fenotipo comportamental de individuos con SXF y TEA comórbido en comparación con individuos con TEA puede arrojar luz sobre el debate de si los individuos con dicha comorbilidad son más similares a aquellos con TEA o a aquellos con SXF exclusivamente así como ayudar a delimitar las

implicaciones fenotípicas de la comorbilidad con el autismo en SXF. Igualmente, teniendo en cuenta la elevada comorbilidad entre individuos con SD y autismo, dicha variable debería ser controlada en los estudios sobre problemas de comportamiento y competencia social ya que la comorbilidad se ha visto que afecta a ambas variables. Por añadido, y de acuerdo con Cochran et al. (2015) los estudios futuros deben tener en cuenta el desarrollo dentro de las características autistas asociadas con los síndromes genéticos y centrarse en cómo se desarrollan a lo largo de la vida en dichos individuos tratando de alejarse de la imagen estática que proporcionan los estudios transversales.

Por lo que respecta a la competencia social, existe la necesidad de desarrollar una herramienta evaluativa que recoja de manera fiable los diferentes constructos que se agrupan bajo el término buscando utilizar un instrumento que recoja los diferentes elementos principales que puede presentar el mismo adaptado a las personas con DI, en lugar de utilizar instrumentos que recogen algunos de los componentes aislados relacionados con la misma. También, se hace fundamental que los estudios que investigan sobre variables relacionadas con el constructo competencia social, lo identifiquen para poder aunar el conocimiento teniendo en cuenta las diferentes facetas que presenta.

Finalmente, cabe señalar que pese a que se ha observado que en los individuos con SXF es común la presencia de ansiedad social, son escasos los estudios que se han encontrado tratando de relacionar dicho problema con su competencia social buscando áreas específicas en las que se puedan beneficiar de una intervención para su mejora. Por lo que respecta a individuos con SD como se señala en el estudio 3, también escasean los estudios realizados sobre la ansiedad, en este caso como comorbilidad, en individuos con SD lo cual lleva a dificultades para establecer incluso la prevalencia de la misma.

3.6. Referencias

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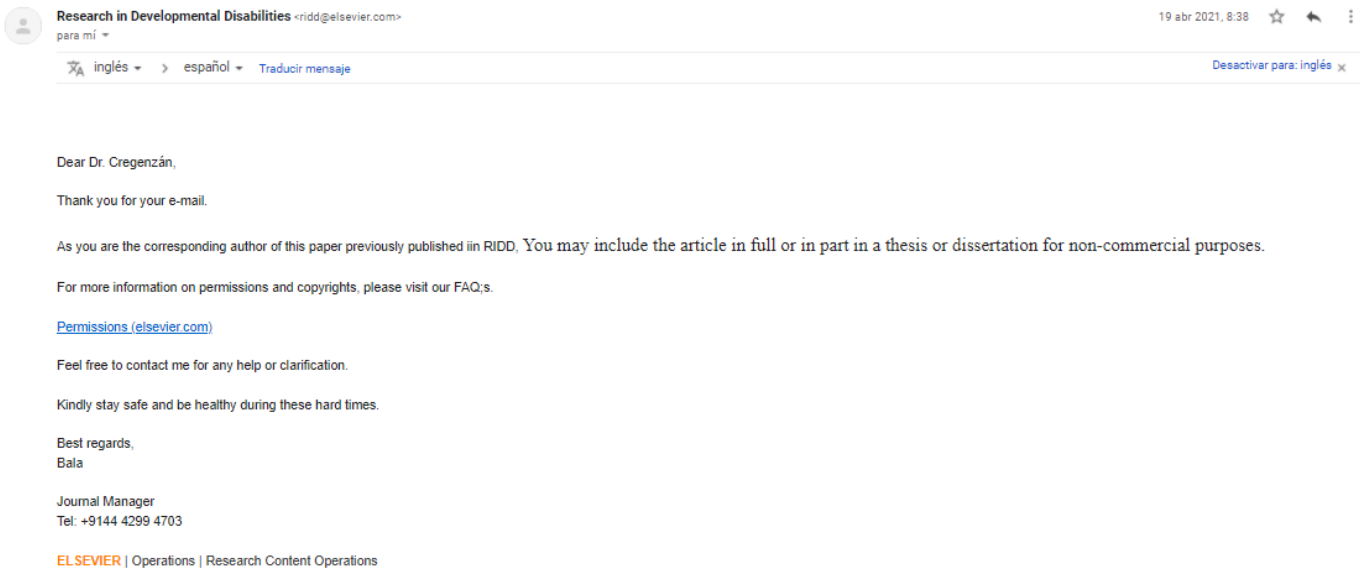

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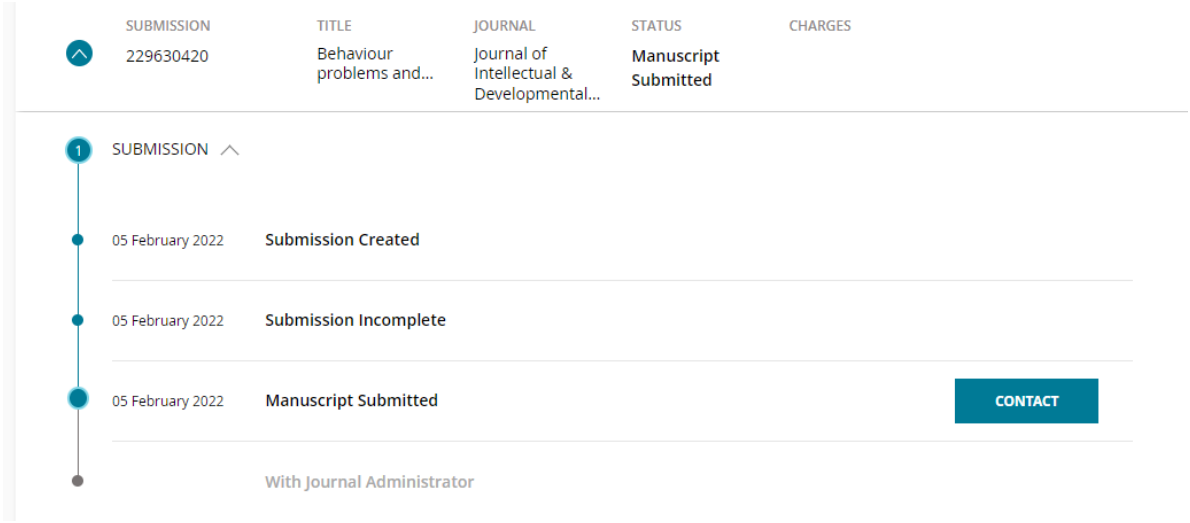

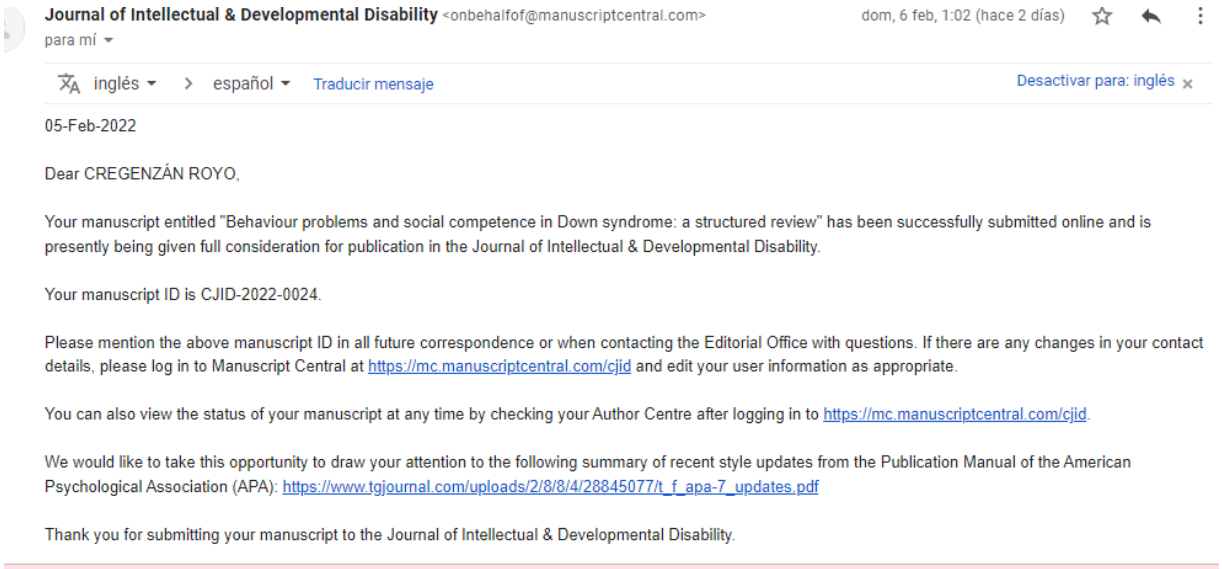

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