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**Comorbilidad del Trastorno Negativista
Desafiante y los Trastornos de Ansiedad en
Preescolares**

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Presentación

Formato de la tesis

Esta tesis se presenta como un compendio de tres trabajos empíricos originales de investigación científica que han sido realizados durante mi estancia como investigadora en la *Unitat d'Epidemiologia i de Diagnòstic en Psicopatologia del Desenvolupament* de la Universitat Autònoma de Barcelona (<http://www.ued.uab.cat>), bajo la dirección de la Dra. Lourdes Ezpeleta. Los tres trabajos versan sobre la presencia de la comorbilidad del trastorno negativista desafiante y del trastorno de ansiedad durante la edad preescolar y de sus correlatos clínicos y funcionales.

Los tres trabajos se han elaborado en formato artículo a partir de una amplia muestra de niños escolarizados a las edades 3 y 5 años procedentes de un estudio longitudinal sobre problemas de comportamiento (*PSI2009-07542*). Se han enviado a revistas indexadas en el ISI. La Tabla 1 detalla las referencias de estos artículos y el orden en el que serán referidos a lo largo de esta tesis. El primer manuscrito ya ha sido publicado, el segundo está en prensa y el tercero está enviado.

Tabla 1. Trabajos empíricos que forman la tesis.

Artículo	Referencia-estado
Trabajo 1	Martín, V., Granero, R., y Ezpeleta, L. (2014). Comorbidity between oppositional defiant disorder and anxiety disorders in preschoolers. <i>Psicothema</i> , 26(1), 27-32. doi: 10.7334/psicothema2013.75.
Trabajo 2	Martín, V., Granero, R., Domènech, J. M., y Ezpeleta, L. (2016). Factors related to the comorbidity between oppositional defiant disorder and anxiety disorders in preschool children. <i>Anxiety, Stress, & Coping</i> . (En prensa).
Trabajo 3	Martín, V., Granero, R., Domènech, J. M., y Ezpeleta, L. (2016). Executive functions in preschoolers with comorbid oppositional defiant disorder and anxiety disorders. (Enviado).

Objetivos

El trastorno negativista desafiante (TND) es una condición clínica de aparición precoz durante la primera infancia, que tiende a persistir a lo largo de la niñez y la adolescencia. Su diagnóstico se basa en la identificación clínica de un patrón recurrente de conductas de enfrentamiento, hostilidad y oposición a las normas del contexto. Es frecuente que durante el curso del TND se presenten otras comorbilidades, en especial por comportamientos disruptivos y/o de tipo disocial, y con menos frecuencia también trastornos de ansiedad (TA). Existen sin embargo pocos trabajos empíricos que estimen la frecuencia de la presencia concurrente del TND y los TA (TND+TA) durante la etapa preescolar, de los potenciales factores de riesgo de esta comorbilidad a edades tempranas y del rol que ejercen las funciones ejecutivas. Los trabajos empíricos de esta tesis abordan tres objetivos principales:

- Estimar la frecuencia de la presencia comórbida del TND+TA en niños preescolares de la población general española, de forma transversal y longitudinal entre los 3 y los 5 años, y valorar en qué grado esta condición clínica influye sobre el grado de funcionamiento cotidiano de los niños. Estos objetivos se abordan en el trabajo empírico 1.
- Explorar los principales factores de riesgo que conducen a presentar TND+TA de forma conjunta. El trabajo empírico 2 presenta un modelo predictivo con los principales factores que incrementan la probabilidad de ocurrencia de la comorbilidad.
- Analizar la alteración en las funciones ejecutivas en preescolares con comorbilidad TND+TA. El trabajo empírico 3 desarrolla y aporta evidencias empíricas que contrastan este objetivo.

Como objetivo secundario, en esta tesis se valora el potencial rol moderador del sexo de los niños en las relaciones objeto de estudio. En los trabajos empíricos 1 a 3 se incluyen interacciones para valorar este posible efecto.

Los resultados obtenidos en los tres trabajos empíricos que se presentan en esta tesis aportan evidencia empírica sobre la relevancia de la asociación entre TND+TA en la etapa preescolar, de sus variables predictoras y del grado en que esta comorbilidad afecta a la vida de los niños y de sus familias. Esta información resulta de notable ayuda para mejorar la detección precoz de esta condición comórbida y poder desarrollar programas de intervención adecuados.

1. Introducción

1.1 Relevancia de la comorbilidad TND+TA en edad preescolar

El trastorno negativista desafiante (TND) forma parte del grupo de los trastornos del comportamiento que se presentan durante la infancia y se caracteriza por conductas negativistas, desafiantes, desobedientes y hostiles, en particular dirigidas hacia las figuras de autoridad (APA; American Psychiatric Association, 2000). Este trastorno ocasiona marcadas dificultades en la relación con los padres, profesores y compañeros (Barkley, Benton, y Maughan, 2008). La prevalencia estimada en muestras infantiles difiere entre los estudios, aunque tiende a estar comprendida en países desarrollados dentro del intervalo 2% a 15% (Lahey, Miller, Gordon, y Riley, 1999; Loeber, Burke, Lahey, Winters, y Zera, 2000; Maughan, Rowe, Messer, Goodman, y Meltzer, 2004).

En el ámbito general de la salud mental, y en particular en el contexto de la psicopatología infantil, el TND ha cobrado una gran relevancia por la alta comorbilidad que suele presentar y el deterioro que ocasiona en el funcionamiento de las personas, lo cual hace especialmente importante un adecuado diagnóstico precoz (Cunningham y Ollendick, 2010). Entre los trastornos con los que se asocia con más frecuencia destacan el trastorno por déficit de atención con hiperactividad (TDAH), el trastorno de conducta (TC), el abuso de drogas, la personalidad antisocial, la depresión y los trastornos de ansiedad (TA) (Boylan, Vaillancourt, Boyle y Szatmari, 2007; Stringaris y Goodman, 2009). Puesto que el TND se ha mostrado como un potente precursor/mediador de otras formas de patología, su detección temprana resulta crucial para interrumpir la cadena de potenciales complicaciones (Burke, Loeber, Lahey, y Rathouz, 2005).

Por otro lado, los TA también se han identificado como un problema de relevancia en la infancia y la adolescencia, con prevalencias dentro del rango 15% y 20% (Beesdo, Knappe, y Pine, 2011). Estos trastornos se presentan como cuadros clínicos caracterizados por un exceso ansiedad, miedo, nerviosismo, preocupación o terror. La ansiedad demasiado constante o demasiado intensa puede hacer que una persona se sienta preocupada, distraída, tensa, siempre alerta (con numerosos síntomas fisiológicos) y conducen a la instauración de conductas de evitación persistentes que suponen un alto grado de interferencia en la vida cotidiana.

Esta tesis doctoral aporta evidencia empírica sobre la condición clínica que resulta de la asociación concurrente del TND y los TA a edades tempranas, concretamente durante la

etapa preescolar (edades 3 a 5 años). Los estudios que se han realizado han incluido una amplia muestra de niños preescolares procedentes de población general. Los estudios previos publicados en la literatura, con muestras de niños más mayores, indican que la concurrencia TND+TA presenta altos valores de prevalencia tanto en muestras de población general como en muestras clínicas (Drabick, Ollendick, y Bubier, 2010). En concreto, para niños de edad preescolar la comorbilidad TND+TA se presenta con prevalencias dentro del rango 7% al 14%, con razones de odds (OR) de entre 4.3 y 5.9 (Ezpeleta, de la Osa, y Doménech, 2014; Wichstrøm et al, 2012).

Pero a pesar de la alta prevalencia del TND+TA, de su inicio temprano y del consiguiente incremento que supone en el uso de servicios sanitarios (Keenan y Wakschlag, 2004; Sterba, Egger y Angold, 2007), la mayoría de los estudios empíricos realizados hasta el momento se centran en la presencia de esta comorbilidad durante las etapas escolar y juvenil. En muestras de niños escolarizados entre 6 y 9 años se ha observado que la ansiedad comórbida (definida como la presencia conjunta de diferentes tipos de ansiedad) puede fortalecer la asociación TND+TDAH (especialmente del tipo combinado), lo cual convierte a la ansiedad comórbida en un potente factor de riesgo del desarrollo de problemas exteriorizados (Humphreys, Aguirre y Lee, 2012). En niños de entre 8 y 12 años, los síntomas del TND “discusiones” y “molestar a otros” se han relacionado también con la presencia de síntomas de ansiedad (Polier, Vloet, Herpertz-Dahlmann, Laurens y Hodgins, 2012). Durante el rango de edad 6 a 18 años, se ha observado que los niveles más altos de ansiedad y de TND tienden a correlacionar con la presencia de síntomas de irritabilidad e ira (en comparación con aquellos que no mostraban estos síntomas) (Drabick y Gadow, 2012). Finalmente, en un estudio longitudinal con jóvenes entre 12 y 26 años se observó que los síntomas de ansiedad persistían en la edad adulta, mientras que los síntomas de negativismo tendían a estabilizarse o disminuir (Leadbeater, Thompson y Gruppuso, 2012).

Se han propuesto diferentes explicaciones para la concurrencia TND+TA. Lavigne, LeBailly, Hopkins, Gouze, y Binns (2009) señalan que, o bien los TA y la depresión están presentes en los años preescolares pero se presentan enmascarados por los síntomas de TND, o bien los problemas producidos por el TND en el rendimiento académico o el funcionamiento social pueden dar lugar posteriormente a TA y a otros posibles trastornos del estado de ánimo. También se ha propuesto que el TND se compone de distintas dimensiones (irritabilidad, oposicionismo y agresividad) (Boylan et al., 2007; Burke y Loeber, 2010; Stringaris y Goodman, 2009) que pueden facilitar la asociación con otros distintos trastornos. Estas dimensiones se han identificado en niños preescolares y a estas edades se ha encontrado

asociación entre la irritabilidad y los TA (Ezpeleta, Granero, de la Osa, Penelo y Doménech, 2012). Otras posibles explicaciones para la comorbilidad TND+TA son la precedencia temporal (un diagnóstico podría preceder al otro) (Burke et al., 2005; Lavigne et al., 2001), la existencia de factores de riesgo comunes (Bubier y Drabick, 2009) y los procesos etiológicos comunes (Drabick et al., 2010).

Aunque no existe consenso unánime en los resultados de la literatura científica, la mayoría de los estudios concluyen que la condición de TND acompañada de TA implica complicaciones académicas, sociales y familiares (Drabick, Gadow, y Loney, 2008). La investigación epidemiológica longitudinal también indica que la concurrencia TND+TA de forma temprana en la vida es un fuerte predictor de una perspectiva de secuelas psicológicas negativas durante la adolescencia y la edad adulta, como la depresión mayor, el consumo y abuso de sustancias o una incorrecta integración con los compañeros (Bubier y Drabick, 2009). Estas evidencias instan a la realización de nuevos estudios que aporten nuevos datos que ayuden a esclarecer cuáles son los mecanismos etiológicos, los procesos de riesgo y las implicaciones clínicas de esta comorbilidad en edades precoces.

1.2 Factores de riesgo de la comorbilidad TND+TA en preescolar

La concurrencia del TND+TA se ha abordado desde distintas perspectivas y modelos, entre los que destacan las mencionadas anteriormente (Bubier y Drabick, 2009; Burke et al., 2005, Lavigne et al., 2001). Las variables más comúnmente asociadas a esta comorbilidad identificadas en la infancia tardía son: alta emotividad negativa y bajo control inhibitorio, estilos concretos de crianza (por ejemplo, el rechazo) y niveles altos de psicopatología de los padres (Drabick et al., 2008; Franco, Saavedra, y Silverman, 2007; Muris, de Jong, y Engelen, 2004; Roelofs, Meesters, ter Huurne, Bamelis, y Muris, 2006).

Pero los estudios dirigidos a la identificación de variables explicativas-predictivas de la comorbilidad TND+TA en edad preescolar son escasos. Un estudio longitudinal que evaluó el temperamento de los niños de 21 meses a 6 años sugiere que un predictor común de trastornos de comportamiento perturbador y trastornos interiorizados es la presencia de desinhibición conductual (Hirshfeld-Becker et al., 2007). Otro estudio sobre los factores de riesgo infantiles asociados a trastornos interiorizados, exteriorizados, y coocurrencia de problemas de conducta, en niños de 5 meses a 5 años de edad, mostró que síntomas de ansiedad y depresión maternos, edad temprana de maternidad, y conflictos familiares, de manera independiente, predijeron problemas concurrentes tempranamente. Además, en un

contexto de crianza hostil, los niños con altos niveles de ira estaban en mayor riesgo de desarrollar coocurrencia de problemas de forma más temprana (Edwards y Hans, 2015). Estos hallazgos sugieren que el temperamento, la psicopatología de los padres y los factores de estrés pueden ser variables predictoras de TND+TA en niños en edad preescolar.

La psicopatología de los padres juega un papel importante en el desarrollo de los niños. Los síntomas de psicopatología materna se asocian con problemas exteriorizados, problemas interiorizados, y problemas sociales en preescolares y los síntomas de psicopatología paternos se asocian con problemas interiorizados a los 3 y 6 años de edad (Breux, Harvey, y Lugo-Candelas, 2014). Numerosos estudios han demostrado que la psicopatología en los padres se asocia con problemas emocionales y de comportamiento en los niños (Beardslee, Gladstone, y O'Connor, 2011; Phares y Compas, 1992). Los hijos de padres con psicopatología muestran problemas de conflicto en la relación progenitor-hijo y niveles elevados de trastornos exteriorizados similares a los niños de madres con psicopatología (Weitzman, Rosenthal, y Liu, 2011).

El temperamento del niño, las relaciones entre progenitores-hijos, los sesgos en el procesamiento de la información social, o la exposición a la violencia del vecindario, según la literatura existente, pueden ser factores de riesgo para la coocurrencia de TND+TA precoz (Drabick, Ollendick, y Bubier, 2010). Así, Bubier y Drabick (2009) han sugerido que el estilo temperamental difícil, la tendencia a percibir las situaciones como amenazantes y hacer atribuciones hostiles, y el aumento de la activación autonómica en situaciones sociales estresantes pueden contribuir a agravar los síntomas de ansiedad y de agresión reactiva y, consecuentemente, conducen a la identificación clínica de ansiedad comórbida con trastornos del comportamiento disruptivo en niños. Podrían existir tres procesos comunes en la aparición de esta comorbilidad (Fraire y Ollendick, 2013): a) el proceso de disregulación emocional, que puede abarcar dificultades en la regulación de la excitación emocional, bajo control autorregulado y dificultades con el manejo de la ira y la ansiedad; b) el déficit en el procesamiento de la información en problemas interiorizados y exteriorizados, lo que puede dar lugar a la interpretación de situaciones ambiguas como situaciones amenazantes; y c) el control psicológico parental excesivo y una pobre expresividad emocional parental.

Otros autores presentan una hipótesis alternativa que establece que la ansiedad afecta a los síntomas de TND mediante dos vías (Drabick et al., 2010): 1) los síntomas de TA pueden mitigar los síntomas de TND; y 2) los síntomas de TA pueden agravar los síntomas de TND. En referencia a la primera vía, un niño con TND y ansiedad social, por ejemplo, puede mostrar una mayor sensibilidad a las recompensas sociales y castigos sociales que, a su vez,

pueden reducir el comportamiento disruptivo. Y de acuerdo con la segunda vía, la ansiedad y el TND de forma conjunta aumentarían la probabilidad de interpretar erróneamente las situaciones sociales, y a la vez, aumentarían la aparición de conflictos episódicos, ya que las situaciones se verían alteradas por un sesgo negativo.

Cabe también destacar los estudios que proponen la secuencia temporal de los trastornos que conforman la comorbilidad TND+TA, esto es, la posibilidad de que un trastorno preceda y constituya un riesgo para la emergencia del otro (Bufferd, Dougherty, Carlson, Rose, y Klein, 2012). Bubier y Drabick (2009) sugieren que la presencia de TND en la primera infancia puede conferir de manera más probable riesgo de presentar trastornos de ansiedad. De este modo, el temperamento difícil de los niños con TND podría dificultar el desarrollo de estrategias de resolución de conflictos y por lo tanto incrementar la dificultad para enfrentarse a situaciones sociales, lo cual generaría una sensación recurrente de falta de control y un incremento del riesgo de manifestar reacciones ansiosas. Siguiendo esta línea de argumentación, lo opuesto también podría ser plausible: los síntomas de ansiedad podrían aumentar el riesgo para padecer trastornos exteriorizados, y que con el fin de evitar los contextos percibidos como temerosos, los niños con síntomas de ansiedad pudieran llegar a mostrarse inconformistas y agresivos (por ejemplo, cuando un niño con ansiedad se está acercando a la adolescencia, la perturbación emocional constante y frecuente que experimenta durante esta etapa puede conducir a problemas exteriorizados, particularmente a TND).

La vía dual también encuentra apoyo empírico en una revisión reciente de Drabick et al. (2010), quienes sintetizando los datos empíricos sobre la concurrencia TND+TA concluyeron de que ambas hipótesis duales que caracterizan las relaciones entre TND y TA pueden coexistir: la hipótesis amortiguadora (ansiedad acciona la mitigación o disminución de los niveles de TND) y la hipótesis de multiplicidad de problemas (la presencia de ansiedad agrava o aumenta comportamientos TND). De hecho, en un estudio previo Walker et al. (1991) presentaron datos que apoyan el modelo de amortiguación en una muestra de niños de 7 a 12 años, en los que los trastornos disruptivos combinados, además de TA mostraron menor deterioro social que el trastorno disruptivo solo. Más tarde, Lansford et al. (2008) observaron que la presencia de la conducta disruptiva comórbida junto con la adición de condiciones internalizadas en participantes de 12 a 22 años se asoció con aumentos abruptos en el consumo de sustancias ilícitas en la adolescencia conforme transcurría el tiempo.

Pero las hipótesis explicativas basadas en la secuencia temporal y las hipótesis duales pueden no disponer de evidencia empírica suficiente. Un reciente estudio que valoró en qué grado el nivel en que se presentan las distintas dimensiones del TND en preescolares y de su

potencial continuidad heterotípica con sintomatología de ansiedad evidenció que el factor de comportamiento TND y el factor de afecto negativo TND no mejora la capacidad predictiva de los niveles iniciales de ansiedad de forma longitudinal prospectiva (Lavigne, Gouze, Bryant, y Hopkins, 2014). Por lo tanto, se requiere evidencia adicional para determinar en qué grado estos modelos son plausibles, en particular en muestras de preescolares.

1.3 Funciones ejecutivas en preescolares con TND+TA

Las funciones ejecutivas (FEs) constituyen habilidades cognitivas complejas autodirigidas internamente al servicio de una meta, que resultan indispensables para lograr un objetivo específico de una manera flexible (Chan, Shum, Toulopoulou y Chen, 2008). Las FEs son responsables de dirigir nuestra conducta (autorregulación), así como también nuestra actividad cognitiva y emocional. Este tipo de funciones implican la coordinación de varios subprocesos necesarios para resolver problemas nuevos, gestionar el tiempo y la atención, planificar y organizar, recordar detalles, integrar la experiencia pasada con las acciones presentes, cambiar de enfoque y modificar el comportamiento basado en la nueva información (Funahashi, 2001). Anatómicamente, los estudios con neuroimagen sitúan a las FEs en el lóbulo prefrontal cerebral, de manera que cuando esta área se ve alterada o dañada el control del comportamiento es pobre.

Las FEs son generalmente consideradas como innatas (aunque los niños no nacen con estas habilidades, nacen con el potencial para desarrollarlas). La maduración del cerebro y la interacción con el medio ambiente facilitan el desarrollo de las FEs pero son relativamente estables desde la niñez temprana en los primeros años escolares (Kochanska y Knaack, 2003). La investigación neuropsicológica indica que las FEs son cruciales para el funcionamiento neuropsicológico global del desarrollo de los niños, y juegan un papel importante en su cognición, desarrollo conductual y social-emocional (Isquith, Crawford, Espy, y Gioia, 2005). Los niños con impedimentos en la FEs suelen presentar dificultades en: anticipación, selección objetiva, iniciación de la actividad, autorregulación, flexibilidad mental, despliegue de la atención y utilización de la retroalimentación (Anderson, 2002). Algunos estudios han demostrado que las FEs inadecuadas se relacionan en edades tempranas a tomas de decisiones incorrectas, desinhibición conductual, peores habilidades intelectuales, y mayor vulnerabilidad a la aparición y desarrollo de diversos trastornos físicos/psicológicos (Muris y Ollendick, 2005). En consecuencia, es importante identificar los déficits en las FEs tan pronto como sea posible con el fin de intervenir y minimizar sus efectos sobre la psicopatología y el

funcionamiento diario (rendimiento escolar, emocional, conductual y problemas sociales) (Anderson y Reidy, 2012).

Muchos estudios sobre las FEs en los niños de edad preescolar que presentan conductas disruptivas han incluido muestras con condiciones heterogéneas, y esto limita el conocimiento sobre el proceso subyacente específico del TND (Thorell y Wahlstedt, 2006). En esta línea, Raaijmakers et al. (2008) encontraron que los niños preescolares con problemas de conducta (comportamiento específicamente agresivo) mostraron alteraciones en la inhibición, independientemente de los problemas de atención. Drabick et al. (2008), en un estudio relacionado de manera más específica con la presencia de TND, informaron que las personas que presentan este trastorno mostraron déficits en algunos dominios de las FEs, específicamente en: atención, concentración, planificación e inhibición. Blair (2007) también concluyó que los problemas con las FEs en la primera infancia podrían conducir a dificultades en la representación de las expectativas de refuerzo, que son cruciales para la inhibición de las respuestas agresivas y negativistas observadas posteriormente en los jóvenes con diagnóstico de TND.

La investigación sobre la etiología de los TA también sugiere que la disfunción en las FEs puede ser la base de la hipervigilancia, la atención a una amenaza-relativa a estímulos y respuestas autonómicas observadas en personas con síntomas de ansiedad (Guyer et al., 2008), que perciben erróneamente estímulos neutros o ambiguos como amenazantes. La investigación con muestras de jóvenes ha demostrado que las FEs caracterizadas por bajos niveles de aprendizaje verbal y déficits en la memoria de trabajo están relacionadas con fobia social (Asmundson, Stein, Larsen, y Walker, 1994), y que la memoria de trabajo pobre parece ser un factor subyacente en TA (Kushnir y Sadeh, 2010). En edad preescolar, una buena capacidad para cambiar la atención se asoció con bajo riesgo de síntomas de ansiedad, mientras que un buen control inhibitorio aumentó el riesgo para presentar ansiedad (White, McDermott, Degnan, Henderson, y Fox, 2011).

Las FEs pueden aumentar o disminuir la probabilidad de comorbilidad TND+TA (Fraire y Ollendick, 2013), incluso en edades tempranas. Aunque la evidencia de la investigación en esta área es escasa, algunos estudios sugieren explicaciones plausibles. Coy, Speltz, DeKlyen y Jones (2001) observaron que los preescolares que presentan TND pueden generar soluciones más agresivas y codifican la información social con menos precisión que los niños del grupo control, y llegaron a la conclusión de que TA y TND están relacionados con sesgos comparables en múltiples etapas del procesamiento de la información, incluyendo hipervigilancia, interpretaciones negativas de situaciones sociales y atribuciones hostiles.

Reid, Salmon y Lovibond (2006), en una línea similar de investigación, concluyeron que los sesgos en el procesamiento de la información social en la infancia pueden ser la base de esta comorbilidad, ya que estos procesos constituyen la base común de las respuestas emocionalmente reactivas de agresión y ansiedad. En resumen, en la edad preescolar, el deterioro en los cambios de atención y el control inhibitorio parecen moderar la relación entre los síntomas de ansiedad y los problemas de conducta, lo que aumenta las probabilidades de presentar estas condiciones comórbidas (Asmundson, et al., 1994). En esta línea de investigación, Zelazo et al. (2003) propusieron un modelo desde un punto de vista funcional para las FEs compuestas de diferentes secuencias de representación-ejecución encaminadas a lograr una meta. Cada secuencia requeriría la capacidad del niño para generar e implementar sistemas de reglas condicionales que rigen el comportamiento, la cognición y las emociones. Las FEs estarían involucrados en las diversas etapas de esta secuencia dirigida a la resolución de problemas, pero los niños con comorbilidad TND+TA tendrían sesgos en el procesamiento de la información para gestionar con éxito el primer paso en la secuencia de las FEs (representación del problema) que darían lugar a errores sistemáticos.

En síntesis, estudios etiológicos y de factores de riesgo han encontrado una asociación entre la fisiopatología del TND y de los TA con disfunciones en el sistema límbico y la corteza pre-frontal (Blair, 2007; Crowe y Blair, 2008). Dado que estas áreas están involucradas en las FEs relacionadas con el procesamiento de las emociones, crucial para la expresión de ambos trastornos (estímulo de refuerzo/estímulo-respuesta del aprendizaje, reconocimiento y procesamiento del significado emocional de los estímulos sensoriales y sociales, planificación la modulación de la respuesta), cabría esperar que las FEs jugarán un rol importante en el origen y la evolución de ambos trastornos (TND y TA), incluso a edades tempranas.

1.4 Rol del sexo para la comorbilidad TND+TA en preescolar

Algunos estudios han hallado que las asociaciones entre TND y TA están moderadas por el sexo. Costello, Mustillo, Erkanli, Keeler y Angold (2003) encontraron que la comorbilidad concurrente heterotípica era más marcada en niñas pero otros autores no han hallado esa interacción (Munkvold y Lundervold, 2011).

Por otro lado, parece que el sexo puede interactuar con las variables potencialmente asociadas con los trastornos interiorizados y exteriorizados, teniendo un efecto diferente en función de si se trata de un sexo u otro. Los hallazgos sugieren que los niños (varones) que se

caracterizan por tener niveles altos de actividad y niveles bajos de miedo en la infancia tienen más síntomas de trastornos exteriorizados y de trastornos interiorizados, mientras que los niños con niveles bajos de actividad y niveles altos de miedo, muestran más síntomas interiorizados (Colder, Mott, y Berman, 2002). Por lo tanto, es importante que al examinar las variables asociadas a la comorbilidad TND+TA, se consideren las vías específicas que tiene el sexo de los niños.

La literatura revela un potencial efecto moderador del sexo de los niños (preescolares y jóvenes) en la expresión de las FE: las niñas presentan niveles más altos de funcionamiento en comparación con los niños en el mismo rango de edad. Se ha informado de que las niñas de edades comprendidas entre 3 y 13 años mostraron mejores puntuaciones clínicas que sus pares masculinos en diversas dimensiones del manejo de la atención (Else-Quest, Hyde, Goldsmith, y Van Hulle, 2006). Duckworth y Seligman (2006) también observaron en un estudio longitudinal que las adolescentes mostraron más autocontrol que sus homólogos masculinos. Estas diferencias en el nivel de autocontrol en función del sexo podrían estar relacionadas con la posterior psicopatología presentada (por ejemplo, niveles más altos de problemas disruptivos en niños y niveles más altos de TA en niñas).

Además, maestros del jardín de infancia han confirmado que las niñas, en comparación con los niños, tienen mejor rendimiento en memoria de trabajo, atención y control inhibitorio (Matthews, Ponitz, y Morrison, 2009), y los niños en edad preescolar presentan más deterioro en atención-cambio, inhibición, memoria de trabajo y fluidez verbal que las niñas de la misma edad (Raaijmakers et al., 2008). Un estudio longitudinal que abarca el período comprendido entre edades de 1 a 3 años, encontró que el auto-control del comportamiento fue mejor en las niñas (Kochanska, Murray, y Harlan, 2000), mientras que también se informó de que las niñas preescolares mostraron mejor autorregulación cognitiva (Vallotton y Ayoub, 2011).

1.5 Planteamiento de objetivos e hipótesis empíricas

El estudio de la asociación de trastornos exteriorizados e interiorizados a edades tempranas constituye un tema de gran relevancia clínica, tanto por las dificultades que plantea su explicación, como por las consecuencias a corto y largo plazo que pueden llegar a suponer. Aunque se dispone de bibliografía epidemiológica sobre la frecuencia de distintos trastornos

de forma individual, pocos estudios han evaluado la concurrencia de distintas condiciones diagnósticas en niños preescolares. El objeto de este trabajo es contribuir al conocimiento empírico-científico de la presencia conjunta de TND+TA en niños durante la etapa preescolar.

En los siguientes puntos se listan los objetivos específicos de los tres trabajos empíricos que conforman este compendio.

1.5.1 Trabajo empírico 1

Objetivos

- Estimar la presencia de comorbilidad TND+TA de forma transversal y longitudinal en niños preescolares de población general española y el grado en que dicha condición clínica afecta la funcionalidad de los niños.
- Examinar el rol del sexo y del nivel socioeconómico en la presencia del TND+TA en preescolar.

Hipótesis empíricas. Dado el carácter básico exploratorio de la investigación, no se formularon.

1.5.2 Trabajo empírico 2

Objetivos

- Examinar los principales factores de riesgo para la comorbilidad TND+TA en edad preescolar, entre los que se incluyen rasgos de temperamento, comportamiento agresivo, estilo educativo parental y psicopatología parental.
- Examinar el rol del género como variable de interacción para la identificación de los factores de riesgo del TND+TA en preescolares.
- Valorar la estabilidad temporal de la comorbilidad TND+TA durante la etapa preescolar.

Hipótesis empíricas. La probabilidad de TND+TA será mayor para niños con problemas relacionados con afecto negativo, dificultad en autocontrol y agresividad. Esta comorbilidad también se consideró que podría incrementarse en niños que vivieran en familias cuyos padres presentaran mayor nivel de psicopatología, y con estilos parentales caracterizados por niveles bajos de positividad y niveles elevados de control.

1.5.3 Trabajo empírico 3

Objetivos

- Explorar la alteración en las FEs en niños preescolares que presentan comorbilidad TND+TA en edad preescolar. Concretamente, comparar cuatro grupos diagnósticos: preescolares que presentan de forma concurrente TND+TA, preescolares que presentan únicamente TND, preescolares con únicamente TA y preescolares que no presentan TND ni TA.
- Examinar el potencial rol del sexo de los niños en la relación entre el grupo diagnóstico y las FEs en preescolar.

Hipótesis empíricas. La presencia comórbida del TND+TA se asociará con un mayor déficit en FEs, y esta relación será más intensa en niños que en niñas.

2. Método

2.1 Participantes

Los datos de esta tesis forman parte de un proyecto longitudinal sobre los factores de vulnerabilidad a la psicopatología en edad preescolar (PSI2009-07542). El diseño de recogida de datos se efectuó mediante un diseño en doble fase (Ezpeleta, de la Osa, y Doménech, 2014), ilustrado en la Figura 1.

En la primera fase se efectuó una selección aleatoria de entre todos los niños que formaban parte del censo de niños escolarizados en P3 en la ciudad de Barcelona. Un total de 2283 familias, fueron invitadas a participar, siendo 1341 familias las que aceptaron la invitación. Sesenta y tres niños en edad preescolar fueron excluidos debido a problemas de lenguaje o problemas generales de desarrollo, y los restantes 1278 fueron seleccionados utilizando la escala de problemas de comportamiento de *Strengths and Difficulties Questionnaire for parents of 3- to 4-year-olds* (SDQ3-4; Goodman, 1997), además de cuatro síntomas TND (molesta deliberadamente a otras personas, acusa a otros de sus errores o mal comportamiento, es susceptible, colérico y resentido) del Manual Diagnóstico y Estadístico de los Trastornos Mentales (DSM-IV-TR; APA, 2000) que no están presentes en el cuestionario. El cribado se considera positivo para aquellas puntuaciones ≥ 4 en la escala de los problemas de conducta SDQ3-4, o una opción de respuesta de 2 ('cierto') para cualquiera de los 8 síntomas DSM-IV-TR de TND. Se invitó a participar a todos aquellos niños que puntuaron por encima del punto de corte fijado para identificar posibles casos de problemas conductuales y a un 30% de los que puntuaban por debajo ($n=756$). Para los análisis se realizó una ponderación para corregir la sobrerrepresentación de los niños con altas puntuaciones en síntomas de TND.

La segunda fase incluyó un total de 622 niños, de los cuales 417 procedían de la cohorte con cribado positivo y los restantes 205 del cribado de negativos.

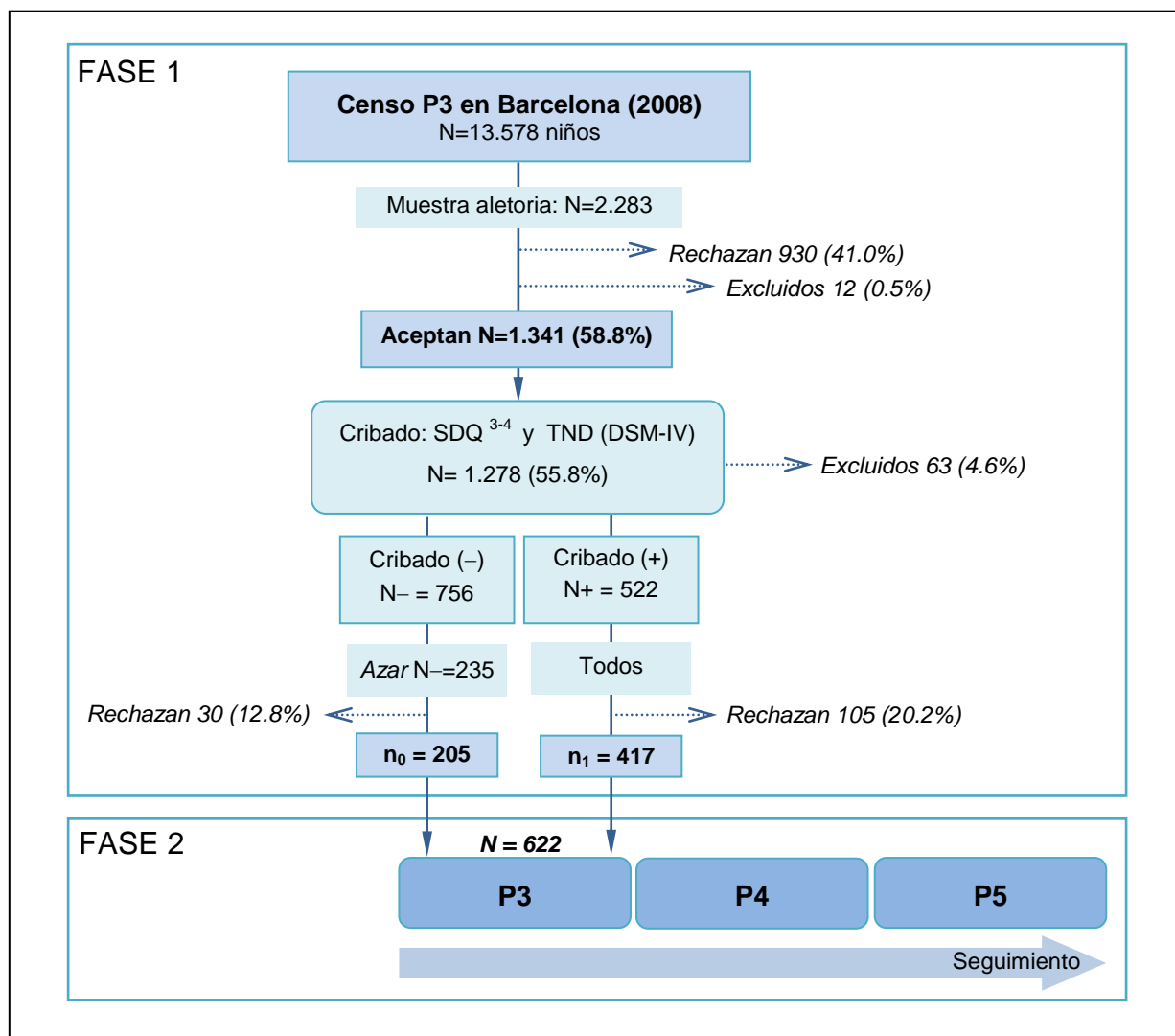


Figura 1. Diseño del proyecto (publicada en Ezpeleta et al., 2014).

2.1.1 Trabajo empírico 1

Los datos analizados en este primer trabajo corresponden a las evaluaciones realizadas a los 3 y a los 5 años de edad. La Tabla 2 presenta los principales descriptivos en la línea base y la prevalencia de los principales grupos diagnósticos identificados en ambas evaluaciones.

2.1.2 Trabajo empírico 2

Para el segundo trabajo, de la muestra inicial total de 622 niños, a los 3 años de edad se seleccionaron $n=103$ participantes: los que tenían únicamente TND ($n=44$, el 35.7% masculino), únicamente TA ($n=42$) o comorbilidad TND+TA ($n=17$). La distribución por sexo fue de 50 niñas (48.5%) y 53 niños (51.5%). El nivel socioeconómico (SES; Hollingshead, 1975) se distribuía de la siguiente manera: 52 niños con nivel alto o medio-alto (50.4%), 19 con nivel medio (18.4%) y 32 con nivel medio-bajo o bajo (31.0%).

A la edad de 5 años, se disponía de datos de $n=537$ niños que iniciaron el seguimiento. De esta muestra, $n=106$ niños fueron seleccionados debido a la presencia de únicamente TND ($n=31$), únicamente TA ($n=60$) o comorbilidad TND+TA ($n=15$). No surgieron diferencias significativas en la distribución por sexo ($p=.284$) y SES ($p=.258$) al comparar los grupos diagnósticos.

Tabla 2. Descriptivos de la muestra ($n=622$).

Sociodemográficos		Línea base		Diagnósticos DSM-IV		3 años		5 años	
Sexo (masculino)		310	49.8%	Trastornos disruptivos		87	10.0%	67	9.6%
SES	Alto	205	33.0%	Tr déficit-atención-hiperact.		33	3.6%	30	4.2%
	Medio-alto	195	31.4%	Tr negativismo desafiante		61	6.9%	46	6.6%
	Medio	88	14.1%	Tr disocial		10	1.4%	5	0.5%
	Medio-Bajo	99	15.9%	Trastornos de ansiedad		59	7.7%	75	11.7%
	Bajo	35	5.6%	Depresión mayor		4	0.4%	3	0.3%

2.1.3 Trabajo empírico 3

La muestra inicial de 622 participantes fue clasificada en cinco grupos de acuerdo con su diagnóstico: sin diagnóstico ($n=380$; incluyó los niños sin trastornos disruptivos: TDAH, TND, TC, y sin trastornos de ansiedad: ansiedad de separación, ansiedad generalizada, fobia específica y fobia social); otros trastornos, al menos un trastorno diagnosticado diferente de TND y TA ($n=140$; incluyó niños con TDAH o TC); TND sin TA ($n=44$; niños que presentaban los criterios del DSM-IV para el TND, pero no para TA, y que podrían - o no - presentar otras condiciones comórbidas diferentes), TA sin TND ($n=41$; niños con los criterios del DSM-IV para TA pero no para TND, y que podrían presentar (o no) el resto de condiciones comórbidas), y TND+TA ($n=17$; niños que presentaron criterios del DSM-IV tanto para TND como TA, y que podrían también presentar otras condiciones comórbidas diferentes). Los grupos de niños sin diagnóstico, con TDAH o TC se denominarán en adelante como grupos de control. Además, para simplificar, se etiquetarán los grupos como: sin trastorno, otros (trastorno diferente a TND y/o TA), únicamente TND, únicamente TA y TND+TA. La Tabla 3 muestra los descriptivos en la línea base.

A los 5 años, se disponía de datos para $n=574$ de los niños que comenzaron la fase de seguimiento, y la distribución fue la siguiente: sin diagnóstico ($n=347$), al menos un diagnóstico ($n=127$), únicamente TND ($n=35$), únicamente TA ($n=54$), y TND+TA ($n=11$). No se encontraron diferencias estadísticamente significativas para los participantes que abandonaron a los 5 años atribuibles al SES ($p=.07$) o a sexo ($p=.29$).

Tabla 3. Descriptivos de la muestra del trabajo empírico 3 en la línea base ($n=622$).

		Sin trastorno $n=380$	Otros $n=140$	TND sin TA $n=44$	TA sin TND $n=41$	TND+TA $n=17$
Sexo	<i>Femenino</i>	181 47.6%	81 57.9%	20 45.5%	22 53.7%	8 47.1%
Nacido en España	<i>Sí</i>	369 97.6%	135 96.4%	41 93.2%	38 95.0%	17 100%
Etnia	<i>Caucásica-Europa</i>	341 89.7%	126 90.0%	38 86.4%	36 87.8%	13 76.5%
SES	<i>Alto + medio-alto</i>	269 70.8%	82 58.6%	22 50.0%	19 46.3%	8 47.1%
	<i>Medio</i>	50 13.2%	19 13.6%	8 18.2%	6 14.6%	5 29.4%
	<i>Medio-bajo + bajo</i>	61 16.1%	39 27.9%	14 31.8%	16 39.0%	4 23.5%

2.2 Instrumentos

Los instrumentos de evaluación utilizados en los 3 trabajos empíricos que conforman la tesis forman parte de la batería epidemiológica informatizada de la *Unitat d'Epidemiologia i de Diagnòstic en Psicopatologia del Desenvolupament*.

2.2.1 Psicopatología y funcionamiento

Diagnostic Interview for Children and Adolescents for Parents of Preschool and Young Children (DICA-PPYC; Reich y Ezpeleta, 2009) es una entrevista semiestructurada adaptada a la población española (Ezpeleta, de la Osa, Granero, Doménech, y Reich, 2011), y está diseñada para evaluar los trastornos mentales siguiendo los criterios diagnósticos del DSM-IV en niños de 3-7 años. En este estudio, TA incluyó ansiedad de separación, trastorno de ansiedad generalizada, fobia específica y fobia social. El tiempo de administración promedio es de aproximadamente 50 minutos. La entrevista se utilizó para la formación de los grupos diagnósticos, y se administró a los 3 y 5 años de edad.

Preschool and Early Childhood Functioning Assessment Scale (PECFAS; Hodges, 1999) evalúa el deterioro funcional de los niños de 3 a 7 años de edad, tras la evaluación clínica (tiempo de administración: 10-15 minutos). Incluye siete áreas (escuela, hogar, comunidad, comportamiento hacia los demás, humor-emociones, humor-autolisis y cognición-comunicación) y cada área incluye varios ejemplos de deterioro en el funcionamiento. Cada escala se califica en cuatro niveles de deterioro (0 = no hay deterioro o es mínimo; 10 = leve malestar; 20 = moderado, y 30 = grave). La puntuación total (medida global de deterioro funcional) se define como la suma de las puntuaciones en las siete escalas individuales (rango: de 0 a 210). Las propiedades psicométricas del PECFAS son apropiadas y se han descrito en Murphy et al. (1999).

Strengths and Difficulties Questionnaire (SDQ; Goodman, 2001), cribado de 25 ítems para identificar niños con alto riesgo de comportamiento disruptivo. Se estructura en cinco dimensiones: síntomas emocionales, problemas de conducta, hiperactividad, relación con los compañeros y conducta prosocial. Incluye una puntuación total que se genera como la suma directa de las cuatro escalas primarias. En este estudio, se empleó la versión contestada por los padres.

2.2.2 Factores de riesgo

Protocolo de Factores de Riesgo (PFR; Unitat d'Epidemiologia i de Diagnòstic en Psicopatologia del Desenvolupament, 2009) es una entrevista que contiene un listado de situaciones que pueden tener un impacto significativo en el desarrollo de los trastornos mentales. Se analizó el número de eventos estresantes vitales.

Children's Behavior Questionnaire for 3–7 years (CBQ3-7; Rothbart, Ahadi, Hershey, y Fisher, 2001) evalúa el temperamento reactivo y de autorregulación mediante 94 ítems con escala Likert (de 1= *Completamente falsa* a 7 = *Completamente verdadera*) organizados en 15 escalas de primer orden, que también hace que sea posible obtener 3 dimensiones de temperamento de segundo orden: afectividad negativa, extraversión y control autorregulado. La información contenida en este instrumento fue proporcionada por los padres (8.0%), madres (62.8%) o ambos (29.3%). Las propiedades psicométricas de este instrumento son adecuadas (de la Osa, Granero, Penelo, Doménech, y Ezpeleta, 2014).

Alabama Parenting Questionnaire (APQ; Frick, 1991) evalúa los diferentes estilos educativos parentales. Utilizamos el APQ-Pr (de la Osa, et al., 2014), una adaptación a la edad preescolar, que consta de 42 ítems que son calificados en una escala Likert (de 1 = *Nunca* a 5 = *Siempre*). El instrumento evalúa cinco escalas: de participación, de estilo crianza positiva, castigo corporal, disciplina inconsistente y supervisión deficiente. Este estudio agrega dos escalas: normas y autonomía (Meunier y Roskam, 2009). Las propiedades psicométricas de este instrumento son apropiadas (de la Osa et al., 2014).

Children's Aggression Scale (CAS; Halperin y McKay, 2008) evalúa el comportamiento agresivo mediante 22 ítems con escala Likert (de 0 = *Nunca* a 4 = la mayoría de los días). Para los análisis se utilizaron las escalas agresión verbal, agresión física y agresión total (compuesta por las dos anteriores). El cuestionario fue contestado por los profesores cuando los niños tenían 3 años de edad. La escala en su conjunto tiene una excelente fiabilidad (Halperin, McKay, Grayson, y Newcorn, 2003).

Adult Self-Report (ASR; Achenbach y Rescorla, 2003) se administró para evaluar los problemas psicológicos y el funcionamiento psicosocial de los padres y consta de 2 partes: funcionamiento adaptativo y síndrome. Se utilizaron las puntuaciones de 5 escalas de funcionamiento adaptativo (amigos, pareja, familia, trabajo y educación), 8 escalas del síndrome con 126 ítems (ansiedad-depresión, retraimiento, quejas somáticas, problemas del pensamiento, problemas de atención, conducta agresiva, conducta de violar normas e intrusividad) y 3 preguntas de uso de sustancias (tabaco, alcohol y drogas). En este estudio se

analizaron las respuestas de los padres y de las madres. El ASR es ampliamente utilizado y tiene buenas propiedades psicométricas (Achenbach y Rescorla, 2003).

Kaufman Brief Intelligence Test (K-Bit; Kaufman y Kaufman, 2000) se utilizó como medida del nivel intelectual de los niños. Se aplicó cuando los niños tenían 4 años. Consiste en una breve prueba diseñada para personas de edades comprendidas entre 4 y 90 años. Se emplearon dos escalas en el tercer trabajo: Vocabulario (verbal) y Matrices (no verbal). La puntuación global se obtuvo promediando las puntuaciones de Vocabulario y Matrices, y fue considerada una covariable en el trabajo.

2.2.3 Funciones ejecutivas

Behavior Rating Inventory of Executive Function preschool version (BRIEF-P; Gioia, Espy y Isquith, 2003) mide las FEs en niños de 2-5 años. Los profesores completaron el cuestionario cuando los niños tenían 3 años de edad. La escala incluye 63 ítems recodificados en una escala de 3 puntos (de menor a mayor frecuencia; a mayor frecuencia, mayor es la disfunción ejecutiva) y estructurada en 5 dimensiones de primer orden: Inhibición, Control emocional, Cambio, Memoria de trabajo y Plan-Organización, y 3 dimensiones de segundo orden: Índice de Auto-Control Inhibitorio (ISCI, que incluye Inhibición y Cambio), Índice de Flexibilidad (FI, que es la suma de Cambio y Control Emocional) e Índice de Metacognición Emergente (EMI, añadiendo Memoria de Trabajo y Planificar-Organizar). La puntuación de la Composición Global Ejecutiva (GEC) indica el rendimiento ejecutivo general (Ezpeleta, Granero, Penelo, de la Osa, y Doménech, 2015).

2.3 Procedimiento

El proyecto del cual proceden los datos fue aprobado por el Comité de Ética de la Universidad Autónoma de Barcelona. La investigación fue explicada con detalle a directores y directoras de las escuelas participantes, y se les solicitó su colaboración.

Una vez obtenido el consentimiento de la escuela, se invitó a participar a todas las familias con niños escolarizados en P3 y se les pidió un consentimiento por escrito en caso de aceptar. Entrevistadores ampliamente entrenados para utilizar la DICA-PPYC entrevistaron a los padres en las escuelas. Los cuestionarios fueron contestados por los padres (en la escuela o en su propio domicilio) y por los profesores de los niños participantes.

2.4 Análisis estadístico

Se realizó con el programa SPSS20 para Windows. Debido al diseño multifase, se utilizó el módulo de muestras complejas (*Complex Samples*), asignando a cada participante un peso de ponderación igual a la probabilidad inversa de selección en la segunda fase de muestreo (después del cribado). A continuación se listan los procedimientos estadísticos empleados en los tres trabajos empíricos de esta tesis. Todos los análisis fueron ajustados a la covariable *presencia de otros trastornos diferentes de TND y TA*.

Trabajo empírico 1

- Regresión logística binaria. Se empleó para: a) estimar la comorbilidad TND+TA (transversal y longitudinal), con coeficientes OR; b) medir la capacidad discriminativa específica de cada síntoma TND para identificar la presencia de trastornos de ansiedad, entrando la lista los síntomas TND simultáneamente en el mismo bloque (método ENTER); y c) valorar la asociación entre el deterioro funcional (definido como un resultado binario: 0=no deterioro y 1=de leve a alto) y el grupo diagnóstico.
- Modelo Lineal General (GLM). Permitió valorar la asociación entre la puntuación total del PECFAS (medida de deterioro global) y el subtipo diagnóstico.
- Correlación de Pearson. Para estimar la asociación entre los síntomas de TND y TA.
- Modelos de regresión multinomial. Permitieron conocer la asociación entre sexo y SES con el perfil/grupo diagnóstico.

Trabajo empírico 2

- Regresión multinomial. Se empleó para valorar el mejor modelo predictivo del subtipo diagnóstico. Este modelado incluyó el parámetro de interacción sexo×variables asociadas para valorar el potencial papel de moderación del género.

Trabajo empírico 3

- Análisis de la variancia (ANOVA). Se utilizó para comparar las puntuaciones del BRIEF-P entre los distintos grupos diagnósticos del estudio, ajustados por las covariables sexo y coeficiente intelectual del niño, y SES familiar. Estos modelos incluyeron el parámetro de interacción grupo×sexo, para valorar el potencial rol de moderación del sexo.

3. Resultados

Los siguientes apartados listan las principales evidencias empíricas obtenidas en los tres trabajos empíricos. Se incluye una tabla para cada trabajo con la selección de los resultados más relevantes.

3.1 Trabajo empírico 1

- Se ha identificado comorbilidad concurrente y longitudinal para la presencia de los diagnósticos DSM-IV de TND+TA en edad preescolar. La OR a la edad de 3 años fue de 5.9 (IC95%: 2.8-12.6). a los 5 años fue de 3.9 (IC95%: 1.8-8.4) y longitudinalmente el coeficiente alcanzó el valor 2.0 (IC95%: 0.90-4.6).
- Algunos síntomas específicos de TND (es susceptible o fácilmente moleestado por otros, desafía activamente a los adultos o rehúsa cumplir sus demandas, culpa a los demás) se asociaron con la presencia de algún TA, de forma transversal y también longitudinal.
- La comorbilidad TND+TA a los 3 años de edad se asocia con un mayor deterioro funcional en las relaciones con los demás (comparado con TA). A los 5 años, presentar esta asociación clínica se relacionó con mayor deterioro hacia los otros y con mayor nivel en dificultades emocionales (en comparación con TND). Longitudinalmente, la comorbilidad TND+TA a los 3 años incrementó el riesgo de deterioro en la escuela dos años después (comparado con TA).
- No se encontró asociación significativa entre el grupo de diagnóstico y el sexo de los niños o el SES familiar.

Tabla 4. Resultados principales del trabajo empírico 1 (porcentaje de niños con deterioro).

Grupo ; Deterioro	3 años ; 3 años			5 años ; 5 años			3 años; 5 años*		
	TND n=44	TA n=42	TND+TA n=17	TND n=31	TA n=60	TND+TA n=15	TND n=41	TA n=38	TND+TA n=14
Colegio	50.1	31.5	28.7	46.6	18.5	47.6	32.0	14.9	43.9
Hogar	100	51.0	100	90.75	45.6	100	73.9	24.2	43.9
Comunidad	0	1.77	0	11.6	0.00	15.9	2.14	3.73	6.27
Otros	58.0	40.5	80.9	60.5	41.2	94.7	40.5	27.8	31.4
Humor/Emociones	38.0	65.0	62.0	34.9	71.6	89.4	31.9	61.1	37.6
Humor/Autolisis	2.01	1.77	4.1	2.34	1.10	10.6	0	1.87	0
Cognición	2.01	7.07	4.79	0.00	7.62	5.29	0	3.73	18.8

Nota. TND= Trastorno negativista desafiante; TA= Trastornos de ansiedad; TND+TA= Comorbilidad entre el trastorno negativista desafiante y los trastornos de ansiedad. * Grupo con 3 condiciones diagnósticas (TND, TA o ambas) a los 3 años y deterioro a los 5 años de edad.

3.2 Trabajo empírico 2

- Transversalmente, a los 3 años la probabilidad de TND+TA se incrementa para: a) niveles elevados en la dimensión de temperamento enfado-frustración y valores bajos en las dimensiones de control inhibitorio, agresión verbal y alto nivel de agresividad de la madre (cuando se compara con el grupo de únicamente TA); y b) puntuaciones altas en psicopatología del padre (cuando se compara con el grupo de únicamente TND).
- Longitudinalmente, la probabilidad de presentar la comorbilidad TND+TA a los 5 años se incrementa para niños con puntuaciones elevadas en anticipación-positiva y puntuaciones bajas en sonrisa. En comparación con niños que únicamente presentan TND, la comorbilidad TND+TA es más probable en niños con puntuación baja en castigo corporal. Pero en comparación con niños que presentan sólo TA, la concurrencia TND+TA se asocia a puntuaciones altas en agresividad total.
- Los resultados indican una asociación moderadora del género entre la comorbilidad TND+TA y el miedo. El grupo de niños (varones) con TND+TA presentaba bajos niveles de miedo, y el grupo de niñas con TND+TA presentaba altos niveles de miedo.
- La comorbilidad TND+TA se presentó de forma crónica persistente en un 0.35% de los niños (IC95%: 0.10-1.3). El riesgo de comorbilidad durante las edades 3 a 5 años fue del 1.6% (IC95%: 0.84-3.0).

Tabla 5. Resultados principales del trabajo empírico 2 (regresión multinomial).

Edad	Variable independiente	TND+TA vs TND		TND+TA vs TA		
		OR	IC 95%	OR	IC 95%	
3 años	CBQ: Enfado-frustración	2.33	(0.48; 11.4)	41.3	(3.67; 465)	
	CBQ: Miedo	1.47	(0.59; 3.68)	0.50	(0.13; 1.83)	
	CBQ: Control inhibitorio	1.18	(0.30; 4.67)	0.10	(0.01; 0.96)	
	CBQ: Timidez	1.12	(0.20; 6.36)	0.15	(0.02; 1.08)	
		<i>Niñas</i>				
		<i>Niños</i>	7.63	(0.92; 63.0)	10.5	(0.92; 120)
	CAS: Verbal agresión	0.97	(0.95; 1.00)	0.97	(0.95; 0.99)	
	APQ: Disciplina inconsistente	0.63	(0.37; 1.07)	1.00	(0.50; 2.00)	
	ASR-Madre: Agresión	1.13	(0.80; 1.60)	2.52	(1.36; 4.65)	
ASR-Padre: Total	1.20	(1.04; 1.38)	1.00	(0.87; 1.16)		
5 años	CBQ: Anticipación positiva	31.3	(1.86; 528)	18.7	(1.23; 283)	
	CBQ: Miedo	0.01	(0.00; 0.25)	0.01	(0.00; 0.21)	
		<i>Niñas</i>				
		<i>Niños</i>	11.9	(1.34; 106)	13.6	(1.47; 125)
	CBQ: Sonrisa	0.02	(0.00; 0.35)	0.02	(0.00; 0.46)	
	CAS: Total	1.05	(0.98; 1.14)	1.11	(1.02; 1.20)	
APQ: Castigo corporal	0.13	(0.03; 0.64)	0.46	(0.10; 2.12)		

Nota. Negrita: resultado significativo (nivel .05). TND= Trastorno negativista desafiante; TA= Trastornos de ansiedad; TND+TA= Comorbilidad entre el trastorno negativista desafiante y los trastornos de ansiedad; IC= Intervalo de confianza.

3.3 Trabajo empírico 3

- A los 3 años, los niños que presentaban TND+TA presentaron más dificultades en las FEs: a) en inhibición y cambio en comparación con los niños con únicamente TND; b) en flexibilidad en comparación con los niños con únicamente TA.
- A los 5 años de edad, la condición comórbida TND+TA presentó más dificultades en las FEs: a) índice ISCI (únicamente en las niñas), en comparación con los niños con únicamente TND; b) todas las dimensiones del BRIEF (excepto cambio y memoria de trabajo), en comparación con los niños con únicamente TA.
- Aparecieron dos efectos de moderación para el sexo en las escalas de flexibilidad (a la edad de 3 años) y autocontrol inhibitorio (a los 5 años): las niñas con diagnóstico de comorbilidad TND+TA obtuvieron puntuaciones medias más bajas que las niñas en las otras condiciones de diagnóstico, mientras que los niños diagnosticados con TND+TA obtuvieron puntuaciones medias más altas que los niños en los otros grupos.

Tabla 6. Resultados principales del trabajo empírico 3 (ANOVA).

		Medias ajustadas			Comparaciones múltiples			
		TND <i>n</i> =44	TA <i>n</i> =41	TND+TA <i>n</i> =17	TND vs TND+TA <i>Dif.med.</i>	<i> d </i>	TA vs TND+TA <i>Dif.med.</i>	<i> d </i>
Edad 3								
		24.70	22.25	20.23	-4.48	0.61	-2.02	0.29
		12.34	15.16	14.68	2.35	0.61	-0.48	0.12
		13.02	12.12	12.39	-0.63	0.15	0.27	0.07
		23.13	22.01	20.90	-2.23	0.34	-1.11	0.17
		13.61	13.19	13.44	-0.18	0.04	0.24	0.06
		37.72	34.37	32.62	-5.10	0.49	-1.75	0.18
	Niñas	23.41	25.70	23.25	-0.16	0.04	-2.46	0.64
	Niños	27.49	28.85	29.69	2.19	0.34	0.84	0.12
		36.75	35.20	34.34	-2.41	0.23	-0.87	0.08
		86.83	84.79	81.64	-5.19	0.27	-3.15	0.16
Edad 5		<i>n</i>=35	<i>n</i>=54	<i>n</i>=11				
		26.49	21.28	28.03	1.54	0.17	6.75	0.83
		13.95	14.02	14.54	0.59	0.14	0.52	0.12
		14.16	12.01	16.08	1.92	0.33	4.08	0.76
		24.24	22.43	26.29	2.05	0.25	3.85	0.48
		14.55	12.99	15.48	0.92	0.18	2.48	0.54
	Niñas	38.66	34.40	31.70	-6.96	0.74	-2.70	0.44
	Niños	42.67	32.44	48.03	5.37	0.48	15.59	1.56
		28.10	25.97	30.63	2.53	0.28	4.66	0.55
		38.79	35.43	41.77	2.97	0.23	6.34	0.51
		93.38	82.68	100.41	7.03	0.25	17.73	0.68

Nota. Negrita: resultado significativo (nivel .05). ISCI=Inhibición y Cambio; FI= Índice de Flexibilidad; EMI= Memoria de Trabajo y Planificar-Organizar; GEC= Composición Global Ejecutivo. TND= Trastorno negativista desafiante; TA= Trastornos de ansiedad; TND+TA= Comorbilidad entre el trastorno negativista desafiante y los trastornos de ansiedad; IC= Intervalo de confianza.

4. Discusión

Esta tesis presenta resultados empíricos sobre la asociación del TND+TA en una muestra de niños de la población general que fueron seguidos de los 3 a los 5 años. En los siguientes apartados se resumen brevemente los principales hallazgos.

Trabajo empírico 1

Los resultados principales del trabajo empírico 1 indican que es posible identificar la comorbilidad TND+TA en la etapa preescolar (edades 3 a 5 años). Una posible explicación a la comorbilidad del TND+TA en esta etapa evolutiva puede hallarse en la propia dimensionalidad inherente al TND. Distintos trabajos han obtenido una estructura factorial para este trastorno en niños de corta edad, caracterizada por tres componentes (Burke y Loeber, 2010; Ezpeleta et al., 2012; Stringaris y Goodman, 2009): irritabilidad (o afecto negativo), conducta de confrontación y comportamiento agresivo. Parece que de forma específica es la dimensión de irritabilidad del TND la que más estrechamente se asocia con la emergencia de trastornos emocionales en preescolares (Boylan et al., 2007) y también con distintas formas de ansiedad (Stringaris, 2011). Podría suponerse según esta hipótesis explicativa que bajo el enfado típico de la irritabilidad subyace una alta susceptibilidad que en sí misma se presenta como una característica altamente desadaptativa que puede conducir a la emergencia de síntomas de ansiedad.

En este primer trabajo no se evidenciaron asociaciones estadísticamente significativas entre la comorbilidad y el sexo de los niños o el nivel socioeconómico de las familias, aunque de forma global sí emergió asociación entre la concurrencia TND+TA y la presencia de mayor grado de deterioro funcional en las relaciones hacia los otros, en el área emocional y en la escuela. Los datos obtenidos parecen ir en la línea de los publicados por Cunningham y Ollendick (2010) y Lavigne y cols. (2009), quienes establecieron un gradiente de afectación funcional encabezado por la comorbilidad TND+TA, seguido por el TND y finalizado por el TA. El deterioro en la escuela en niños con comorbilidad TND+TA se ha evidenciado en este estudio, es relevante destacar que numerosos estudios realizados con niños que presentan TND de forma aislada indican que este trastorno suele ocasionar mayor dificultad en la propia familia, y en ocasiones puede aparecer incluso desapercibido en otros contextos como en el colegio.

Trabajo empírico 2

Los resultados del trabajo empírico 2 mostraron que es posible identificar de forma transversal y longitudinal factores asociados con la presencia de comorbilidad TND+TA, tanto a los 3 como a los 5 años de edad. El temperamento de los niños preescolares que presentaban comorbilidad TND+TA en comparación con los otros grupos diagnósticos se caracterizó por una alta emotividad negativa, bajo control inhibitorio y baja frecuencia de agresión verbal, problemas en la desregulación emocional y bajo control inhibitorio. Estos resultados son coherentes con los hallazgos publicados en la literatura, que muestran que los estilos temperamentales difíciles (tales como la emotividad negativa, irritabilidad y baja tolerancia a la frustración), se asocian con la presencia de ansiedad y también con comportamiento de tipo agresivo (Bubier y Drabick, 2009; Ortiz y del Barrio, 2006). Además, este rasgo temperamental (afecto negativo) puede provocar respuestas del cuidador (por ejemplo prácticas parentales rígidas y severas), que podrían conducir a problemas que se externalizarán más adelante y que pueden formar parte de una dinámica entre progenitor-hijo alimentando negativamente el trastorno. Los resultados también parecen encajar con el modelo propuesto por Drabick et al. (2010), según el cual la ansiedad puede exacerbar los síntomas de TND y la falta de control inhibitorio, y la impulsividad propia de la comorbilidad TND+TA podría precipitar a los niños afectados a situaciones de conflicto (que tenderían a interpretar situaciones ambiguas como hostiles y se verían incapaces de elegir estrategias adecuadas de control). Respecto a la asociación con agresividad, nuestros hallazgos irían en la línea de Bubier y Drabick (2009), que observaron como más plausible en niños con TA y concurrencia de trastornos disruptivos la agresividad reactiva, la agresividad que muestran los niños con TND+TA es más física que verbal, parece que estos niños muestran una agresividad más primitiva. Cabe destacar que los niños con TND+TA muestran un grado de agresividad superior a los niños con TA y seguramente esto es debido a la adición del TND: un trastorno perturbador, de conducta y del control de los impulsos.

Un temperamento caracterizado por la tendencia a experimentar miedo también se asoció a la presencia de TND+TA. La asociación fue moderada por el género, de manera que el miedo podría ser un factor de protección para niñas y un factor de riesgo para los niños. De acuerdo con la hipótesis de socialización (Maccoby y Jacklin, 1974), la expresión del miedo es socialmente más aceptada en las niñas que en los niños, por lo que cuando un niño se enfrenta a una situación temerosa con una respuesta agresiva socialmente no es algo que se vea muy alejado a lo que se espera de los niños varones (niños fuertes, valientes y sin llantos).

Las puntuaciones bajas en la escala de temperamento sonrisa-risa en este estudio se asociaron a TND+TA. Esta escala es una medida de la cantidad de afecto positivo en respuesta a los cambios de los estímulos. La asociación inversa entre dicha escala y la comorbilidad objeto de estudio podría explicarse según los resultados publicados por Fraire y Ollendick (2013), que relacionan este resultado con la propia expresión de los padres en cuanto a sonrisa-risa: la expresión emocional en padres con hijos que presentan TND+TA acostumbra a ser menos positiva que la de los padres de niños sin TND+TA. Incluso sería lógico suponer que el malestar personal que sentirían los niños afectados por trastornos de distinta naturaleza les hiciera más vulnerables y menos expresivos de felicidad. Se abriría aquí una vía explicativa para otras posibles asociaciones como la evolución hacia cuadros de tipo depresivo en el futuro de estos niños si no se interviene adecuadamente (De Pauw y Mervielde, 2010).

La psicopatología de los padres también parece ser un factor importante asociado a la comorbilidad TND+TA. Estudios recientes apuntan que el papel del padre resulta cada vez más importante en relación con la salud mental de sus hijos. Sin embargo, la cantidad de investigación recopilada sobre la figura paterna es muy inferior a la de la figura materna, debido primordialmente a que los hombres tienden a participar en menor grado en los estudios empíricos. Bögels y Phares (2008) hallaron que los padres podrían tener una influencia aún mayor que las madres sobre el desarrollo de la ansiedad social de los niños, ya que ejercerían un papel crucial en el proceso de socialización de sus niños. Hallazgos recientes han sugerido que la psicopatología del padre puede estar asociada con un mayor riesgo de problemas para los niños, independientemente del bienestar psicopatológico de la madre (Ramchandani y Psychogiou, 2009). Nuestros resultados van en esta línea. En cuanto a la influencia de la psicopatología de las madres sobre la presencia conjunta TND+TA, la dimensión de agresión ejerce el papel más relevante. Frente a este hallazgo, existen dos potenciales vías explicativas (Wahl y Metzner, 2011): genética (genes compartidos) y/o modelado (que favorece también personalidades y tipos de comportamiento).

Con respecto a los resultados que indican que los estilos parentales con bajos niveles de castigo predicen TND+TA, es importante destacar que este hallazgo se produce únicamente al comparar con TND (y no con TA). Esto sugiere que la ansiedad puede tener un efecto atenuante sobre la expresión del trastorno comórbido y es por esta razón por la que los niños son menos castigados.

Trabajo empírico 3

Finalmente, en el trabajo empírico 3 se observó que la presencia comórbida TND+TA se asocia a una expresión más pobre de las FEs durante la etapa preescolar, que la asociación es mayor a la edad de 5 años, y que las dificultades en las FEs a los 3 años de edad poseen capacidad predictiva sobre el riesgo de desarrollar comorbilidad TND+TA durante los dos años siguientes.

A los 3 años de edad, la comparativa entre niños con TND, TA y comorbilidad TND+TA mostró pocas diferencias significativas y clínicas. De hecho, el grupo que incluyó niños con TND (pero no TA) presentó mayor nivel de dificultad en cambio y también en Índice de Flexibilidad (IF) (aunque este último resultado sólo fue obtenido en las niñas). Los resultados en la escala de cambio podrían explicarse por la baja tolerancia, alta hostilidad y quebrantación de normas propias de los niños que presentan simultáneamente ambos trastornos (Halperin et al., 1995).

A medida que los niños se hicieron más mayores, el grupo caracterizado por la concurrencia de TND+TA sí presentó mayor déficit en la expresión de las FEs que los grupos caracterizados por únicamente TND o TA (la diferencia fue especialmente relevante al comparar con TA). Este resultado parece coherente con el modelo dual propuesto por Drabick et al. (2008), según el cual podrían estar operando dos procesos: a) la concurrencia múltiple de TND+TA hace que los síntomas de ansiedad exacerben los de TND contribuyendo así a disminuir la capacidad neurobiológica del córtex para regular el funcionamiento del sistema límbico (Garai, Forehand, Colletti, y Rakow, 2009); y b) la hipótesis amortiguadora supondría que frente a la presencia conjunta del TND+TA los síntomas de TA mitigarían los del TND, lo cual podría suponer una sobreactivación del sistema límbico en respuesta a sentimientos de ira o tristeza (Crowe y Blair, 2008).

El sexo, sin embargo, no presentó un papel moderador relevante en las relaciones existentes entre las FEs y la concurrencia de TND+TA. Aunque únicamente emergieron dos parámetros de interacción, su presencia debe tenerse en consideración. De forma particular se constató que las niñas con TND+TA presentaban menos dificultades en los índices (IF) e Inhibición y Cambio (ISCI) en comparación con niñas que únicamente fueron diagnosticadas de TND o de TA, aspecto que haría suponer que la hipótesis amortiguadora es más aplicable a niñas que a niños (y a la inversa, la hipótesis de la múltiple concurrencia sería más verosímil para sexo masculino).

4.1 Limitaciones

El primer artículo cuenta con la limitación de que los análisis se basan únicamente en la información proporcionada por los padres. Cabe sin embargo argumentar que el TND, en edades tan tempranas, se muestra más intensamente en el hogar, lo que significa que los padres suelen ser los primeros en percibir los problemas ocasionados por este trastorno y los convierte por ello en buenos informantes. Esta limitación también es extensiva al segundo artículo, que analiza información que en ningún caso es obtenida directamente de los propios niños. En este segundo trabajo, sin embargo, sí se dispone de información recogida de los maestros. En el tercer artículo, se consideraron como clínicamente relevantes únicamente las diferencias de medias con moderado a alto tamaño del efecto, y a pesar del tamaño pequeño de la muestra, en esta condición concreta, emergieron las relaciones entre diagnóstico y FEs.

La principal limitación de los artículos fue el bajo tamaño de la muestra para la condición TND+TA lo que podría reducir el poder estadístico para algunas comparaciones por pares, pero se tomaron medidas para reducir el impacto de esta limitación.

4.2 Fortalezas

La tesis incluye tres estudios de investigación original con notables puntos destacables:

- Origen y tamaño de la muestra. Los datos proceden a una amplia muestra comunitaria que incluye un total de $n=622$ niños de población general.
- Diseño longitudinal, con medidas repetidas durante el período preescolar (edades 3 a 5 años).
- Las medidas incluyen tanto entrevista diagnóstica (para valorar la presencia de los trastornos DSM-IV) como cuestionarios.
- Se dispone de diferentes informantes según el constructo que se valora (padres, maestros y/o participantes).

4.3 Implicaciones

En términos globales de los resultados obtenidos en este proyecto se derivan varias implicaciones prácticas, particularmente cuestiones directamente orientadas al área de la prevención. La asociación observada entre TND y TA en preescolares se debe considerar como un factor de riesgo importante por la presencia de deterioro en el funcionamiento global de los niños, y advierte de la necesidad de una identificación temprana de las condiciones de diagnóstico, los factores de riesgo y los patrones transversales y longitudinales de la comorbilidad TND+TA. Según los resultados del segundo estudio, también es fundamental considerar que las intervenciones que se dirigen a niños con TND+TA deberían considerar tanto las relaciones con los padres como su propio estado psicopatológico.

Sin embargo, intervenir una vez se ha presentado el problema puede no ser suficiente. Las complicaciones que la literatura evidencia en el tratamiento de síntomas interiorizados y exteriorizados cuando ya están presentes en edades tempranas (Rapee et al., 2013), así como también las consecuencias negativas a largo plazo de presentar comorbilidad TND+TA, alertan sobre la importancia del estudio de los factores de riesgo y de los mecanismos subyacentes que facilitan estas asociaciones, con el fin de preparar planes de prevención precoz que resulten eficaces. Desde el ámbito preventivo, la identificación de los factores de riesgo para TND+TA debe incluir tanto los rasgos temperamentales de los propios niños como la evaluación de las características de la propia familia (padres con altos niveles de psicopatología o con estilos educativos de alto riesgo). El sexo de los niños también debe tenerse en cuenta en esta evaluación, ya que nuestros resultados señalan que las niñas miedosas necesitan estrategias adecuadas para el manejo de las emociones de miedo.

El tercer estudio empírico constata la relación entre TND+TA el déficit de las FEs durante el período preescolar, transversalmente y longitudinalmente. Los programas de prevención e intervención para niños en edad preescolar con diagnóstico TND+TA deben promover el desarrollo adecuado de las funciones ejecutivas para ayudarles a construir habilidades de flexibilidad mental y autocontrol. El control emocional del miedo y la ira, la flexibilidad en la interpretación de las señales ambientales, y la mejora en habilidades de inhibición y cambio podrían fortalecer los diferentes componentes de las FEs, y esto, a su vez, podría ayudar a reducir la expresión de problemas de TND y TA, y a minimizar la posibilidad de que ambos trastornos emerjan y concurren.

5. Conclusiones

Para concluir, es posible identificar comorbilidad TND+TA en edad preescolar. Concretamente, la dimensión de irritabilidad que compone el diagnóstico TND se asocia con los TA.

Por otro lado los factores relacionados con comorbilidad TND+TA son tener un temperamento difícil caracterizado por elevado/a enfado-frustración, escaso control inhibitorio y agresión verbal. El miedo también se asocia con la presencia de TND+TA pero de manera diferencial según el género: ser niña podría ser un factor de protección y ser niño un factor de riesgo. Además, desde una perspectiva longitudinal, los preescolares anticipadores y que sonríen poco están en riesgo de presentar comorbilidad TND+TA. Otro factor de riesgo para presentar ambos trastornos conjuntamente es que la madre tenga altos niveles de agresividad, y respecto al padre, la psicopatología paterna es muy relevante. Comparando con los trastornos de manera independiente, los preescolares con este trastorno comórbido son más agresivos en general que los niños que sólo presentan TA, y la práctica parental del castigo corporal es menos usada en niños con comorbilidad TND+TA que en niños con sólo TND.

Los preescolares con comorbilidad TND+TA presentan déficits en las FEs. Si se compara con TND, las FEs más afectadas de manera negativa son las relativas a inhibición y cambio; si se compara con TA, las FEs más afectadas negativamente corresponden a las áreas de flexibilidad. Al final de la etapa preescolar, se observa una alteración en la mayoría de FEs (excepto cambio y memoria de trabajo) en niños con comorbilidad TND+TA comparados con niños con TA.

El sexo tiene un papel importante en la alteración de las FEs. La flexibilidad y el autocontrol inhibitorio varían en función del sexo: las niñas con diagnóstico de comorbilidad TND+TA son menos disfuncionales en estas áreas que las niñas con los diagnósticos por separado, mientras que los niños diagnosticados con TND+TA tienen estas áreas más perjudicadas que los niños en los otros grupos.

Finalmente, es de crucial importancia el diagnóstico precoz de la comorbilidad TND+TA por el deterioro y el malestar que ocasiona. Concretamente, ocasiona deterioro funcional en las relaciones con las personas de alrededor y relevantes dificultades emocionales. Además, los preescolares que padecen dicha comorbilidad incrementan el riesgo de presentar problemas en la escuela con el paso del tiempo.

Es debido a esto que se puede concluir que entre los principales factores para que los preescolares presenten comorbilidad TND+TA, destacan tener un temperamento difícil y presentar alteraciones en las funciones ejecutivas. Además existen diferencias según el sexo y los progenitores (padre incluido) juegan un papel importante en la emergencia y desarrollo de la comorbilidad TND+TA. Todo esto ocasiona malestar significativo a los niños que presentan esta condición conjunta y se deberían implementar estrategias específicas de intervención temprana.

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7. Publicaciones

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Comorbidity of oppositional defiant disorder and anxiety disorders in preschoolers

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Abstract

Background: The aim was to study the comorbidity of oppositional defiant disorder (ODD) and anxiety disorders (AD) among preschool children of the general population, and to assess the contribution of comorbidity to the child's functional impairment. **Method:** 622 children were assessed at the ages of 3 and 5, through a diagnostic interview. They were clustered into three diagnostic groups: only ODD, only AD and comorbid ODD+AD. **Results:** At age 3, ODD was associated with specific phobia, OR = 4.7, 95% CI [1.4, 14.1], and at age 5, with any anxiety disorder, OR=3.9; 95% CI [1.8, 8.4]. ODD at age 3 was predictive of separation anxiety at age 5, OR=4.1; 95% CI [1.2, 14.3]. Comorbid ODD+AD cases showed a higher risk of functional impairment at school and in behavior toward others. Sex and socioeconomic status were not related to the diagnostic group. **Conclusions:** ODD+AD comorbidity can be identified in preschool children. Early identification of this association is needed to adequately treat the affected children.

Keywords: Comorbidity, anxiety disorder, oppositional defiant disorder, preschool.

Resumen

Comorbilidad del trastorno negativista desafiante y los trastornos de ansiedad en preescolares. **Antecedentes:** se analiza la comorbilidad entre el trastorno negativista desafiante (TND) y los trastornos de ansiedad (TA) en preescolares de población general, y el deterioro funcional con que se asocian. **Método:** 622 niños fueron evaluados a los 3 y los 5 años con una entrevista diagnóstica. Se compararon 3 grupos diagnósticos: únicamente TND, únicamente TA y comorbilidad TND+TA. **Resultados:** a los 3 años se halló asociación entre TND y fobia específica (OR = 4.7, IC95%: 1.4÷14.1) y a los 5 años entre TND y TA, OR= 3.9; 95% IC [1.8, 8.4]. La presencia de TND a los 3 años fue predictiva de ansiedad de separación a los 5 años (OR = 4.1; IC95%: 1.2÷14.3). La comorbilidad se asoció con mayor deterioro funcional en la escuela y en el comportamiento hacia los demás. Sexo y nivel socioeconómico no se asociaron al grupo diagnóstico. **Conclusiones:** la comorbilidad TND+TA se puede identificar en edad preescolar. Es necesaria la detección temprana de estos trastornos para el adecuado tratamiento de los niños afectados.

Palabras clave: comorbilidad, trastorno de ansiedad, trastorno negativista desafiante, preescolar.

Oppositional defiant disorder (ODD) is characterized by negativistic, defiant, disobedient, and hostile behavior, particularly towards authority figures (American Psychiatric Association, 2000), which causes marked difficulties with parents, teachers and peers (Barkley, Benton, & Maughan, 2008). ODD is the most common disruptive disorder in childhood. In recent years, ODD has received a lot of interest because of the high level of comorbidity that it usually presents (Cunningham & Ollendick, 2010). ODD is also a potent precursor/mediator of other disorders, and its early detection is crucial for breaking the chain of complications (Burke, Loeber, Lahey, & Rathouz, 2005). The disorders most often associated with ODD include attention deficit/hyperactivity disorder (ADHD), conduct disorder, substance abuse, antisocial personality, depression and anxiety disorders (AD) (Boylan,

Vaillancourt, Boyle, & Szatmari, 2007; Stringaris & Goodman, 2009).

Despite the high frequency of comorbidity between ODD and AD (ODD+AD), its early onset and the increase in services use (Keenan & Wakschlag, 2004; Sterba, Egger, & Angold, 2007), most studies have focused on the child and adolescent stages. In school age samples of 6-9 year-olds, comorbid anxiety may strengthen the association of ODD and ADHD (especially the combined type). This makes comorbid anxiety a powerful risk factor for the development of externalizing problems (ODD or conduct disorder) (Humphreys, Aguirre, & Lee, 2012). In a clinical sample of children between 8 and 12 years, the symptoms of ODD "excessively arguing with adults" and "deliberately trying to annoy or upset others" were associated with the presence of anxiety symptoms (Polier, Vloet, Herpertz-Dahlmann, Laurens, & Hodgins, 2012). Higher levels of anxiety and ODD (ages 6-18 years) are associated with symptoms of anger/irritability compared with those who did not show these symptoms (Drabick & Gadow, 2012). In a longitudinal study comprising ages 12 to 26 years, anxiety symptoms persisted into adulthood while negativistic symptoms tended to stabilize or decrease (Leadbeater, Thompson, & Gruppuso, 2012).

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The association between ODD+AD has raised some controversy. Some studies suggest that anxiety may be an epiphenomenon of ADHD or depression and, therefore, in the absence of ADHD or depression, the ODD+AD relationship would not appear (Angold & Costello, 2001). Other studies found that ODD+AD associations were moderated by sex (comorbidity was present only in girls) (Costello, Mustillo, Erkanli, Keeler, & Angold, 2003), but others did not find such interaction (Munkvold & Lundervold, 2011).

Although scarce, there are some empirical data on the ODD+AD association in preschoolers. In the general population, Wichstrøm et al. (2012) reported a 7.1% odd ratio (OR = 5.6) prevalence of ODD+AD comorbidity. Lavigne, LeBailly, Hopkins, Gouze and Binns (2009) found, at the age of four years, an OR of 3.44 for the association between ODD and separation anxiety disorder. Egger and Angold (2006), in 2 to 5 year-old preschool children, found associations between generalized anxiety/separation anxiety and ODD of OR = 4.4. Bufferd, Dougherty, Carlson, and Klein (2011) indicate that 9.2% of a sample of preschoolers (age 3) had two or more diagnoses, and one of the most significant comorbidities was ODD+AD (OR = 2.03). In addition, a study of posttraumatic stress disorder and comorbid disorders in 70 children (ages 3-6) in the wake of Hurricane Katrina revealed that 88.6% had at least one comorbid disorder, the most common being ODD and separation anxiety disorder (Scheeringa & Zeanaha, 2008). These results support the idea that ODD and AD coexist at a very early age.

Several explanations have been put forward for the comorbidity of ODD+AD. Lavigne et al. (2009) propose that either AD or depression are present in the preschool years but are masked by the symptoms of ODD, or that problems caused by ODD in academic performance or social functioning may subsequently lead to AD and depression. It has also been proposed that ODD is composed of different dimensions (irritable, headstrong, and hurtful) (Boylan et al., 2007; Burke & Loeber, 2010; Stringaris & Goodman, 2009) that may facilitate its association with various disorders. These dimensions have been identified in preschool children, and a significant relationship has been reported between irritability and AD (Ezpeleta, Granero, de la Osa, Penelo, & Doménech, 2012).

It is also possible that socioeconomic status is associated with ODD+AD comorbidity. Amone P'Olak et al. (2009) found that low SES creates a risk for internalizing (depression and anxiety) and externalizing (ODD, ADHD, conduct disorder) problems.

More empirical evidence is needed to help clarify the magnitude of the association between ODD+AD, and how it affects children's lives, in order to improve detection and intervention of these common problems. The aim of this study is to examine the presence of cross-sectional and longitudinal comorbidity ODD+AD in preschool children from the general population, assess the role of gender and socioeconomic status in this association and assess the association with functional impairment in the lives of children.

Method

Participants

The sample is part of a large research project into developmental trajectories for behavioral disorders in childhood. A two-phase design was employed (Ezpeleta, de la Osa, & Doménech, in press). A total of 2,283 families, obtained from the census of all 3-year-old children attending school in Barcelona ($N = 13,578$), were invited

to participate, with 1,341 accepting the invitation (participation ratio: 58.8%). Sixty-three children were excluded due to language issues or generalized developmental problems, and the remaining 1,278 were screened through the behavioral problems scale of the Strengths and Difficulties Questionnaire (parent version) for 3- to 4-year-olds (SDQ³⁺; Goodman, 1997). All children with a positive screening score were invited to participate ($N = 522$ cases, 42.9%), as well as a random 30% of the $N = 756$ children with a negative screening score.

The final sample included 622 children (417 with a positive screening score and 205 negative). At 5 years old, 537 children were assessed again. Table 1 shows the descriptive statistics for participants.

Instruments

The Diagnostic Interview for Children and Adolescents for Parents of Preschool and Young Children (DICA-PPYC; Reich & Ezpeleta, 2009) is a semi-structured interview with good psychometric properties validated in the Spanish population (Ezpeleta, Osa, Granero, Doménech, & Reich, 2011). The DICA-PPYC assesses the most common mental disorders of children from 3 to 7 years old, according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR; American Psychiatric Association, 2000). The anxiety disorders analyzed include separation anxiety, generalized anxiety, specific phobia and social phobia. The variable "other comorbidity" includes ADHD, conduct disorder, and major depression. The average administration time for the first DICA-PPYC was 49.8 minutes, and was 41.7 minutes for the second.

Table 1
Descriptive ($N = 622$)

	3 years-old		5 years-old	
Sex (male); n (%)	310	(49.8)		
Age (years-old); mean (SD)	2.97	(0.16)	5.23	(0.48)
SES; n (%)				
High	205	(33.0)		
Mean-high	195	(31.4)		
Mean	88	(14.1)		
Mean-Low	99	(15.9)		
Low	35	(5.6)		
	3 years-old		5 years-old	
DSM-IV disorders	N	(%) ¹	N	(%) ¹
Disruptive behavioral disorders	87	(10.0)	67	(9.6)
Attention deficit hyperactivity dis.	33	(3.6)	30	(4.2)
Oppositional defiant disorder	61	(6.9)	46	(6.6)
Conduct disorder	10	(1.4)	5	(0.5)
Anxiety disorders	59	(7.7)	75	(11.7)
Separation anxiety	18	(2.1)	8	(1.3)
Generalized anxiety	1	(0.1)	5	(0.5)
Specific phobia	27	(3.6)	53	(8.3)
Social phobia	16	(1.9)	20	(3.6)
Major depression disorder	4	(0.4)	3	(0.3)

SD: standard deviation. SES: socioeconomic status (Hollingshead, 1975).

¹ Weighted prevalences

The Preschool and Early Childhood Functioning Assessment Scale (PECFAS; Hodges, 1999) assesses the functional impairment of children from 3 to 7 years old, as rated by a clinician following the DICA-PPYC (rating time of 10-15 minutes). It includes seven areas (school, home, community, behavior toward others, mood-emotions, mood-autolysis and cognition-communication) and each area includes several examples of impaired functioning. Each scale is scored based on four levels of impairment (0 = *no or minimal*; 10 = *mild or distress*; 20 = *moderate*, and 30 = *severe*). A total score (global measure of functional impairment) is defined as the sum of the scores on the seven individual scales (range: 0 to 210). The psychometric properties of the PECFAS are appropriate and have been described in Murphy et al. (1999).

Procedure

Approval was obtained from the Ethics Review Committee of the authors' institution. Head teachers of the participating schools were provided with a full description of the research, and their collaboration was also requested. Families were invited to participate and asked for their written consent. Interviewers trained to use the DICA-PPYC interviewed parents at the schools. The interview panel consisted of 10 members who completed an intensive 1-week training period consisting of learning the characteristics of the symptoms and disorders, methods of identifying these characteristics and how to code the symptoms. It included an overview of developmental psychology and the psychopathology of preschool children, as well as interviewing skills. Finally, interviewers completed the PECFAS based on the responses registered during the diagnostic interview.

Data analysis

Data analysis was carried out with SPSS20 for Windows, through the Complex Samples module (due the two-phase design), defining a planning project with weights equal to the inverse probability of selection in the second phase of the design. Cross-sectional ODD+AD comorbidity (at ages 3 and 5 years old) and longitudinal comorbidity (from 3 to 5 years old) were estimated with OR coefficients in binary logistic regressions adjusted for the presence of other disorders different to ODD and AD. This statistical procedure was also used to measure the specific discriminative capacity of each ODD symptom for identifying the presence of anxiety disorders, entering the list of ODD symptoms simultaneously in the same block (ENTER method).

The association between the number of symptoms for ODD and AD was estimated with Pearson's correlation, considering $|r| \geq 0.30$ to be a good effect size (Cohen, 1988).

For the study of the relationship between the diagnostic profile, sex, socioeconomic level (SES) and impairment, participants were divided into three groups. One group included children diagnosed with ODD but without AD ($N = 44$ at 3 years old, 35.7% male); another group was comprised children with AD but without ODD ($N = 42$; 45.2% male) and the third group included comorbid ODD+AD children ($N = 17$; 19.0% male). At 5 years old, the group sizes were, respectively: ODD = 31 children, AD = 60 and ODD+AD = 15. The association between sex and SES with the diagnostic profile was analyzed using multinomial regression models, with children's sex and SES entered as predictors, the group as criterion and the covariate being other comorbidities different to ODD and AD. The

association between functional impairment (defined as a binary outcome: 0 = *not-impaired* vs. 1 = *mild to high*) and the diagnostic group were studied cross-sectionally and longitudinally through binary logistic regression, adjusted for other comorbidities. For the PECFAS-total score (measure of global impairment) a General Linear Model (GLM) was defined.

Results

Comorbidity between ODD and anxiety

Table 2 shows the cross-sectional and longitudinal ODD+AD association. At the age of 3, ODD was associated with the group of anxieties and with specific phobia; at the age of 5, ODD was related with the group of anxieties. At the age of 3 ODD was a statistical predictor of separation anxiety at the age of 5.

Association between ODD symptoms and the presence of anxiety disorders

The logistic regressions analyzing the association of the ODD-symptoms list and anxiety disorders, adjusted for other comorbidity, showed that at the age of 3 the symptom "touchy or easily annoyed by others" was cross-sectionally related to the group of anxieties, OR = 3.14, 95% CI [1.4, 6.9]. At the age of 5, the symptom "actively defies to comply with adults' requests or rules" was also cross-sectionally related with the group of anxieties and with social phobia, OR = 6.36, 95% CI [1.8, 22.2], and the symptom "blames others" was negatively related to the group of anxieties, OR = 0.39, 95% CI [0.16, 0.94], and with specific phobia, OR = 0.35, 95% CI [0.14, 0.89]. Longitudinally, the presence of the symptom "touchy or easily annoyed by others" at age 3 was associated at age 5 with the group of anxieties, OR = 2.16, 95% CI [1.1, 4.1], and social phobia, OR = 2.98, 95% CI [1.2, 7.4].

No statistical association was found between the number of ODD symptoms and the number of anxiety symptoms ($r < .10$ at 3 years-old and $r < .13$ at 5 years-old).

Association between sex, socioeconomic status and the diagnostic group

No statistical association emerged for the relationship between sex and diagnostic group ($p = .717$ and $p = .956$ at 3 and 5 years old, respectively) and SES and diagnostic group ($p = .395$ and $p = .521$).

	ODD and AD at 3 (N = 622) OR (IC95%)	ODD and AD at 5 (N = 573) OR (IC95%)	ODD at 3 and AD at 5 (N = 573) OR (IC95%)
Anxiety disorders	5.88* (2.76;12.6)	3.89* (1.79;8.42)	2.04 (0.90;4.64)
Separation anxiety	2.63 (0.68;10.1)	1.46 (0.21;10.2)	4.12* (1.18;14.3)
Generalized anxiety	-	2.64 (0.19;37.1)	-
Specific phobia	4.72* (1.43;14.1)	1.31 (0.52;3.31)	1.34 (0.43;4.15)
Social phobia	0.76 (0.13;4.59)	2.99 (0.74;12.0)	1.90 (0.44;8.18)

ODD: oppositional defiant disorder. AD: anxiety disorders.
- Not-estimable (low prevalence). *Significant OR (.05 level).

Socioeconomic status was not associated with ODD+AD comorbidity. Regarding the relationship between the diagnostic subtype and the presence of functional impairment, our results suggest that ODD+AD comorbidity implies the highest level of global impairment for children, followed by ODD, and then AD. This result is in line with those found by Cunningham and Ollendick (2010) and Lavigne et al. (2009). In our study, the presence of ODD is also associated with an increased risk of impairment at home (compared to AD), which could be explained by the greater level of disobedience that is characteristic of children with ODD (who are more confrontational and argue more than children with AD), behavior that is especially relevant in the home and with principal carers. The presence of AD appears to be predictive of increased risk only on the mood / emotions scale of PECFAS, which could be because this scale measures more aspects of emotional psychopathology than functional impairment.

It should be recognized that this study has the limitation that the analysis is based solely on parent reports. However, it should also be noted that at very early ages, ODD shows most strongly in the home, which means that parents are often the first to perceive the problems caused by this disorder, making them good informants. In addition, despite the availability of a large sample of the general population, the size of the groups with ODD, AD

and both is relatively small, and this affects the statistical capacity for establishing meaningful relationships. However, despite this lack of power, the significant relationships which have emerged have important practical implications. Finally, the percentage of refusals during the sampling was higher for families of low socioeconomic status, and this must be taken into account when making generalizations.

The results of the study have several practical implications, including those oriented to the area of prevention: the association observed between ODD and AD in preschool should be considered an important risk factor for the presence of impairment in the global functioning of the children, and warns of the need for early identification of diagnostic conditions, risk factors and transverse and longitudinal ODD+AD comorbidity patterns.

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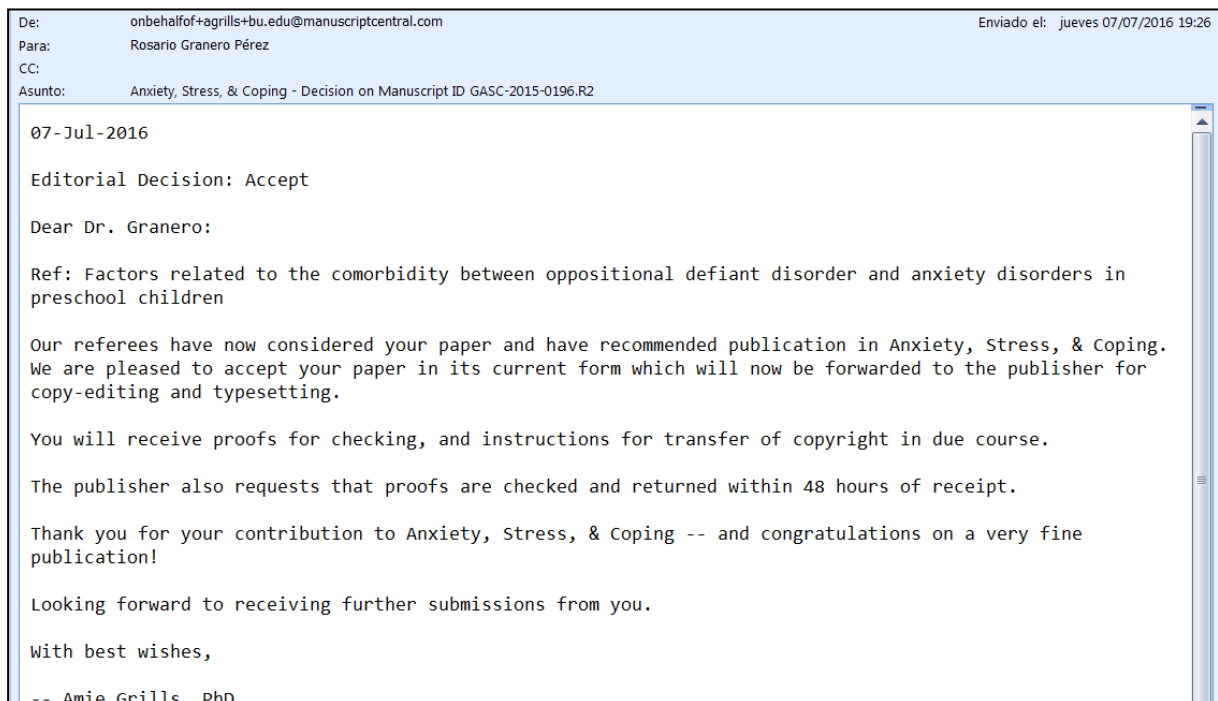
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Factors related to the comorbidity between oppositional defiant disorder and anxiety disorders in preschool children

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All persons who have made substantial contributions to the work reported in the manuscript (e.g. data collection, data analysis, or writing or editing assistance).

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Abstract

Background: The aim of the study is to identify the main factors related to comorbid oppositional defiant disorder (ODD) and anxiety disorders (AD), for preschoolers, and to assess the moderating role of the children's sex. Design: The initial sample of 622 children was assessed longitudinally at the ages of 3 and 5 years by means of questionnaires and a diagnostic interview. **Methods:** For the analysis, children diagnosed with ODD and/or AD were selected: n=103 at 3 years old (44 ODD, 42 AD and 17 ODD+AD) and n=106 at 5 years old (31 ODD, 60 AD and 15 ODD+AD). **Results:** High levels of the child's negative affectivity and the mother's aggressive behavior (versus AD), and high scores in the father's psychopathology measurements (versus ODD) are related to the presence of comorbid ODD+AD at the age of 3. High scores in the child's approach-positive anticipation, fears (only in boys, in girls the reverse effect occurred) compared to ODD and AD independently and aggressive behavior (versus AD), and low scores for smiling and laughter (versus ODD only and AD only) are predictive of comorbidity at the age of 5. **Conclusions:** Temperament traits may be a common factor in explaining longitudinal ODD+AD comorbidity.

Keywords: anxiety disorders; comorbidity; oppositional defiant disorder; preschool age; risk

Introduction

Oppositional defiant disorder (ODD) is characterized by negativistic, defiant, disobedient and hostile behavior, particularly towards figures of authority (American Psychiatric Association, 2000). An anxiety disorder (AD), on the other hand, is characterized by excessive worries or fears, behavioral avoidance, a high degree of interference and usually physiological symptoms. Rates of ODD in children ranged from 2% to 15% (Lahey, Miller, Gordon, & Riley, 1999; Maughan, Rowe, Messer, Goodman, & Meltzer, 2004), and the lifetime prevalence of anxiety disorders in children and adolescents is about 15% to 20% (Beesdo, Knappe, & Pine, 2011).

Heterotypic continuity of ODD with concurrent and subsequent internalizing disorders has not been studied as much as the homotypic comorbidity of ODD with externalizing disorders (Lavigne, Gouze, Bryant, & Hopkins, 2014). Currently, the findings indicate high concurrent heterotypic between ODD and AD (Greene et al., 2002) and between AD and ODD (Drabick, Gadow, & Loney, 2008). In preschoolers, ODD and AD comorbidity (ODD+AD) ranges from 7% to 14% (Martín, Granero, & Ezpeleta, 2014; Wichstrøm et al., 2012). There is evidence that ODD+AD comorbidity in 3 to 5 year-old preschoolers is associated with greater functional impairment in relationships with others and in school (Martín et al., 2014). Therefore it is essential to study the association of both disorders early in life in order to minimize its impact (Champion, Goodall, & Rutter, 1995) since early diagnosis and interventions can have immediate and long-term effects (Mash & Hunsely, 2007).

Several associated variables have been identified for ODD at young ages: harsh and inconsistent parenting, maternal depression, parental psychopathology, high levels of impulsivity, disinhibition and dysphoria (Dougherty et al., 2011; Fossum, Mørch, Handegard, Drugli, & Larsson, 2009; Krueger, McGue, & Iacono, 2001; Munson, McMahon, & Spieker,

2001; Owens & Shaw, 2003; Silverman, Cerny, Nelles, & Burke, 1988). On the other hand, the variables more strongly related to the presence of early AD include early childhood anxiety symptoms, reactive temperament, high levels of inhibition, negative learning experiences, stressful life events, adverse family factors, parental depression, shyness, emotional reactivity/inhibition, fear, low exuberance, low sociability and behavioral inhibition, negative emotionality, attention-deficit/hyperactivity disorder, parental anxiety, peer victimization, lower positive affectivity, sleep problems and a deficit in social skills (Dougherty et al., 2011; Dougherty et al., 2013; Kagan, Snidman, Zentner, & Peterson, 1999; Mian, Wainwright, Briggs-Gowan, & Carter, 2011; Muris, van der Pennen, Sigmond, & Mayer, 2008; Prior, Smart, Sanson, & Oberklaid, 2000; Spence, Najman, Bor, O'Callaghan, & Williams, 2002; Tellegan, 1985; Wichstrøm, Belsky, & Berg-Nielsen, 2013).

Few studies have examined the predictors of ODD and AD when present together. Reported associated variables for ODD+AD in later childhood are high negative emotionality and low inhibitory control, parenting styles (e.g. rejection) and parental psychopathology (Drabick et al., 2008; Franco et al., 2007; Muris, de Jong, & Engelen, 2004; Roelofs, Meesters, ter Huurne, Bamelis, & Muris, 2006). Studies into comorbidity associated variables in preschoolers are scarce. A longitudinal study evaluating the temperament of children from 21 months to 6 years suggests that a common predictor of disruptive behavior disorders and internalizing disorders is a history of behavioral disinhibition (Hirshfeld-Becker et al., 2007). Another study about infant risk factors associated with internalizing, externalizing, and co-occurring behavior problems in children from 5 months to 5 years old showed that maternal anxious and depressive symptoms, younger maternal age, and family conflict independently predicted early co-occurring problems. Additionally, in the context of hostile parenting, children high in anger were at increased risk of developing early co-occurring problems

(Edwards & Hans, 2015). These findings suggest that temperament, parental psychopathology and stressors may be predictors of comorbid ODD+AD in preschoolers.

Parental psychopathology plays an important role in the development of children. Maternal psychopathology symptoms were associated with externalizing, internalizing, and social problems in preschoolers and paternal psychopathology symptoms were associated with internalizing problems at age 3 and 6 (Breux, Harvey, & Lugo-Candelas, 2014). Numerous studies have shown that psychopathology in fathers is associated with a variety of negative emotional and behavioral outcomes in children (Beardslee, Gladstone, & O'Connor, 2011; Phares & Compas, 1992). Children of fathers with psychopathology showed similar rates of parent-child conflict and elevated rates of externalizing disorders to children of mothers with psychopathology (Weitzman, Rosenthal, & Liu, 2011). From a development perspective, a mutual relationship between the variables may even be postulated: children with difficult temperament features could hinder parenting practices, particularly in those caregivers who experience and perceive their own psychological problems, while parents who present psychological difficulties could aggravate children's internalizing and externalizing behaviors.

Several hypotheses have been proposed to explain the association between ODD and AD. Firstly, shared associated variables could lead to co-occurrence of ODD+AD. Potential leading associated variables include child temperament, parent-child processes, social information processing biases, or exposure to neighborhood violence (Drabick, Ollendick, & Bubier, 2010). Bubier and Drabick (2009) suggest that a difficult temperamental style, a tendency to perceive situations as threatening and to make hostile attributions, and heightened autonomic arousal in stressful social situations may contribute to and exacerbate symptoms of anxiety and reactive aggression and consequently lead to clinically identifiable comorbid anxiety and disruptive behavior disorders among children. Fraire and Ollendick (2013)

suggested that three processes are common in the occurrence of this comorbidity: a) the process of emotional dysregulation, which may encompass difficulties in regulating emotional arousal, low effortful control, and difficulties with both anger and anxiety; b) the information processing deficits in internalizing and externalizing problems of behavior, which may lead to interpreting ambiguous situations as threatening; and c) the parental psychological overcontrol and poor parental emotional expressivity.

Secondly, AD affects ODD symptoms in two pathways: a) AD symptoms may mitigate ODD symptoms; b) AD symptoms may exacerbate ODD symptoms (Drabick et al., 2010). Following the first pathway, a child with ODD and social anxiety, for example, may show more sensitivity to social rewards and social punishment, which may reduce disruptive behavior. And following the second path, anxiety and ODD associated with the misinterpretation of social situations may increase the occurrence of episodic conflicts, since the situation would be altered by a negative bias.

And thirdly, one disorder may predict the other (Bufferd, Dougherty, Carlson, Rose, & Klein, 2012). Bubier and Drabick (2009) suggest that ODD in early childhood may be more likely to confer a risk of anxiety disorders. This could happen because the child with ODD has a difficult temperament, which could lead to situations in which poor conflict resolution could generate a feeling of lack of control and carry potential anxiety. Nevertheless, a recent study on the dimensions of oppositional defiant disorder in young children and heterotypic continuity with anxiety (Lavigne et al., 2014) indicated that the behavior factor of ODD and the negative affect factor of ODD did not improve the predictive ability of initial levels of anxiety for subsequent anxiety levels. The opposite may also be possible, with anxiety symptoms increasing the risk of externalizing a disorder. Bufferd et al. (2012) found that anxiety at age 3 predicts ODD at age 6 but not vice versa. It is possible that in order to avoid fearful contexts, children with anxious symptoms may become non-compliant and aggressive

to avoid fearful contexts and stimuli. Specifically, generalized anxiety disorder and separation anxiety disorder in late childhood and adolescence may predict the development of ODD and conduct disorder in adolescence. When a child with anxiety is approaching the adolescent stage, the constant emotional disturbance frequently experienced during this stage can lead to externalizing problems, particularly ODD. Furthermore, it appears that sex can interact with potential associated variables for the internalizing and externalizing disorders, with a different effect for boys and girls. Findings suggested that boys characterized by their high activity level and low levels of fear in infancy escalated in both externalizing and internalizing symptoms, whereas boys with high fear and low activity levels showed an increase in internalizing symptoms (Colder, Mott, & Berman, 2002). It is therefore important to examine associated variables by considering gender-specific pathways to disorders.

The aim of this work is to identify the main variables associated with the comorbidity of ODD+AD in a longitudinal design of n=622 community preschoolers followed from age 3 to 5. Of these 622 preschoolers, who were diagnosed with ODD only, AD only or both concurrently, we selected: n=103 at 3 years old (44 ODD only, 42 AD only and 17 ODD+AD) and n=106 at 5 years old (31 ODD only, 60 AD only and 15 ODD+AD), and we sought to evaluate the potential role of the child's sex as a moderating variable in the previous relationships. The list of potential variables related to comorbidity ODD+AD include the child's temperament traits and aggression levels, parental style and the parents' psychopathology scores, reported by parents and teachers. According to the accumulated evidence in literature, we hypothesize that the dimensions of temperament pertaining to negative affectivity and effortful control will be associated with the presence of comorbid ODD+AD. This comorbid disorder will also have higher levels of aggressiveness because children have a negative affect that predisposes them to solve situations aggressively. Also, we hypothesized that the degree of risk associated ODD+AD comorbidity with paternal

psychopathology is comparable to that associated with maternal psychopathology. We hypothesize that low positive parenting style and high over-controlling parenting style are part of the underlying processes of ODD+AD comorbidity. Finally, we expect ADs to exacerbate ODD in childhood. All these variables could differently affect ODD+AD comorbidity depending on the sex of children.

Methods

Participants

The sample is part of a large research project on behavioral disorders in childhood. A two-phase design was employed, extensively described in Ezpeleta, de la Osa and Domènech (2014). A total of 2,283 families were obtained from the census of all 3-year-old children attending school in Barcelona (N = 13,578). A total of 1,341 agreed to participate in the first phase. Sixty-three children were excluded due to language issues or overall developmental problems, and the remaining 1,278 were screened using the behavioral problems scale of the Strengths and Difficulties Questionnaire (parent version) for 3 to 4 year-olds (SDQ3-4; Goodman, 1997) plus four symptoms from the Diagnostic and Statistical Manual of Mental Disorders ODD (DSM-IV-TR; American Psychiatric Association, 2000) not present in the questionnaire (deliberately annoys people, blames others, is touchy, angry and resentful). A positive screening was considered to be raw scores of ≥ 4 in the SDQ3-4 conduct problems scale or a response option of 2 ('certainly true') in any of the 8 DSM-IV ODD symptoms list.

All children with a positive screening score were invited to participate (N = 522 cases, 42.9%), as well as a random 30% of the N = 756 children with a negative screening score. The final sample at the end of the screening phase included 622 children (417 with a positive screening score and 205 negative). This work includes data from assessments at ages 3 and 5.

From the initial sample of 622 participants at age 3 years, $n=103$ children were selected for the analysis: those who had ODD only ($n = 44$), AD only ($n = 42$) or ODD+AD comorbidity ($n = 17$). The sex distribution was 50 girls (48.5%) and 53 boys (51.5%). Socioeconomic status (Hollingshead, 1975) was distributed as follows: 52 subjects at high or medium-high levels (50.4%), 19 at a medium level (18.4%) and 32 at medium-low or low levels (31.0%).

At the age of 5, data was available for $n=537$ (86.3%) of the children who initiated the follow-up. No statistical differences emerged between dropouts during the follow-up and completers in sex ($p=.44$) nor socioeconomic status ($p=.29$). From this sample, $n=106$ children were selected with ODD only ($n = 31$), AD only ($n = 60$) or ODD+AD comorbidity ($n = 15$). No significant differences emerged for sex distribution ($p = .284$) and socioeconomic status ($p = .258$) when comparing the diagnostic groups.

Instruments

The *Diagnostic Interview for Children and Adolescents for Parents of Preschool and Young Children (DICA-PPYC; Reich & Ezpeleta, 2009)* is a semi-structured interview adapted to the Spanish population (Ezpeleta, de la Osa, Granero, Domènech, & Reich, 2011), and is designed to assess mental disorders in children aged 3-7 years according to the DSM-IV criteria. The diagnoses of the interview were used to form the groups (ODD, AD and ODD+AD). In this study AD included separation anxiety, generalized anxiety disorder, specific phobia and social phobia. The "other comorbidity" variable included as a covariate (control value) in the analysis included ADHD, conduct disorder, depression and dysthymia. The instrument showed acceptable test-retest agreement and moderate convergence with other measures of psychopathology. The inter-rater reliability for DICA-PPYC showed good kappa concordance for ODD and AD (Ezpeleta et al., 2011).

The *Children's Behavior Questionnaire for 3–7 years (CBQ3-7*; Rothbart, Ahadi, Hershey, & Fisher, 2001) assesses reactive and self-regulatory temperament for 94 items organized into 15 scales of the first order, which also makes it possible to obtain 3 overall dimensions of temperament: negative affectivity, surgency and effortful control. The information in this tool was provided by the parents. Mothers completed the questionnaire in 62.8% of the cases, fathers in 8.0% and both parents completed it together in 29.3% of the cases. The psychometric properties of this instrument are adequate (Gagne, Van Hulle, Aksan, Essex, & Goldsmith, 2011).

The *Alabama Parenting Questionnaire (APQ*; Frick, 1991) assesses the different parental educational styles. We used the APQ-Pr (de la Osa, Granero, Penelo, Domènech, & Ezpeleta, 2013) preschool adaptation consisting of 42 items rated on a Likert scale (from 1 "never" to 5 "always") adapted from the wording of the original eight-item questionnaire, which was considered unsuitable for preschoolers. This evaluates five scales: involvement, positive parenting style, corporal punishment, inconsistent discipline and poor supervision. This study aggregated two scales: norms and autonomy (Meunier & Roskam, 2009). The good psychometric properties of this instrument are detailed in de la Osa et al. (2013).

The *Children's Aggression Scale (CAS*; Halperin & McKay, 2008) assesses aggressive behavior for 22 items with a Likert scale (from 0 = "never" to 4 = "many days"). In this study, verbal aggression, physical aggression and total aggression were analyzed. The questionnaire was answered by teachers when the children were 3 years old. The scale as a whole has excellent reliability (Halperin, McKay, Grayson, & Newcorn, 2003).

The *Risk Factors Schedule (PFR* in Spanish; Unitat d'Epidemiologia i de Diagnòstic en Psicopatologia del Desenvolupament, 2009) consists of a listing of situations which can have a significant impact on the development of mental disorders. The number of stressful life events was analyzed.

The *Adult Self-Report (ASR; Achenbach & Rescorla, 2003)* was used to assess the psychological problems and psychosocial functioning of parents for 126 items. This made it possible to obtain scores on 5 scales of adaptive functioning (friends, couples, family, work and education), 8 syndrome scales (anxiety-depression, withdrawal, somatic complaints, thought problems, attention problems, aggressive behavior, rule breaking and intrusive behavior) and 3 scales of substance use (snuff, alcohol and drugs). In this study the responses of fathers and mothers were analyzed. The ASR is widely used, and has strong research foundations and psychometric properties (Achenbach & Rescorla, 2003).

This study analyzed the diagnoses generated with the DICA interview in children of 3 and 5 years of age, and scores from questionnaires obtained when the participants were 3. The internal consistency of the analyzed scales is included in Table A (online).

Procedure

Approval was obtained from the Ethics Review Committee of the authors' institution. Head teachers of the participating schools were provided with a full description of the research, and their collaboration was also requested. Families were invited to participate and asked for their written consent. Interviewers trained to use the DICA-PPYC interviewed parents at the schools. The interview panel consisted of 10 members who completed an intensive 1-week training period consisting of learning the characteristics of the symptoms and disorders, the methods for identifying these characteristics and how to code the symptoms. The questionnaires were answered at the center by the participants' parents.

Data analysis

Data analysis was carried out using SPSS20 for Windows. Due to the multi-phase design the analysis was weighted, assigning to each participant a weight equal to the inverse probability of selection in the second phase of sampling (after the screening).

To obtain the best predictors of the criterion (dependent variable) diagnostic subtype (ODD only, AD only or ODD+AD comorbidity), regression analyses were estimated considering the potential risk factors of the independent variables. Since the response in this modeling corresponds to a multilevel nominal variable, multinomial logistic regression was carried out. This statistical procedure (also known as polytomous LR, multiclass LR or multinomial logit) constitutes an extension of the binary logistic regression to multiclass dependent variables (categorical outcomes with more than two levels), and consequently each estimated B-parameter in regressions with multiple predictor variables represents the expected change in the log odds of being in the corresponding class of the criterion (compared to other reference groups) for a unit increase in the corresponding independent variable while holding the other predictor variables constant at a certain value. Each exponentiated eB coefficient is the ratio of two odds (odds ratio, OR), or the change in odds in the multiplicative scale for a unit increase in the corresponding predictor variable while controlling for the other variables.

The estimation of the predictive models was done in two steps. Firstly, due to the large list of independent variables, initial single multinomials were adjusted (one regression for each independent variable). Each single model was controlled by the covariates “presence of comorbidities other than ODD and AD” and children’s sex. And since one objective of the analysis was to obtain evidence about the potential moderating role of the children’s sex on the relationship between the independent variables and the diagnostic subtype, the interaction parameter of the children’s sex was tested for each potential predictor; non-relevant interaction parameters ($p > .10$) were excluded from the model while relevant interactions (p

$\leq .10$) were retained and single effects were estimated (single effects represent the contribution of the risk factor on the criterion separately for boys and girls).

The second step of the multinomial regression analysis consisted of multivariate models with significant predictors for the diagnostic subtype (ODD only, AD only or ODD+AD). Stepwise procedure was used considering as independent variables all the significant predictors identified in the single models. Two final multinomial regressions were obtained, one with the main variables explaining the diagnostic subtype at age 3 and the other with the main predictors at age 5 (this last model included as predictors the variables measured at 3 years, and as the criterion the diagnostic subtype at age 5). Both of these final models included the covariates children's sex and other comorbidities different to ODD and AD (at baseline, age 3). The Fadden R² coefficient estimated the overall predictive ability of the final regressions.

Results

Table A (online) presents the list of the associated variables analyzed in this study and their distribution (percentages and means) in the three diagnostic groups separately at ages 3 and 5. The frequency distributions for two additional reference groups have also been included with the aim of facilitating the interpretation of the results: a healthy group with children who did not meet criteria for any psychopathological disorder in the diagnostic interview and a group with the children who met the criteria for any disorder different to ODD and AD.

Table B (online) contains the correlation matrix for the main variables considered as potential risk factors for the presence of the ODD+AD comorbidity during preschool age.

Cross sectional associations of associated variables and ODD+AD comorbidity at age 3

Model 1 included in Table 1 corresponds to the final multinomial regression with the main associated variables (measured at age 3) of the diagnostic subtype (also at age 3, classified as ODD only, AD only and ODD+AD comorbidity). The results of this model are adjusted to the covariates of the children's sex and comorbidities other than ODD and AD. These two variables played the role of covariates and were adjusted according to the many empirical results evidencing strong associations between young children's gender and the presence of psychological disorders with the potential risk factors (a lack of adjustment could lead to biased results). The odds of presenting a comorbid diagnosis ODD+AD (compared with ODD only) are increased by high scores on the ASR-father-total. The odds of presenting a comorbid ODD+AD (compared with AD only) are increased by high scores on CBQ-anger frustration, low scores on CBQ-inhibitory control, low scores on CAS-verbal aggression and high scores on ASR-mother aggressive behavior. This model obtained a very good overall predictive ability ($R^2a = .580$, adjusted to the covariates included in the regression). Comparing the presence of AD only and ODD only, high scores on anger/frustration and mothers aggression are associated with ODD only, while high scores on fear, inhibitory control and shyness (for females) are associated with AD only.

--- Insert Table 1 ---

Age 3 predictors of ODD+AD comorbidity at age 5

The second model in Table 1 presents the predictive multinomial model valuing the main associated variables (measured at age 3) of the diagnostic subtype (measured at age 5). This model was also adjusted by the children's sex and the presence of disorders other than ODD and AD at baseline. The presence of the comorbid ODD+AD (compared with both ODD only and AD only) was predicted by high scores on the CBQ-Approach-Positive Anticipation, and low scores on CBQ-Smiling/Laughter. Moreover, the CBQ-Fear score

showed a significant interaction with sex ($p < .001$), in the sense that high scores were linked to reduced ODD+AD comorbidity in girls and predictors of such comorbidity in boys. The odds of ODD+AD comorbidity (compared with ODD only) were associated with low scores on APQ-corporal punishment, while high scores on CAS-Total score predicted ODD+AD comorbidity (compared with AD only). The overall predictive capability of Model 2 was also very good ($R^2a = .433$, adjusted to the covariates included in the regression). The comparison of AD only versus ODD only shows that the odds of ODD are increased for children with high CAS-Total and APQ-Punitive parenting scores.

Stability ODD+AD comorbidity from ages 3 to 5

Considering the whole sample of participants with the data available at age 5 ($n=574$), 4 children (weighted prevalence equal to 0.35%; 95% CI: 0.10% to 1.27%) presented persistent chronic comorbid ODD+AD during the follow-up between ages 3 and 5, eleven children (1.50%; 95% CI: 0.71% to 2.74%) were comorbid only at age 3, the other 11 only at age 5 (1.50%; 95% CI: 0.71% to 2.74%), and 548 children (96.7%; 95% CI: 94.9% to 97.9%) were free of comorbid ODD+AD during preschool age 3 to 5. According to these results, the risk of developing the comorbidity during ages 3 to 5 (the incidence of children with ODD+AD present at age 5 among those starting the comorbidity absent at baseline) was 1.60% (95% CI: 0.84% to 3.02%), and the risk of remission of the comorbidity during follow-up (the incidence of children without ODD+AD at age 5 among those with the comorbidity present at baseline) was 80% (95% CI: 49.0% to 94.3%).

In the cohort of children aged 3 diagnosed with ODD only (and taking the whole sample of children with complete data at the end of the follow-up, $n=574$, as a reference), the diagnostic subtype was distributed at age 5 as follows: 35.7% in the health control group (absence of any psychological disorder), 28.6% in disorders other than ODD and AD, 25.0% remained in the same diagnostic condition (ODD-only), 3.6% were reclassified into the AD

only and 7.1% into the ODD+AD comorbidity groups. The subsample of children aged 3 diagnosed with AD only was distributed as follows two years later: 33.3% in the health control group, 18.2% in the group with disorders other than ODD and AD, 3.0% in the ODD only condition, 42.4% in the AD only condition and 3.0% in the ODD+AD comorbidity.

Discussion

The results of this study make it possible to identify specific associated variables for ODD+AD comorbidity (cross-sectionally and longitudinally) in the general population of preschoolers. Cross-sectionally, at age 3, the factors associated with ODD+AD comorbidity differ in degree from those of ODD; only the father's psychopathology (higher) is specifically associated with ODD+AD comorbidity. The factors associated with ODD+AD comorbidity differ more in comparison with those which are associated with the presence of AD only; in this case the comorbidity is associated with higher levels of anger-frustration, less inhibitory control, less verbal aggression and with high levels of the mother's aggressive behavior, which indicates that these risk characteristics are more attenuated in children who suffer only from AD. Longitudinally however, ODD+AD comorbidity has consistently different levels in its predictors when compared with the disorders individually. The risk profile for ODD+AD comorbidity at 5 years of age would be marked by a temperament characterized by high approach, low fear (in girls), high fear (in boys) and low positive affect, high aggressive behavior when compared with AD, and lower body punishment when compared to ODD at age 3. Therefore ODD+AD comorbidity seems to have specific predictors, which are more clearly established as the children progress in their development. The results of the temporal stability of comorbid ODD+AD indicated that the risk of developing the comorbidity from ages 3 to 5 was 1.60%, and the risk of remission of the comorbidity during follow-up was 80%.

Child temperament

The temperament characteristics of children with comorbid ODD+AD at age 3 are characterized by a high negative emotionality, low inhibitory control and a low frequency of verbal aggression. Firstly, difficult temperamental styles, such as negative emotionality, irritability and low frustration tolerance, have been linked to both anxiety and aggression (Bubier & Drabick, 2009), and, in particular, reactive aggression (Ortiz & del Barrio, 2006). This frustration/anger and overt aggression may involve reactive negative affect, and children may become frustrated and angry, and are more likely to lash out at others (Deater-Deckard et al., 2010). Two types of aggression can be distinguished: proactive and reactive. Proactive aggression responds to an instrumental pattern, well-organized and goal-directed, motivated by obtaining reward and regulated by the reinforcement. Reactive aggression, however, responds to a reactive and uncontrolled stimulus, and it is motivated by a challenge pattern, by fear and irritability (Hubbard, Romano, McAuliffe, & Morrow, 2010). Reactive aggression is more linked to hostile attribution and ambiguous stimulus, both elements usually present in children who present the comorbid ODD+AD condition. Low language skills are typical of preschool age, and aggressive behaviors tend to be more physical than verbal. It is not surprising that children with ODD+AD choose physical aggression to deal with problematic situations. Underlying biological processes may contribute to both negative emotionality and the subsequent behavioral problems (Rothbart & Bates, 1998). In addition, this temperamental trait (negative emotionality) may elicit caregiver responses (e.g. harsh discipline), that might lead to problems being externalizing later.

Secondly, we also found that problems in emotional dysregulation and a low inhibitory control indicate a higher probability of experiencing ODD+AD comorbidity. According to the model proposed by Drabick et al. (2010) in which anxiety can exacerbate ODD symptoms, the lack of inhibitory control and impulsivity characteristic of ODD+AD

comorbidity could precipitate children into conflict situations, since on the one hand, anxiety may lead them to interpret ambiguous situations as hostile, and a lack of control does not allow them to stop and choose appropriate types of behavior. Children with comorbid ODD+AD will have more difficulties in following rules, will present more impairment at school, and will receive more punishment; which in turn will generate more anger and frustration. Thirdly, reactive aggression and anxiety symptoms are related to ODD+AD comorbidity (Bubier & Drabick, 2009). For example, children with ODD+AD comorbidity and in an ambiguous situation construed as threatening first attempt to flee, rather than initiating conflict with verbal aggression. It is therefore more likely that the type of aggression in children with comorbid ODD+AD is more physical than verbal in nature.

Longitudinally, temperament characteristics at age 3 were differentially predictive of comorbidity in comparison with the individual disorders. It may be that underlying processes trigger a behavioral activation system in which reward-seeking behavior, when impeded, increases the likelihood of internalizing and externalizing problems for some children (Deater-Deckard et al., 2010). Therefore, interventions aimed at regulating frustration and anger may be more effective if they also address the management of approach behavior. A temperament with a tendency to experience fear is also predictive of ODD+AD comorbidity. The association was moderated by sex, with fear being a protective factor for girls and a related factor for boys. In line with a socialization hypothesis (Maccoby & Jacklin, 1974), the expression of fear is more acceptable for girls than for boys, which can mean that for fearful boys, hostile situations that are better coped with by adopting an aggressive response. The Smiling and Laughter scale in this study assessed the amount of positive affect in response to changes in stimulus intensity, rate, complexity, and incongruity. The low level on this scale could also be explained by the interaction with parents, since, as indicated by Fraire and Ollendick (2013), emotional expression in parents of children with ODD+AD

comorbidity is less positive than in parents of children without ODD+AD comorbidity. One possible explication of why children with ODD+AD comorbidity smile and laugh less frequently than children without this comorbidity might be that the internal discomfort of having two disorders together leads to less smiling probably because they are less happy than children who do not suffer from any disorders. Along similar lines, comparing ODD only and AD only, the ODD+AD group at age 5 had lower positive affect than at age 3. It is possible that this is a developmental pathway to depression (De Pauw & Mervielde, 2010). This suggests that low positive affect predicts depression and so does ODD and anxiety. Both high approach and low positive affect were linked to comorbid ODD+AD. A positive affect when accompanied by an intense, impulsive approach is associated with externalizing disorders (Stifter, Putnam, & Jahromi, 2008) and AD could exacerbate ODD symptoms (Drabick et al., 2010).

Parental psychopathology and parental practices

The psychopathology of the fathers is becoming increasingly important in relation to the mental health of their children at age 3, but few studies have data on parents due to their lower participation. In a study into parental depression, Kane and Garber (2004) found that only the father's depression, compared with the mother's depression, was associated with internalizing and externalizing problems in children. In our study, there is evidence that the psychopathology of the father is associated with comorbid ODD+AD and AD when compared with ODD only. Studies on family systems recognize the importance of parental influence on children and family (Bell et al., 2007), but despite this there is still much less research about fathers. Bögels and Phares (2008) found that fathers might have an even greater influence than mothers on the development of children's social anxiety, and a possible explanation for this would be in the role played by the father in socializing their children. That is, parental anxiety may cause the relationship of parents with their offspring to be less affectionate and

more conflictual, which would lead children to be at risk for anxiety symptoms. Recent findings have suggested that the father's psychopathology can be associated with an increased risk of problems for children, regardless of maternal psychiatric wellbeing (Ramchandani & Psychogiou, 2009). In other studies, the impact of paternal psychopathology on child outcomes appears modest but given the constraints of the time factor, as fathers spend less time with their children compared to mothers, this could make it seem that mothers have more effect on their children (Pilowsky et al., 2014). Regarding the influence of mothers, the association of maternal aggression and ODD+AD comorbidity can be explained by shared genes or by modelling that favors similar personalities and types of behavior (Wahl & Metzner, 2011). Mothers of aggressive children can therefore model a hostile attribution because of the tendency to view the ambiguous actions of others as hostile, increasing the probability of responding with aggression (MacBrayer, Milich, & Hundley, 2003).

With regard to parental practices, the results of this study indicate that low levels of punitive parenting predict ODD+AD comorbidity, given that children with comorbid ODD+AD or AD alone are spanked less than children with ODD alone. This suggests that anxiety may have a mitigating effect on the expression of the comorbid disorder and it is for this reason that children are punished less.

Stability of ODD+AD

In terms of the stability of ODD+AD comorbidity, preschoolers with ODD are likely to continue to exhibit the disorder, with increasing comorbidity with anxiety disorders. Our study into the stability of ODD+AD comorbidity from ages 3 to 5 was weak. Lavigne et al. (2001) found that ODD+AD stability in preschoolers was moderate to high. Longer stability studies with larger samples are necessary in order to draw conclusions about the question of the stability of ODD+AD.

We expected that anxiety may exacerbate ODD, but our results do not necessarily support this argument. For instance, at age 3 the ODD+AD and ODD groups only differed on total father's psychopathology, whereas the ODD+AD and AD groups differ on several variables. This suggests that it is the addition of ODD that seems to be related to more problematic characteristics. Thus, ODD is likely to be the more impairing problem at age 3. Based on these findings, very few differences emerge when the comorbid group is compared with the ODD only group, which suggests that the ODD is contributing to the impairment, not the addition of the AD. We were hoping that AD exacerbates ODD but it could be the addition the ODD diagnosis which implies further impairment in children. It is true that children with ODD+AD comorbidity are less verbally aggressive compared to children with anxiety, but when aggression is recognized in all its forms, children with ODD+AD comorbidity are more aggressive than children who only meet the anxious diagnosis. So it may be that anxiety decreases a particular type of aggressiveness in children with ODD.

Limitations

The sample from which this study's diagnostic subtypes are drawn is very large, and therefore, since it is a general population, the size of the subtypes for ODD, AD and ODD+AD comorbidity is reduced, which is to be expected. This study provides no direct information from children, even though at this age parents are one of the best sources of information and also have information for teachers. In addition, significant associations were found that have important practical implications. Finally, it must be considered that although some studies have found moderate reliability (homotypic and heterotypic comorbidity) in the presence of some psychiatric disorders during the preschool age (Bufferd et al., 2012), the validity of psychiatric diagnoses in young children is as yet debated in the scientific literature and the potential lack of stability for ODD and AD symptoms during the preschool period analyzed in this work could affect the variables retained in the predictive models.

Implications

The main contributions of this work are the inclusion of a large set of potential variables that could influence the presence of the comorbid ODD+AD condition, the availability of a large community sample of young children, the prospective longitudinal design (follow-up between ages 3 to 5), and the analysis of measures including questionnaire and diagnostic structured interview data.

This work promotes a greater understanding of the presence of the comorbid condition ODD+AD at very young ages, its prevalence and main risk factors. Our results underline the relevance of assessing the relationships between children at high risk of externalizing and internalizing symptoms and their caregivers. The negative consequences of having comorbid ODD+AD and the considerable influence of comorbidity on treatment efficacy (Rapee et al., 2013) highlight the importance of studying the factors that facilitate these partnerships in order to direct tasks of early prevention more accurately. We should be alert to certain temperament traits in preschoolers that may indicate a risk of developing ODD+AD comorbidity, with the negative consequences that this entails and the high risk of further psychopathology during school age and even adolescence (Leadbeater & Homel, 2015). Future research into developing appropriate measurement instruments to easily identify this comorbid condition at young ages, and new studies on the etiology and developmental trajectories are needed in order to further prevention and treatment strategies, and to verify the effectiveness of the existing therapy protocols.

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Table 1

Final predictive multinomial models for the diagnostic subtype

Comparison →	ODD+AD / ODD		ODD+AD / AD		AD / ODD	
	OR	95% CI (OR)	OR	95% CI (OR)	OR	95% CI (OR)
Model 1. AV=age 3; Diag=age 3. ($R^2_a=.580$)						
CBQ: Anger-Frustration	2.33	(0.48; 11.4)	41.3	(3.67; 465)	0.06	(0.01; 0.45)
CBQ: Fear	1.47	(0.59; 3.68)	0.50	(0.13; 1.83)	2.96	(1.02; 8.62)
CBQ: Inhibitory control	1.18	(0.30; 4.67)	0.10	(0.01; 0.96)	11.62	(1.70; 79.3)
CBQ: Shyness	1.12F	(0.20; 6.36)	0.15F	(0.02; 1.08)	7.70F	(2.06; 28.8)
	7.63 ^M	(0.92; 63.0)	10.5 ^M	(0.92; 120)	0.73 ^M	(0.17; 3.17)
CAS: Verbal aggression	0.97	(0.95; 1.00)	0.97	(0.95; 0.99)	1.00	(0.99; 1.01)
APQ: Inconsistent discipline	0.63	(0.37; 1.07)	1.00	(0.50; 2.00)	0.63	(0.37; 1.07)
ASR-Mother: aggressive behavior	1.13	(0.80; 1.60)	2.52	(1.36; 4.65)	0.45	(0.26; 0.78)
ASR-Father: Total Score	1.20	(1.04; 1.38)	1.00	(0.87; 1.16)	1.19	(1.04; 1.37)
Model 2. AV=age 3; Diag= age 5. ($R^2_a=.433$)						
CBQ: Approach-Positive Anticipation	31.3	(1.86; 528)	18.7	(1.23; 283)	1.68	(0.51; 5.50)
CBQ: Fear	0.01^F	(0.00; 0.25)	0.01^F	(0.00; 0.21)	1.24 ^F	(0.52; 2.95)
	11.9^M	(1.34; 106)	13.6^M	(1.47; 125)	0.88 ^M	(0.29; 2.64)
CBQ: Smiling/Laughter	0.02	(0.00; 0.35)	0.02	(0.00; 0.46)	0.71	(0.27; 1.86)
CAS: Total Score	1.05	(0.98; 1.14)	1.11	(1.02; 1.20)	0.95	(0.92; 0.99)
APQ: Punitive parenting	0.13	(0.03; 0.64)	0.46	(0.10; 2.12)	0.28	(0.11; 0.68)

Note. Results obtained in multinomial regression adjusted by the sex covariates and the presence of comorbidities other than ODD and AD. $R^2_a = R^2$ coefficient adjusted to covariates. Bold: significant parameters (.05 level).

ODD: Oppositional Defiant Disorder. AD: Anxiety Disorder. ODD+AD: ODD+AD comorbidity.

OR: Odds ratio. CI: Confidence Interval.

CBQ: Children's Behavior Questionnaire. CAS: Children's Aggression Scale. APQ: Alabama Parenting Questionnaire. ASR: Adult Self-Report. RF: associated variables. ^FSingle effects for girls (females). ^MSingle effects for boys (males).

Model 1: associated variables (AV) and diagnostic group (Diag) measured at age 3 ($n=103$).

Model 2: associated variables (AV) measured at age 3 and diagnostic group (Diag) at age 5 ($n=106$).

7.3 Tercer trabajo empírico: artículo enviado

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Executive functions in preschoolers with comorbid oppositional defiant disorder and anxiety disorders

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The suggested running head

Executive functions with ODD and AD

Executive functions in preschoolers with comorbid oppositional defiant disorder and anxiety disorders

Abstract

The co-occurrence of oppositional defiant disorder (ODD) and anxiety disorders (AD) is well established in the literature, but its underlying processes are not clear at early ages. The present study aims to identify the role of the executive functions (EF) in preschoolers who presented ODD+AD comorbidity in comparison to children with only-ODD, only-AD and those without these diagnostic conditions. An initial community sample of $N=622$ preschoolers was assessed longitudinally at ages 3 and 5 years by means of a diagnostic interview and EF's questionnaire. At age 3, the comorbidity ODD+AD was related to dysfunction in the EF shift dimension, and at age 5 to dysfunctional EF in inhibition, emotional control and plan-organize. Girls with ODD+AD comorbidity were less impaired in some EF than girls in the other diagnostic conditions. As children with ODD+AD became older showed significant impairment in EF. Anxiety (only in females) could affect ODD symptoms buffering them.

Keywords: anxiety disorders; comorbidity; executive functions; oppositional defiant disorder; preschool

Introduction

Oppositional defiant disorder (ODD) is defined by negativistic, defiant, disobedient and hostile behaviors, particularly towards figures of authority [1]. Its prevalence in childhood differs between studies, and usually ranges from 2% to 15% [2, 3, 4]. Anxiety disorder (AD) involves excessive worries or fears, behavioral avoidance, a high degree of impairment, and usually physiological symptoms, and its lifetime prevalence in children and adolescents is about 15% to 20% [5]. Concurrent ODD and AD (ODD+AD) is high in both community and clinical samples [6], and in preschoolers it ranges from 7% to 14% [7, 8]. The odds ratio of ODD in the presence of AD or vice versa is between 4.3 and 5.9, depending on the study [8,9]. Although there is some inconsistency in research results, most studies conclude that the condition of ODD accompanied by AD involves a more severe clinical condition and academic, social and family-related complications [10]. Longitudinal epidemiological research also indicates that concurrent ODD+AD early in life is a powerful predictor of prospective negative psychological sequelae in adolescence and adulthood, such as major depression, substance use/abuse or affiliation with deviant peers [11]. Such findings suggest an urgent need for the rigorous study of the etiological mechanisms and risk processes related to this comorbidity as early as possible in children's lives.

Executive functions (EF) refers to the complex cognitive processing coordinated in the brain's frontal lobe and required to achieve a specific goal in a flexible manner. EF involve the coordination of several sub-processes necessary for the ability to solve novel problems, manage time and attention, plan and organize, remember details, integrate past experience with present actions, switch focus, and modify behavior based on new information [12]. Adequate EF need satisfactory function of the frontal cortex, and when this area is altered or damaged behavior is poorly controlled. In terms of potential common etiological processes and risk factors, some studies have found an association between the

pathophysiology of ODD and of AD with dysfunctions in the limbic system and the pre-frontal cortex [13, 14]. Since these areas involved in EF are strongly related to the emotion processing that is crucial for the expression of both disorders (stimulus-reinforcement learning, recognition and processing of the emotional significance of sensory and social stimuli, planning, stimulus-response learning and response modulation), psychoneurological research should clarify the role of EF in the origin and evolution of both ODD and AD. In a recent review, Drabick et al. [6] synthesized the amount of empirical data on concurrent ODD+AD and concluded that dual pathways that characterized the relations between ODD and AD could coexist: the buffer hypothesis (anxiety actuates mitigation or lessening of ODD levels) and the multiple-problem hypothesis (the presence of anxiety exacerbates or increases ODD behaviors). For example, Walker et al. [15] presented data supporting the buffer model in a sample of children aged 7-12 years, in which the combined disruptive disorders plus AD showed lower social impairment than the disruptive disorder alone. In older samples, the presence of ODD+AD comorbidity was associated with lower odds for substance use problems compared to individuals without co-occurring AD [16]. Further, Lansford et al. [17] found that the presence of the comorbid disruptive behavior plus internalizing conditions in young people aged from 12 to 22 were associated with abrupt increases in illicit substance use during adolescence and over time.

EF are usually considered as inborn (although children are not born with these skills, they are born with the potential to develop them). They are relatively stable from toddlerhood into the early school years, and develop further as a result of brain maturation and interaction with the environment [18]. Neuropsychological research indicates that EF are crucial to the overall neuropsychological functioning of the developing child, and play an important role in children's cognitive, behavioral and social-emotional development [19]. Children with impaired EF usually present difficulties in anticipation, goal selection, initiation of activity,

self-regulation, mental flexibility, deployment of attention and utilization of feedback [20]. Some studies have shown that inadequate EF are related even at early ages to impaired judgment, behavioral disinhibition and debilitated intellectual abilities, and children with defective EF are highly vulnerable to the onset and development of various physical/psychological disorders [21]. Attention deficit hyperactivity disorder (ADHD), conduct disorder (CD), and ODD, all appear in literature related to executive dysfunction in some respects, and contemporary models almost invariably include some aspect of executive self-regulation [22]. Consequently, it is important to identify EF deficits as early as possible in order to intervene and minimize their effects on psychopathology and daily functioning (school performance, emotional, behavioral and social problems) [23].

Many studies on EF in preschool children displaying disruptive behaviors have included samples with heterotypical conduct problems, and this limits our knowledge about the specific underlying process of ODD [24, 25]. Along these lines, Raaijmakers et al. [26] found that preschool children with conduct problems (specifically aggressive behavior) showed impairments in inhibition, regardless of attention problems. Drabick et al. [10], in a study more specifically related to the presence of ODD, reported that individuals who presented this disorder showed deficits in some EF domains, specifically in attention, concentration, planning and inhibition. Blair [13] also concluded that problems with EF in early childhood could lead to difficulties in representing reinforcement expectancies, which are crucial for inhibiting the aggressive and oppositional responses observed later in young people diagnosed with ODD.

Research on the etiology of AD also suggests that dysfunction in EF may underlie the hyper-vigilance, attention to threat-related stimuli and autonomic responses observed in individuals with anxiety symptoms [27], who misperceive neutral or ambiguous stimuli as threatening. Research with young samples has shown that EF characterized by low levels of

verbal learning and deficits in working memory are related to social phobia [28], and that poor working memory seems to be an underlying factor in AD [29]. At preschool ages, high levels of attention shifting were associated with low risk of anxiety symptoms, while high levels of inhibitory control increased the risk for anxiety [30].

Specific EF increase or decrease the likelihood of comorbid ODD and AD [31], even at early ages. Although evidence from research in this area is scarce, some studies suggest plausible explanations. Coy et al. [32] observed that preschool-age ODD boys generate more aggressive solutions and encode social information less accurately than control children, and concluded that AD and ODD are related to comparable biases in multiple stages of information processing including hyper-vigilance, negative interpretations of social situations and hostile attributions. Reid et al. [33], in a similar line of research, concluded that social information processing biases in childhood may underlie this comorbid condition since these processes constitute the common basis of the emotionally reactive responses of aggression and anxiety. In short, at preschool age, impairment in attention-shifting and inhibitory control appears to moderate the association between anxiety symptoms and behavioral problems, increasing the odds of presenting these comorbid conditions [28]. In this line of research, Zelazo et al. [34] proposed a model of a functional view of EF composed of different sequences of representation-execution aimed to achieve a goal. Each sequence would require the child's ability to generate and implement systems of conditional rules governing the behavior, cognition and emotions. The EF would be involved in the various steps of the sequence aimed at solving problems, but children with ODD+AD comorbidity would have information processing biases for successfully managing the first step in the EF sequence (problem representation) that would lead to systematic errors.

The literature on the potential moderating effect of young children's sex on the expression of EF shows that girls present higher levels of functioning compared to boys in the

same age range. It has been reported that girls aged between 3 and 13 showed better clinical measures than their male peers in various dimensions of attention management [35].

Furthermore, kindergarten teachers have confirmed better performance in girls compared to boys in working memory, attention, and inhibitory control [36]. Preschool boys exhibit more impairment in attention-shifting, inhibition, working memory and verbal fluency than girls of the same age [26]. A longitudinal study covering the period from age 1 to 3 years found that behavioral self-control was better in girls [37], while it was also reported that girl preschoolers showed better cognitive self-regulation [38]. Duckworth et al. [39] also observed in a longitudinal study that adolescent girls showed more self-control than their male counterparts, and hypothesized that this sex-related difference could be a factor in the epidemiological differences between boys and girls found in psychopathology related to self-control deficits (for example, the higher levels of disruptive problems in boys and the higher AD levels in girls).

The period between age 3 and age 5 is a key one for the development of skills dependent on EF. However, there is no solid empirical evidence of the relationship between EF and the co-occurrence of ODD+AD during the preschool period in community samples, or on the potential role of children's sex in this relationship. The main objective of the present study is to examine the role of EF in the presence of ODD and AD during the preschool period in a large sample selected from the general population. The EF levels of children diagnosed with concurrent ODD+AD at ages 3 and 5 are compared to those of children with only-ODD and only-AD. As secondary objective, this study explores how the previous three diagnostic conditions differ from a reference group of children with other diagnostic conditions different of ODD and AD, and a control group of children without disorders. Furthermore, we compare scores of EF registered at age 3 with the diagnostic subtypes (no disorder, disorder different to ODD-AD, only-ODD, only-AD and ODD+AD) at 5 years of

age. Moreover, we explore longitudinally the potential moderating role of children's sex in the relationship between EF levels and the presence of comorbid ODD+AD at these two ages. Based on the existing theoretical framework, we hypothesize that the comorbid ODD+AD group would exhibit more dysregulated EF (poor executive functioning) compared to those in the other diagnostic conditions. Regarding differences in the relationships by gender, it is expected that boys with ODD+AD would perform more poorly than girls who present also this comorbid condition.

Method

Sample

The sample derives from an extensive research project on behavioral disorders in childhood. (see Ezpeleta et al. [9], for a description of the two-phase design). A total of 2,283 families, obtained from the census of all 3-year-old preschoolers in the Barcelona region ($N = 13,578$), were invited to participate, with 1,341 accepting the invitation. No statistical differences were found in children's sex ($p=.95$) and family socioeconomic status (SES; Hollingshead [40], 1975) ($p=.15$) when comparing participants and decliners. Sixty-three preschoolers were excluded due to language issues or overall developmental problems, and the remaining 1,278 were screened using the behavioral problems scale of the Strengths and Difficulties Questionnaire for parents of 3- to 4-year-olds (SDQ3-4; Goodman [41], plus four ODD symptoms (deliberately annoys people, blames others, is touchy, angry and resentful) from the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR; American Psychiatric Association [1]) not present in the questionnaire. Screening was considered positive for raw scores ≥ 4 on the SDQ³⁻⁴ conduct problems scale, or a response option of 2 ('certainly true') for any of the 8 DSM-IV-TR ODD symptoms listed.

All preschoolers with a positive screening score were invited to participate ($N = 522$ cases, 42.9%), as well as a random 30% of the $N = 756$ children with a negative screening score. The comparison of the children with a negative screening score selected for the study ($n=235$) and those non-selected with negative screening score ($n=521$) achieved non-significant results for child's sex ($p=.82$) and family SES ($p=.82$). The final sample at the end of the screening phase included 622 preschoolers (417 with a positive screening score and 205 with a negative one). This work includes data from assessments at ages 3 and 5 years.

The descriptive data for the sample of $n=622$ participants at age 3 years are included in Table 1. The children were classified into five groups according to their diagnosis: no diagnosis ($n=380$, children without any of the DSM-IV disorders shown in Table 2), at least one diagnosed disorder different to ODD and AD ($n=140$, children with ADHD, or CD), ODD without AD ($n=44$, children who presented the DSM-IV criteria for ODD but not for AD, and that could present - or not - other different comorbid conditions), AD without ODD ($n=41$, children with the DSM-IV criteria for AD but not for ODD, and that could exhibit - or not - other different comorbid conditions), and comorbid ODD+AD ($n=17$, children who presented the DSM-IV criteria for both ODD and AD, and who could also present other different comorbid conditions). The groups of children with no diagnosis and with ADHD or CD will be referred to henceforth as control groups. In addition, to simplify, the groups will be labelled as: no disorder, disorder different to ODD-AD, only-ODD, only-AD and ODD+AD.

--- Insert Table 1 ---

At age 5, data were available for $n=574$ of the children who began the follow-up phase, and distribution was as follows: no diagnosis=347, at least one diagnosis=127, only-ODD=35, only-AD=54, and ODD+AD=11. No statistically significant differences were found for participants who dropped out at age 5 or by socioeconomic status ($p=.07$) or sex ($p=.29$).

Table 2 shows the distribution of DSM-IV disorders considered in this study in the sample at ages 3 and 5. The number of children who presented a chronic course for ODD between ages 3 and 5 was $n=22$ (weighted prevalence=2.3%), for AD $n=20$ (weighted prevalence=2.8%) and for the comorbid ODD+AD condition $n=4$ (weighted prevalence=0.3%).

--- Insert Table 2 ---

Measures

The Diagnostic Interview for Children and Adolescents for Parents of Preschool and Young Children (DICA-PPYC) [42] is a semi-structured interview designed to assess DSM-IV mental disorders in children aged 3-7 years. In this study, AD included separation anxiety, generalized anxiety disorder, specific phobia and social phobia. Average administration time is around 50 minutes. The interview to parents was used for forming the diagnostic groups, and was administered at ages 3 and 5. The version of the DICA-PPYC adapted to the Spanish preschool population showed sound psychometric properties [43].

The Behavior Rating Inventory of Executive Function preschool version (BRIEF-P) [44] measures EF in children aged 2-5 years. It was answered by teachers when children were 3 years old. The scale includes 63 items recoded on a 3-point scale (from low to high frequency; the higher the frequency, the higher the executive dysfunction) and structured in 5 first-order dimensions: Inhibit, Emotional Control, Shift, Working Memory and Plan-Organize, and 3 second-order dimensions: Inhibitory Self-Control Index (ISCI, which includes Inhibition and Shift), Flexibility Index (FI, which is the sum of Shift and Emotional Control) and Emergent Metacognition Index (EMI, adding Working Memory and Plan-Organize). The Global Executive Composite (GEC) score indicates general executive performance. This questionnaire was administered at age 3. Internal consistency in the sample

was high [45], with Cronbach's alpha values in the range 0.87 (Shift scale) to 0.97 (GEC scale).

The Kaufman Brief Intelligence Test (K-Bit) [46] was used as a measure of the children's IQ. It was applied at age 4. It consists of a brief test designed for people aged 4 to 90. Two scales were used: Vocabulary (Verbal) and Matrix (Nonverbal). A global score was obtained as the mean of Vocabulary and Matrix scores, and was considered a covariate in this study.

The Strengths and Difficulties Questionnaire (SDQ) [47], completed by the parents, was used in the screening phase of the sampling procedure to identify children with high risk of disruptive behaviors. This questionnaire includes 25 items structured on five scales: emotional symptoms, conduct problems, hyperactivity, peer relationship problems, and prosocial behavior. A raw score defined as the sum of the first four scales also provides a total difficulties score (the higher scores, the higher the behavioral and emotional difficulties). Cronbach's alpha in the sample ranged from 0.60 for emotional symptoms to 0.82 for total scale.

Procedure

Approval was obtained from the Ethics Review Committee of the authors' institution. Head teachers of the participating schools were provided with a full description of the research, and their collaboration was requested. Families were invited to participate and asked for their written consent. Interviewers trained to use the DICA-PPYC interviewed parents at the schools. The interviewers completed an intensive one-week training period to learn about the characteristics of the symptoms and disorders, the methods for identifying these characteristics, and how to code the symptoms. Afterwards, the training period was extended until they obtained good agreement with an expert interviewer ($kappa \geq .80$) in an acceptable

number of interviews (not less than five consecutive interviews). The mean inter-rater reliability, measured through kappa computed between two raters over a single interview of a total of 34 interviews, was 0.89, with a range between 0.74 and 1. After the interview parents completed the questionnaires and gave the consent to ask the teachers. The teachers who completed the BRIEF-P had known the 3-year-old children for a mean of 7.6 months (SD = 2.2) before responding to this instrument.

Statistical analysis

Statistical analysis was carried out using SPSS20 for Windows. Due to the multi-phase design the analysis was weighted, assigning to each participant a weight equal to the inverse probability of selection in the second phase of sampling (after the screening).

Analysis of variance (ANOVA) was used for the comparison of the BRIEF-P scores between diagnostic groups at ages 3 and 5, adjusted for the covariates children's sex, socioeconomic status and intelligence quotient. Although it has been reported a strong association between ADHD and EF [48], ADHD was not included as an additional covariate since it was checked the absence of bias due to a confounding effect: in this study ADHD was not statistically related to the diagnostic group at age 3 years old ($p=.17$) nor at age 5 ($p=.21$).

The tested models included the interaction group \times sex parameter: in the case of relevant interaction ($p\leq.20$), this term was retained in the model and single effects indicating the degree of association between EF and diagnoses were obtained separately for boys and girls. For non-relevant interaction ($p>.20$), the group \times sex parameter was excluded from the ANOVA and main effects were estimated and interpreted. In this study, a threshold of 0.20 was selected as indicative of relevant interactions due to the low sample size of some diagnostic groups

Due to the multiple statistical comparison, the analyses were corrected to prevent an increase in the Type-I error through the Bonferroni-Finner procedure, an alternative to the classical Bonferroni method. In addition, since the measurement of the associations' effect size is more relevant than statistical significance, all the pairwise comparisons in the ANOVA were accompanied by Cohen's-*d* coefficients [49]. Only pairwise comparisons with mean differences attaining moderate ($|d|>0.50$) to good effect size ($|d|>0.80$) were considered relevant, and were interpreted as indicating relevant clinical differences between the diagnostic groups. In addition, the partial-eta² coefficient (η^2) was used to measure the global discriminative capacity of each model.

Results

Association between EF and ODD+AD at age 3

The first part of Table 3 includes the comparison of the BRIEF-P mean scores registered at age 3 and between the diagnostic subtypes (the groups were defined also for the diagnosis at 3 years old). The ANOVA procedures are adjusted for child's sex, family's socioeconomic status and IQ. At this age, Inhibit mean score differed for only-ODD compared to comorbid ODD+AD (higher mean for only-ODD). Shift mean score also differed for only-ODD compared to ODD+AD, but in a different way (higher mean for comorbid ODD+AD). One interaction group×sex emerged for the FI index: a) for girls, a higher mean was observed for only-AD versus ODD+AD; b) for boys the comorbid ODD+AD condition attained a higher mean than those for boys with no-ODD and no-AD. At age 3, the comparison between only-ODD and only-AD (final columns in Table 3) yielded only one relevant difference: Shift mean score was higher for only-AD.

--- Insert Table 3 ---

Association between EF and ODD+AD at age 5

The second part of Table 3 contains the results of ANOVA models comparing the BRIEF-P mean scores registered at age 3 with the diagnostic subtypes at 5 years of age. At age 5, many relevant pairwise comparisons were obtained (second part of Table 3). Comorbid ODD+AD obtained higher means compared to the no-diagnosis group for all BRIEF-P scores except Shift, Plan-Organize and ISCI-index, and compared to the “at least one disorder” group means were higher for Emotional Control, FI-index and GEC-index. The comorbid ODD+AD children also obtained higher means compared to the only-AD group in all the BRIEF-P scales except for Shift and Working Memory. A EF×sex interaction emerged for the ISCI-index: a) in girls, a lower mean was obtained for comorbid ODD+AD compared to the “at least one disorder” and only-ODD groups; b) in boys, the ODD+AD condition attained a higher mean compared to all the other diagnostic conditions except only-ODD. At age 5, the comparison between only-ODD and only-AD (final columns in Table 3) yielded relevant differences for Inhibit, Emotional Control and GEC-index (higher scores for only-ODD). At this age, the ISCI-index yielded higher scores for only-ODD compared to only-AD solely in the case of boys.

Discussion

The results of this study revealed some differences in executive functioning at age 3 between the diagnostic groups: comorbid ODD+AD involved more difficulties in shift and in FI (in boys) than the two disorders in isolation; only-ODD presented more difficulties in inhibit, and in the case of girls more difficulties in FI. However, as the development of EF advanced with age, the executive deficits were more markedly confined to ODD+AD, which differed substantially in the higher severity of the deficits (inhibition, emotional control, plan-organize and the combined indexes) from the only-AD group, though ODD+AD was similar

to only-ODD. Anxiety would increase the manifestations of ODD because it increases emotional dysregulation (higher negative affectivity and poorer inhibitory control), resulting in more disruptive behavior. Some sex effects were observable for FI and ISCI.

At age 3 few differences were found between the groups in EF. It was possible to observe that inhibition difficulties were more marked in only-ODD, as reported by Drabick et al. [10]. Shift problems were more pronounced in ODD+AD, which seems congruent with the stubbornness, low tolerance and high hostile and rule-breaking behaviors found in co-occurring ODD+AD, particularly at early ages [50].

At age 5 comorbid ODD+AD showed clearly poorer EF compared to only-AD, but a similar EF profile to that of only-ODD, in particular for the individual EF inhibit, emotional control and plan-organize. This result suggests that when ODD is accompanied by other disorders that also involve EF dysfunction, such as AD or ADHD, executive functioning worsens in the affected children [24]. This seems congruent with the integrative dual-pathway model posited by Drabick et al. [10] addressing both the multiple-problem and the buffer hypotheses (previously reported in the literature) to explain the etiology, risk processes and effects of the co-occurrence of ODD+AD. According to the multiple-problem proposal, in co-occurring ODD+AD anxiety acts to exacerbate ODD, and this would contribute to impaired neurobiological ability of the cortex to regulate limbic system functioning and consequently poorer executive functioning [51]. In contrast, the buffer hypothesis states that in the presence of ODD+AD anxiety symptoms may mitigate ODD, and this could lead to overactive limbic system functioning in response to feelings of anger or sadness, resulting also in a marked deficit in EF [14]. Most comparisons have shown that children with ODD+AD have more impairment than children with AD. However no differences are seen when we compared them with children with only ODD. Therefore, children with ODD+AD have aggravated the difficulties in executive functions. Caution is advised, however, because the comorbid

condition may have no effect on the manifestation of ODD, or as indicated Bubier et al. [11], ODD in early childhood could be the cause of the co-occurrence of anxiety and its negative effects.

This study reveals few sex differences in co-occurring ODD+AD. But two relevant interaction parameters did appear: the global FI (at age 3 years) and ISCI (at age 5) indexes yielded mean scores in the different diagnostic conditions that depended on children's sex. For both interactions, girls diagnosed with ODD+AD obtained lower mean scores than girls in the other diagnostic conditions, while boys diagnosed with ODD+AD obtained higher mean scores than boys in the other groups. Thus, while for boys with comorbid ODD+AD the multiple-problem hypothesis for combined indexes including shift, emotional control and inhibition (FI and ISCI) may apply in girls ODD+AD comorbidity is better explained by the buffer hypothesis. This interaction has implications for treatment, and suggests that improving EF (specifically, shift, emotional control and inhibition) is a necessary component for only-AD girls and for ODD+AD boys. Both global indexes include the BRIEF-P shift scale, which measures the ability to shift thoughts and actions as demanded by the situational context (skill set shifting in this scale is defined by items to assess motor shifting, attention shifting, stimulus shifting and task shifting). Our results are consistent with those of previous studies in older children and in young adults that related high vulnerability to anxiety in females to an autonomic nervous system that lacks flexibility, and consequently hinders adequate decisions about changing one's environment, causing feelings of worry and loss of control and even future anxiety disorders [52,53]. A recent prospective study revealed that difficulties of autonomic flexibility (low scores) in 12-year-old girls from the general population predicted high anxiety levels two years later, whereas this association did not emerge for boys [54].

Strengths and limitations

The strengths of this work are the sample origin (community, general population), large sample size, longitudinal assessment during the preschool period, use of diagnostic interview plus questionnaire, use of multiple-informant reports. With the aim to generalize the results to the whole original population, the complete initial sample was considered and compared according to the children's diagnostic status: only-ODD, only-AD, ODD+AD, a reference group of children with other diagnoses and a healthy-control group. The inclusion of the reference group of children with disorders different to ODD and AD makes possible to explore the secondary objective of the study: how EF differ between ODD-AD and other clinical profiles identified in the original population.

The main limitation was the low sample size for the ODD+AD condition, which could reduce the statistical power for some pairwise comparisons. In this regard, only mean differences with moderate to high effect size were considered as clinically relevant, and despite the small sample size relationships between diagnostic conditions and EF did emerge. In this research, was assessed the presence of clinical conditions and preschoolers' executive function levels by administering questionnaires to parents and teachers, it would have been interesting to evaluate directly to children but it was not possible (except for evaluating children's IQ). To achieve our goal we have considered two "control" groups: children with no diagnosis and children with at least one diagnosis different to ODD and AD (this group included children with ADHD or CD). The exclusion of ADHD or CD from the control group of children who presented at least one disorder different to ODD and AD would prevent to discover how the executive functions are presented in comparison to other disorders including disruptive problems and made not possible to generalize the empirical evidence to the whole original general population, which is considered a highlight of this work. In addition, the difficulty of assessing the presence of diagnoses such as ODD at early ages should be

considered. In fact, it is usually considered that ODD appears in late preschool or early school-aged children, and that it is normal to exhibit oppositional behavior during the child's early development. Despite this, the chronicity of ODD in a group of children from preschool age has been identified [55], but it is also known that diagnoses at early ages may change [56]. Although reassessments were carried out, as recommended by Bunte et al. [57] results must be interpreted with caution.

Summary

In sum, this study provides empirical data about the relationship between comorbid ODD+AD and poorer expression of EF during the preschool period, and also contributes evidence about the predictive capacity of poorer EF at age 3 on prospective ODD+AD comorbidity at age 5, which leads us to conclude that EF dysfunction is a risk factor for comorbid ODD+AD. Prevention and intervention programs for preschoolers diagnosed with ODD+AD should promote the adequate development of executive functions to help them build skills of mental flexibility and self-control. Emotional control of fear and anger, flexibility in interpreting environmental cues, and improved stop and think abilities could strengthen different EF components, and this, in turn, may help to reduce the expression of ODD and AD problems.

Conflict of interest

The authors have no conflicts of interests.

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Table 1

Descriptive for the sample at baseline

		Total		No disorder		Any disorder		Only ODD		Only AD		ODD+AD	
		<i>n</i> =622		<i>n</i> =380		<i>n</i> =140		<i>n</i> =44		<i>n</i> =41		<i>n</i> =17	
Sex (N, %)	<i>Female</i>	312	50.2	181	47.6	81	57.9	20	45.5	22	53.7	8	47.1
	<i>Male</i>	310	49.8	199	52.4	59	42.1	24	54.5	19	46.3	9	52.9
Born in Spain	<i>Yes</i>	600	96.9	369	97.6	135	96.4	41	93.2	38	95.0	17	100
	<i>No</i>	19	3.1	9	2.4	5	3.6	3	6.8	2	5.0	0	0
<i>Ethnic Caucasian-European</i>		554	89.1	341	89.7	126	90.0	38	86.4	36	87.8	13	76.5
<i>Hispanic-South America</i>		40	6.4	24	6.3	7	5.0	5	11.4	2	4.9	2	11.8
<i>Other</i>		28	4.5	15	3.9	7	5.0	1	2.3	3	7.3	2	11.8
<i>SES High and medium-high</i>		400	64.3	269	70.8	82	58.6	22	50.0	19	46.3	8	47.1
<i>Medium</i>		88	14.1	50	13.2	19	13.6	8	18.2	6	14.6	5	29.4
<i>Medium-low and low</i>		134	21.5	61	16.1	39	27.9	14	31.8	16	39.0	4	23.5
Age (years-old)	<i>Mean-SD</i>	3.77	0.33	3.76	0.33	3.75	0.34	3.87	0.33	3.73	0.33	3.76	0.21

Note. SES: socioeconomic status (Hollingshead, 1975). ODD: oppositional defiant disorder. AD: anxiety disorders.

Any disorder: includes any disorder other than ODD and AD.

Table 2.

Prevalence of DSM-IV disorders at ages 3 and 5: frequency and weighted proportions.

<i>N</i> (%)	Age 3	Age 5
No diagnosis	380 (65.1)	347 (63.8)
Disruptive disorders	87 (10.0)	67 (9.6)
Attention-deficit-hyperactivity	33 (3.6)	30 (4.2)
Oppositional defiant disorder	61 (6.9)	46 (6.6)
Conduct disorder	10 (1.4)	5 (0.5)
Anxiety disorder	59 (7.7)	75 (11.7)
Separation disorder	18 (2.1)	8 (1.3)
Generalized anxiety	1 (0.1)	5 (0.5)
Specific phobia	27 (3.6)	53 (8.3)
Social phobia	16 (1.9)	20 (3.6)

Table 3
ANOVA adjusted for children's sex, SES and IQ

	Adjusted mean					Inter Gr.x Sex	Factor Group	p	eta ²	Pairwise comparisons										
	No dis.	≥1 dis.	Only ODD	Only AD	ODD +AD					Reference group: ODD+AD				AD vs ODD						
										No dis.	≥1 dis.	ODD	AD	MD	d					
Age 3	n=380	n=140	n=44	n=41	n=17	p				MD	d	MD	d	MD	d	MD	d	MD	d	
Inhibit	23.3	22.8	24.7	22.3	20.2	.816	.557	.01		-3.0	0.5	-2.5	0.4	-4.5	0.6	-2.0	0.3	-2.5	0.3	
Shift	13.0	12.9	12.3	15.2	14.7	.215	.005	.03		1.7	0.4	1.8	0.5	2.4	0.6	-0.5	0.1	2.8	0.8	
E.Control	12.0	12.2	13.0	12.1	12.4	.281	.826	.01		0.4	0.1	0.2	0.1	-0.6	0.2	0.3	0.1	-0.9	0.2	
W.Mem.	22.7	22.5	23.1	22.0	20.9	.961	.883	.00		-1.8	0.3	-1.6	0.2	-2.2	0.3	-1.1	0.2	-1.1	0.2	
Plan-org.	13.5	13.3	13.6	13.2	13.4	.960	.971	.00		0.0	0.0	0.2	0.0	-0.2	0.0	0.2	0.1	-0.4	0.1	
ISCI	35.3	34.9	37.7	34.4	32.6	.934	.444	.01		-2.7	0.3	-2.3	0.2	-5.1	0.5	-1.8	0.2	-3.4	0.3	
FI	Girls	24.6	25.1	23.4	25.7	23.3	.154	.759	.00		-1.3	0.3	-1.8	0.4	-0.2	0.0	-2.5	0.6	2.3	0.5
		Boys	25.5	24.8	27.5	28.9	29.7		.029	.02	4.2	0.7	4.9	0.8	2.2	0.3	0.8	0.1	1.4	0.2
EMI		36.2	35.8	36.8	35.2	34.3	.964	.912	.00		-1.9	0.2	-1.4	0.1	-2.4	0.2	-0.9	0.1	-1.5	0.2
GEC		84.5	83.6	86.8	84.8	81.6	.967	.909	.00		-2.9	0.2	-2.0	0.1	-5.2	0.3	-3.2	0.2	-2.0	0.1
Age 5	n=347	n=127	n=35	n=54	n=11															
Inhibit	22.7	24.5	26.5	21.3	28.0	.218	.005	.04		5.4	0.6	3.5	0.4	1.5	0.2	6.8	0.8	-5.2	0.7	
Shift	13.1	12.7	14.0	14.0	14.5	.629	.136	.02		1.5	0.4	1.9	0.5	0.6	0.1	0.5	0.1	0.1	0.0	
E.Control	11.8	12.6	14.2	12.0	16.1	.221	.005	.04		4.3	0.8	3.5	0.6	1.9	0.3	4.1	0.8	-2.2	0.6	
W.Mem.	22.3	23.1	24.2	22.4	26.3	.723	.244	.01		4.0	0.5	3.2	0.4	2.1	0.3	3.9	0.5	-1.8	0.3	
Plan-org.	13.3	13.6	14.6	13.0	15.5	.782	.228	.01		2.2	0.5	1.9	0.4	0.9	0.2	2.5	0.5	-1.6	0.4	
ISCI	Girls	32.5	35.9	38.7	34.4	31.7	.141	.021	.02		-0.8	0.1	-4.2	0.6	-7.0	0.7	-2.7	0.4	-4.3	0.4
		Boys	36.4	38.4	42.7	32.4	48.0		<.001	.04	11.6	1.1	9.7	0.9	5.4	0.5	15.6	1.6	-10.2	1.2
FI		24.9	25.3	28.1	26.0	30.6	.365	.009	.02		5.8	0.7	5.3	0.6	2.5	0.3	4.7	0.6	-2.1	0.3
EMI		35.7	36.7	38.8	35.4	41.8	.725	.210	.01		6.1	0.5	5.0	0.4	3.0	0.2	6.3	0.5	-3.4	0.3
GEC		83.2	86.5	93.4	82.7	100.4	.325	.005	.03		17.2	0.6	13.9	0.5	7.0	0.3	17.7	0.7	-10.7	0.5

Note. BRIEF-P: Behavior Rating Inventory of Executive Functioning–Preschool version

ODD: oppositional defiant disorder. AD: anxiety disorders. At least 1 disorder: includes any disorder other than ODD and AD.

ISCI: Inhibitory Self-Control; FI: Flexibility; EMI: Emergent Metacognition; GEC: Global Executive Composite.

Inter Gr*Sex: Interaction of group by sex. MD: mean difference. |d|: Cohen's-d measure of the pairwise effect size.

Bold: significant comparison for MD (.05 level). Bold: moderate (|d|>0.50) to high (|d|>0.80) effect size.