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IMPACTO DEL SUEÑO SOBRE EL RENDIMIENTO COGNITIVO Y ESCOLAR EN NIÑOS CON TRASTORNO POR DÉFICIT DE ATENCIÓN E HIPERACTIVIDAD

Programa Oficial de Doctorado en Psicología (B13.56.1)

(Real Decreto 99/2011)

NOELIA RUIZ HERRERA

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Memoria presentada para la obtención del grado de Doctor por la Doctoranda Noelia Ruiz Herrera, realizada bajo la dirección del Dr. Gualberto Buela Casal y el Dr. Alejandro Guillén Riquelme

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Granada, 31 de enero de 2020

Directores de la Tesis;

Fdo. Dr. Gualberto Buela Casal

Fdo. Dr. Alejandro Guillén Riquelme

Doctoranda;

Fdo. Noelia Ruiz Herrera

Universidad de Granada

Esta tesis doctoral ha sido concebida y desarrollada en el marco de un proyecto de investigación financiado por el Ministerio de Economía y Competitividad, titulado "Impacto del sueño sobre el rendimiento escolar y cognitivo en niños con trastorno por déficit de atención e hiperactividad" concedido al Dr. Gualberto Buela Casal (Referencia: PSI2014-58046-P).

Ten siempre a Ítaca en tu mente.

Llegar allí es tu destino.

Mas no apresures nunca el viaje.

Mejor que se extienda muchos años;

y en tu vejez arribes a la isla,

enriquecido de cuanto hayas ganado en el camino

sin esperar que Ítaca te enriquezca.

(Konstantino Kavafis)

"La magia de librar batallas más allá de lo humanamente soportable se basa en lo mágico que resulta arriesgarlo todo por un sueño que nadie más alcanza a ver excepto tú."

(Millon Dollar Baby)

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ÍNDICE

RESUMEN

Resumen

El sueño es una función esencial para la supervivencia. Sin embargo, los problemas de sueño son algunos de los principales en la salud pública, dado su alto impacto en la vida diaria. En la infancia, el momento clave en el que se está desarrollando el cerebro, el sueño es crucial no solo para un buen desempeño en las aulas, sino para evitar el desarrollo de problemas cognitivo-emocionales que persistan en la vida adulta. El trastorno por déficit de atención e hiperactividad (TDAH) es uno de los trastornos más comunes en la infancia y está relacionado con dificultades en el funcionamiento cognitivo y el rendimiento académico. Además, el TDAH cuenta con problemas de sueño asociados, lo que puede repercutir negativamente en su propia sintomatología y en su rendimiento diurno. Sin embargo, los estudios previos publicados al respecto tienen deficiencias metodológicas que no han permitido dilucidar cuál es la situación real a la que estos niños se enfrentan. Por un lado, el uso de medidas objetivas y subjetivas de evaluación ha generado resultados contradictorios e inconsistentes. Por otro, en muy pocos estudios se ha tenido en cuenta la sintomatología del TDAH (predominancia de síntomas de inatención, de hiperactividad/impulsividad, o combinados) para estudiar el sueño en estos niños. Al respecto de eventos específicos del sueño, tampoco existe ningún estudio disponible que reporte datos sobre las oscilaciones características en la fase 2 del sueño (N2), conocidas como *spindles*. Sin embargo, estos están relacionados con el aprendizaje y el asentamiento de la memoria, dos funciones cognitivas muy importantes en el TDAH. Por último, no existe ningún estudio disponible que reporte cuál es el impacto que tienen las características de sueño en el funcionamiento tanto cognitivo como escolar de estos niños.

Para superar las limitaciones metodológicas previas, el objetivo general de esta tesis doctoral fue evaluar la relación entre el sueño y el rendimiento cognitivo y escolar de niños con TDAH teniendo en cuenta las diferentes presentaciones (TDAH-inatento, TDAH-hiperactivo/impulsivo y TDAH-combinado). Para conseguir este objetivo general, se llevaron a cabo cuatro estudios de los que se derivan los objetivos específicos:

Objetivo 1. Revisar la literatura científica existente sobre el rendimiento cognitivo en los niños con TDAH

Estudio 1. Rendimiento cognitivo en niños con trastorno por déficit de atención/hiperactividad: Meta-análisis

Objetivo. Actualizar los meta-análisis previos sobre el rendimiento cognitivo en niños con TDAH en edad escolar (7-12 años), incluyendo dominios ejecutivos y no ejecutivos y separando entre las presentaciones.

Método. Se realizó una búsqueda exhaustiva a través de Cochrane, Web of Science, PsycINFO, Scopus y PubMed, que incluyó 116 estudios (con 127 muestras independientes). Se realizó un meta-análisis de las diferencias de medias estandarizadas sobre 21 dominios cognitivos en los niños con TDAH en comparación con un grupo de control

Resultados. Se observaron diferencias en 17 de las 21 variables analizadas. Los niños con la presentación combinada fueron los que tuvieron mayores déficits cognitivos, aunque los niños con la presentación inatenta fueron los que mostraron el

perfil cognitivo más específico. En cuanto a la presentación hiperactiva/impulsiva, no se dispuso de datos suficientes para extraer conclusiones.

Conclusión. Estos resultados facilitan la comprensión de los perfiles de TDAH. Sin embargo, se precisa de mayor investigación sobre el rendimiento cognitivo en estos niños teniendo en cuenta las diferentes presentaciones de TDAH.

Objetivo 2. Examinar los patrones de sueño subjetivos y objetivos en niños con TDAH diferenciando entre sus presentaciones.

Estudio 2. El sueño en las diferentes presentaciones del trastorno por déficit de atención/hiperactividad: análisis de medidas objetivas y subjetivas

Objetivo. Examinar los patrones de sueño subjetivos y objetivos de niños con diferentes presentaciones del trastorno por déficit de atención e hiperactividad (TDAH).

Método. Se evaluaron 92 niños (29 TDAH-inatento, 31 TDAH-hiperactivo/impulsivo y 32 TDAH-C) de entre 7–11 años. El *Cuestionario Pediátrico de Sueño*, la *Escala Pediátrica de Somnolencia Diurna* y un diario de sueño se utilizaron como medidas subjetivas de sueño. Para evaluar objetivamente la cantidad, calidad y fragmentación del sueño se utilizó la polisomnografía.

Resultados. Los datos subjetivos indicaron alteraciones del sueño en el 12,7% de la muestra. No se observaron diferencias significativas en ninguna variable objetiva y subjetiva de sueño entre las diferentes presentaciones de TDAH. No obstante, los datos de fragmentación de sueño sugirieron una peor continuidad en el grupo TDAH-hiperactivo/impulsivo. Los análisis correlacionales confirmaron que el sueño se ve afectado por la edad.

Conclusiones. Los niños con TDAH pueden experimentar problemas respiratorios durante el sueño y somnolencia diurna, según lo informado por sus padres, incluso cuando su tiempo total y eficiencia de sueño no se vean afectados. Parece que el sueño en el TDAH no varía en función de la presentación y evoluciona con la edad.

Objetivo 3: Analizar las características de los *spindles* en niños con TDAH diferenciando entre sus presentaciones.

Estudio 3. Características de los *spindles* en niños con trastorno por déficit de atención/hiperactividad

Objetivo. Analizar los *spindles* de una muestra de niños en edad escolar con trastorno por déficit de atención e hiperactividad (TDAH) en términos de número, densidad, duración, amplitud e intensidad.

Método. Se realizó una polisomnografía y se detectaron los *spindles* de sueño en 74 niños (27 con TDAH-inatento, 25 con TDAH-hiperactivo/impulsivo y 22 con TDAH-combinado) de 7 a 11 años de edad. Se obtuvieron datos de las derivaciones frontal (Fz) y parietal (Pz).

Resultados. Hubo mayor número y densidad de *spindles* lentos y fueron más frecuentes en Fz y en la fase 2 del sueño (N2). Los *spindles* lentos duraron más que los rápidos y fueron más duraderos en N2. La amplitud de los *spindles* fue mayor en la fase 3 del sueño (N3) y en Fz. La intensidad fue mayor en N2 y Fz, así como en los *spindles* lentos. No se observaron diferencias entre las presentaciones en ninguna variable. Se observaron correlaciones positivas entre la edad de los participantes y la frecuencia y

densidad de los *spindles* rápidos, mientras que se encontró una correlación negativa entre la edad y la intensidad de los *spindles* en el grupo de TDAH-C.

Conclusiones. La topografía de los *spindles* en los niños con TDAH sigue la misma organización que la de los niños sin TDAH y no difieren entre las presentaciones. En los niños con TDAH, las características de los *spindles* evolucionan con la edad y estas asociaciones son impulsadas principalmente por el grupo TDAH-C. No parece haber asociaciones entre las características de los *spindles* y el cociente intelectual.

Objetivo 4. Analizar la influencia del sueño en el rendimiento cognitivo y escolar en los niños con TDAH

Estudio 4. Sueño, desempeño académico y rendimiento cognitivo en niños con trastorno por déficit de atención/hiperactividad: Un estudio polisomnográfico

***Objetivo*.** Examinar la influencia las características de sueño reportadas por los padres y evaluados mediante polisomnografía (PSG) en el desempeño académico y cognitivo de los niños con trastorno por déficit de atención e hiperactividad (TDAH).

Método. Se evaluaron 91 niños (18 niñas) diagnosticados con TDAH de 7 a 11 años de edad (29 TDAH-inatento, 32 TDAH-hiperactivo/impulsivo y 31 TDAH-combinado). Se utilizaron el Cuestionario Pediátrico de Sueño y la Escala Pediátrica de Somnolencia Diurna para evaluar la calidad sueño percibida por los padres. Las variables objetivas del sueño fueron evaluadas por la PSG. El rendimiento cognitivo se evaluó mediante la cuarta edición de la Escala de Inteligencia Wechsler para Niños y se

utilizó la calificación promedio final del último año escolar como medida del rendimiento académico.

Resultados. La somnolencia diurna predijo el rendimiento académico y, en menor medida, el cognitivo. La respiración alterada durante el sueño y las variables conductuales no predijeron ningún resultado académico o cognitivo. Las siguientes variables objetivas del sueño predijeron el rendimiento académico y cognitivo: tiempo en cama, latencia de inicio de sueño, la cantidad de sueño/vigilia, eficiencia de sueño, porcentaje de las fases 1, 2, 4 y REM, índice de *arousals*, índice de movimientos periódicos de las piernas y la continuidad y organización del sueño. El principal predictor de los resultados académicos fue el índice de *arousals*. Los principales predictores del rendimiento cognitivo fuero el tiempo de sueño y el porcentaje de sueño de la fase 1.

Conclusiones. Los parámetros del sueño están estrechamente asociados con el funcionamiento académico y cognitivo de los niños con TDAH. Dado que estos niños son propensos a sufrir problemas de sueño, corren un mayor riesgo de experimentar problemas cognitivos que pueden llevarlos a un fracaso académico.

SUMMARY

Abstract

Sleep is an essential function for survival. Sleep problems, however, are some of the major public health challenges given their high impact on daily life. In childhood, when the brain is developing, sleep is crucial not only for a good performance in school, but also to avoid cognitive and emotional problems that persist into adulthood. Attention deficit/hyperactivity disorder (ADHD) is one of the most common disorders in childhood, and is related to difficulties in cognitive performance and academic functioning. In addition, ADHD has associated sleep problems, which can impact negatively on the symptomatology of the disorder and daily performance. However, previous studies published on this respect have some methodological shortcomings that have hampered to clarify the real situation these children face. On the one hand, the use of objective and subjective measures has generated contradictory and inconsistent results. On the other hand, very few studies have taken into account the symptomatology of ADHD (predominance symptoms of inattention, hyperactivity/impulsivity, or combined) to study sleep in these children. Regarding specific sleep events, there is also no study available that reports data on characteristic oscillations in stage 2 sleep (sleep spindles). However, spindles are related to learning and memory consolidation, two very important cognitive functions in ADHD. Finally, there is no study available that reports the impact that sleep characteristics have on both cognitive and school functioning of these children.

To overcome previous methodological limitations, the general objective of this doctoral thesis was to assess the relationship between sleep and cognitive and school performance of children with ADHD taking into account the different presentations (ADHD-Innatentive, ADHD-Hyperactive/Impulsive, and ADHD-Combined). To

achieve this general objective, four studies were conducted from which the specific objectives were derived:

Objective 1. To update the existing scientific literature on cognitive performance in children with ADHD

Study 1. Cognitive performance in children with attention deficit/hyperactivity disorder: Meta-analysis

Objective. To update previous meta-analyses on cognitive performance in school-aged children with attention deficit/hyperactivity disorder (ADHD) (7—12 years), including both executive and non-executive domains, and separating among presentations.

Method. A comprehensive search through Cochrane, Web of Science, PsycINFO, Scopus, and PubMed was conducted, which included 116 studies (with 127 independent samples). A meta-analysis of standardized mean differences was carried out reporting data on 21 different cognitive domains in children with ADHD compared to a control group.

Results. Differences were observed in 17 of the 21 variables analysed. Children with the combined presentation were those who present the greatest cognitive deficits, although children with the inattentive presentation were those who show the more particular cognitive profile. Concerning the hyperactive/impulsive presentation, not enough data were available for drawing conclusions.

Conclusion. These results facilitate the understanding of ADHD profiles. However, more research is needed on cognitive performance in these children taking into account the different presentations of ADHD.

Objective 2. To examine the subjective and objective sleep patterns in children with ADHD by differentiating between their presentations.

Study 2. Sleep among presentations of attention-deficit/hyperactivity disorder: Analysis of objective and subjective measures

Objective. To examine subjective and objective sleep patterns in children with different Attention-Deficit/Hyperactivity Disorder (ADHD) presentations.

Method. We assessed 92 children (29 ADHD-Inattentive, 31 ADHD-Hyperactive/Impulsive, and 32 ADHD-Combined) aged 7–11 years. The Pediatric Sleep Questionnaire, the Pediatric Daytime Sleepiness Scale, and a sleep diary were used as subjective sleep measures, and polysomnography was used to objectively assess sleep quantity, quality, and fragmentation.

Results. Subjective data showed impaired sleep in 12.7% of the sample. No significant differences were found between ADHD presentations in any objective and subjective sleep variable. Nevertheless, data on sleep fragmentation suggested a worse sleep continuity for the ADHD-H/I group, and correlation analyses confirmed that sleep is affected by age.

Conclusions. Children with ADHD may suffer from sleep breathing problems and daytime sleepiness, as reported by their parents, even when their total sleep time and sleep efficiency are not affected. It seems that sleep in this population does not

largely vary as a function of the ADHD presentation. Sleep in children with ADHD evolves with age.

Objective 3: To explore the spindles characteristics in children with ADHD by differentiating among their presentations.

Study 3. Characteristics of sleep spindles in school-aged children with attention-deficit/hyperactivity disorder

Objective. To characterize sleep spindles from a sample of school-aged children with attention deficit/hyperactivity disorder (ADHD) in terms of number, density, duration, amplitude, and intensity.

Method. Spindles information was extracted from an overnight polysomnography in 74 children (27 ADHD-Inattentive, 25 ADHD-Hyperactive/Impulsive, and 22 ADHD-Combined) aged 7–11 years. We obtained data of the frontal (Fz) and parietal (Pz) derivations.

Results. Children with ADHD showed a higher number and density of slow compared to fast spindles, which were more frequent in Fz and N2. Slow spindles lasted longer than fast, and lasted longer in N2. The spindles amplitude was greater in N3 and Fz, and the intensity was higher in N2 and in Fz. No differences were observed among ADHD presentations for any spindles characteristics. Spindles frequency increased with age, as well as fast spindles density, indicating an age-dependent maturation of different sleep spindles.

Conclusions. Spindles characteristics in children with ADHD follow the same organization as that of TD children, including topography and frequency, with no

marked difference among the presentations. In children with ADHD, the spindles characteristics evolve with age and these associations are mainly driven by ADHD-C. There seem to be no associations between the characteristics of spindles and IQ.

Objective 4. Analysing the influence of sleep on cognitive and school performance in children with ADHD

Study 4. Sleep, academic achievement, and cognitive performance in children with attention-deficit/hyperactivity disorder: A polysomnographic study

Objective. To examine the influence of parent-reported and polysomnography (PSG)-measured sleep patterns on academic and cognitive performance of children with attention-deficit/hyperactivity disorder (ADHD).

Method. We assessed 91 children (18 girls) diagnosed with ADHD aged 7—11 years (29 ADHD-I, 32 ADHD-H/I and 31 ADHD-C). The *Pediatric Sleep Questionnaire* and *Pediatric Daytime Sleepiness Scale* were used to assess subjective sleep quality, as perceived by parents, and objective sleep variables were assessed by PSG. Cognitive performance was evaluated using the fourth edition of the Wechsler Intelligence Scale for Children, and the final average grade of the last school year was used as a measure of academic performance.

Results. Subjective daytime sleepiness predicted academic and, in a lesser extent, cognitive performance. Sleep-disordered breathing and behavioural variables did not predict any academic or cognitive outcome. Academic and cognitive performance were predicted by the following objective sleep variables: Time in bed, sleep onset latency, sleep/wake time, sleep efficiency, percentage of stages 1, 2, 4, and REM sleep,

arousal index, periodic limb movement index, and sleep continuity and organization. The main predictor of academic outcomes was the arousal index, and of cognitive performance were the sleep time and the percentage of stage 1 sleep.

Conclusions. Sleep parameters are closely associated with the academic and cognitive functioning of children with ADHD. As these children are likely to suffer from sleep problems, they are at higher risk of experiencing cognitive impairments which may lead to their academic failure.

INTRODUCCIÓN

Introducción

En el año 1968, una de las grandes asociaciones en materia de salud mental del mundo (Asociación Americana de Psiquiatría [APA], 1968) incluyó por primera vez el trastorno por déficit de atención e hiperactividad (TDAH) en la segunda edición del *Manual Diagnóstico y Estadístico para los Trastornos Mentales* (DSM-II) con el nombre de «trastorno hipercinético». El psiquiatra Leon Eisenberg fue clave para su inclusión y llegó a ser considerado por muchos como pionero del diagnóstico y tratamiento del TDAH. Desde entonces, el conocimiento sobre el trastorno se ha ido acumulando, aunque sigue sin existir consenso ni claridad en muchos de los aspectos que lo conforman. Esto ha provocado una división en la comunidad científica, clínica y educativa.

En Inglaterra, los psiquiatras infantiles Timimi y Taylor (2004) definieron el trastorno como constructo social, vaciándolo de cualquier base orgánica. En España, psicólogos y psiquiatras también se han referido al TDAH como una invención y al niño «con hiperactividad» como un síntoma de una situación profesional y social (v.gr. García de Vinuesa, González-Pardo y Pérez-Álvarez, 2014; Pérez-Álvarez, 2018; Tizón, 2007). A este respecto, en el año 2012, se publicó una noticia sobre unas declaraciones que hizo L. Eisenberg antes de morir en 2009, en las que cuestionaba el gran número de diagnósticos. De este modo, se propagó la polémica sobre la existencia o no del TDAH, habiendo una parte de la comunidad científica que afirma que se trata de un trastorno neurobiológico (v.gr. Biederman, 2005; Hoogman et al., 2017), mientras que la otra cuestiona su existencia, considerándolo una invención sin base científica protegida por la industria farmacéutica (García de Vinuesa et al., 2014; Pérez-Álvarez, 2018; Timimi y Timimi, 2015).

Como afirma Pérez-Álvarez (2018), es posible que el constructo de TDAH no esté bien definido o que haya sido manipulado por la industria farmacéutica. También puede que la controversia de si *existe* o no, no se resuelva en términos científicos y sea necesaria una aproximación metacientífica y filosófica. Además, según la posición de S. Timimi (24 de julio, 2014), la abolición de las etiquetas diagnósticas podría ayudar en la 'guerra justa' contra la patologización de la infancia, mermando la cronicidad y reduciendo el consumo de medicación psiquiátrica. Sin embargo, lo que ha quedado evidenciado es que estos niños exhiben diferencias a nivel cognitivo y comportamental con respecto a otros niños sin esta etiqueta diagnóstica y estas diferencias podrían ser consideradas problemáticas tanto para ellos como para el entorno que les rodea.

En la actualidad, la gran mayoría de los recursos apoyan financiera y profesionalmente el modelo biomédico para el diagnóstico y tratamiento de niños y adultos con comportamientos similares al TDAH (Erlandsson y Punzi, 2016). La asunción de ese modelo y el reconocimiento del TDAH como un problema de salud pública han hecho posible la realización de este proyecto.

TDAH: diagnóstico y bases neurobiológicas

El TDAH es una de las perturbaciones más comunes en la infancia con una prevalencia estimada a nivel mundial del 3,4% (Polanczyk, Salum, Sugaya, Caye y Rohde, 2015), a nivel europeo del 5 % (Wittchen et al., 2011) y a nivel nacional del 6,8% (Catalá-López et al., 2012). Es más frecuente en niños que en niñas, con una proporción que va desde 2:1 a 10:1 (Arnett, Pennington, Willcutt, DeFries y Olson, 2015; Biederman et al., 2002) y, aunque en estudios recientes se afirme que pueda

remitir con el tiempo (ver revisión de Sudre, Mangalmurti y Shaw, 2018), los síntomas del TDAH pueden persistir en la adultez aproximadamente en dos tercios de los casos (Biederman, Petty, Evans, Small y Faraone, 2010; Turgay et al., 2012). En un estudio reciente sobre calidad de vida relacionada con la salud en niños y adolescentes con TDAH, se ha reportado que estos tienen una peor calidad de vida en comparación a sus pares sin el trastorno en múltiples áreas (bienestar psíquico, estado de ánimo, relación con los padres y amigos así como en ambiente escolar y aceptación social). Además, se ha indicado que aquellos sometidos a tratamiento farmacológico con metilfenidado muestran mejores puntuaciones en el ambiente escolar (López-Villalobos et al., 2019). Por su parte, los padres de los niños con TDAH muestran mayor estrés percibido que aquellos padres sin hijos con TDAH (Cossio-García, Castaño-García y López-Villalobos, 2019). Esto supone no solo un importante problema de salud pública (Hinshaw y Ellison, 2015), sino una importante carga económica para el sistema (ver revisión de Matza, Paramore y Prasad, 2005).

Un sistema de valoración de los trastornos mentales vigente es el DSM-5. Esta clasificación categórica tiene como objetivo principal mejorar la utilidad clínica y como objetivo secundario la investigación. Según este manual, el TDAH es un trastorno del neurodesarrollo que se caracteriza por la existencia de síntomas de inatención, hiperactividad e impulsividad, cuya edad de aparición puede darse antes de los 12 años (APA, 2013). En la versión anterior, el DSM-IV-TR (APA, 2000), el TDAH era considerado un trastorno de la conducta disruptiva y la edad de aparición de los síntomas era previa a los 7 años. Además, en la nueva versión del manual, se cambió la clasificación de ‘subtipos’ a ‘presentaciones’, incluyendo el TDAH con presentación inatenta (TDAH-I), el TDAH-presentación hiperactiva/impulsiva (TDAH-H/I) y el

TDAH presentación combinada (TDAH-C). El diagnóstico se establecería según la presencia predominante de unos síntomas u otros y se propuso que las presentaciones pueden variar en el transcurso de la vida.

Por otra parte, el estándar mundial para la información diagnóstica en materia de salud es la *Clasificación Internacional de Enfermedades*, que va por su undécima edición (CIE-11; Organización Mundial de la Salud [OMS], 2018). Desde sus inicios, la CIE ha sido utilizada para la elaboración de estadísticas de mortalidad. Sin embargo, a partir de la sexta versión (CIE-6; OMS, 1948), la clasificación fue enriquecida con un mayor número de términos diagnósticos y utilizada también para producir estadísticas de morbilidad. Fue también en esta versión en la que se incluyeron los trastornos mentales y del comportamiento. En la CIE-11 (OMS, 2018), el TDAH se integra en el capítulo de trastornos del neurodesarrollo y abandona su clasificación previa de trastorno hipercinético (CIE-10; OMS, 1992). En la CIE se mantiene un conjunto sintomático descriptivo frente al carácter categórico del DSM, en el que no se exige el cumplimiento de un determinado número de criterios para el establecimiento del diagnóstico. Sin embargo, se precisa que la inatención y el exceso de actividad superen los niveles esperados para la edad y el cociente intelectual (CI) de la persona.

Los avances en la tecnología han permitido a los investigadores esclarecer los fundamentos neuroanatómicos y neurofisiológicos del TDAH. Gracias a estos avances se ha podido comprender mejor cuáles son los sustratos cerebrales que subyacen a los síntomas y a los problemas funcionales que presentan estos niños. A continuación, se hará un breve repaso de algunas de las investigaciones más relevantes que han permitido conocer el cerebro de los niños con TDAH, no solo en comparación a los

niños con desarrollo cerebral típico, sino atendiendo también a las diferentes presentaciones del trastorno.

TDAH: estructura y función cerebral atípica. Desde la década de 1970 en la que se denominó al TDAH como disfunción mínima del cerebro (Wender, 1971), se han realizado multitud de estudios que han llevado a entender que el cerebro de las personas con TDAH refleja anormalidades morfológicas en regiones cerebrales discretas y aisladas, así como una conectividad alterada dentro y entre varias redes neuronales.

Según los datos reportados por estudios anatómicos, en el TDAH existe una reducción del volumen cerebral en la corteza prefrontal, los ganglios basales, el cerebelo y las regiones parieto-temporales en comparación al cerebro con desarrollo típico (Castellanos et al., 2002; Nakao, Radua, Rubia y Mataix-Cols, 2011; Valera, Faraone, Murray y Seidman, 2007). Además, los niños con TDAH alcanzan el grosor cortical máximo a edades más tardías que sus pares sin el trastorno (Shaw et al., 2007) y se ha observado que varias regiones cerebrales siguen una organización topológica menos óptima (Beare et al., 2017; Cao et al., 2013). En cuanto al perfil electroencefalográfico (EEG), se han indicado diferencias entre los niños con TDAH en comparación a los niños sin el trastorno (Ibanez-Soria et al., 2018; Ibanez-Soria et al., 2019; Ortiz-Perez y Moreno-García, 2015). Según la diferenciación de las presentaciones clínicas de TDAH, existen estudios que han indicado que el grupo de TDAH-C y el grupo TDAH-I se diferencian en su patrón electroencefalográfico (Aldemir et al., 2018), mientras que en otros estudios no se han descrito dichas diferencias entre las presentaciones (Hermens et al., 2004; Loo et al., 2010; Monastra, Lubar y Linden, 2001). Además, hay estudios que han informado de que las presentaciones de TDAH difieren en sus propiedades micro-estructurales (Ercan et al., 2016; Semrud-Clikeman, Goldenring, Bledsoe y Zhu, 2017).

Entre otros, se han observado volúmenes del núcleo caudado y la corteza cingulada anterior bilateralmente más pequeños en el grupo TDAH-C que en el grupo TDAH-I y en los niños sin el trastorno. Esta estructura atípica implica múltiples sistemas neurales incluyendo la atención, el control cognitivo y la memoria de trabajo (Arnsten y Rubia, 2012).

Las teorías contemporáneas postulan que las alteraciones del comportamiento de estos niños están asociadas a una conectividad funcional anormal entre las regiones y redes cerebrales (Cao, Shu, Cao, Wang y He, 2014; Castellanos y Proal, 2012). Esto es, que el sustrato estructural desviado en el TDAH (que subyace a la conectividad funcional), estaría en la base de su sintomatología y rendimiento. De hecho, una gran parte de la investigación se ha centrado en delinear este circuito neural atípico (ver revisiones de Castellanos y Aoki, 2016; Posner, Park y Wang, 2014; Purper-Ouakil, Ramoz, Lepagnol-Bestel, Gorwood y Simonneau, 2011). Según los resultados de estudios con resonancia magnética funcional, los niños con TDAH muestran una hipoactivación en los sistemas implicados en la función ejecutiva (red frontoparietal) y la atención (red atencional ventral), así como una hiperactivación en la red por defecto, la red ventral atencional y la red somato-motora (Cortese et al., 2012; Purper-Ouakil et al., 2011). Además, se han observado indicios de retraso madurativo y alteraciones subyacentes en redes cerebrales, asociadas con la sintomatología del trastorno (Francx et al., 2015; Nomi et al., 2018). De hecho, se ha confirmado que las diferentes presentaciones del trastorno tienen no solo una organización cerebral diferente (Saad et al., 2017), sino también una topología de la red funcional del cerebro diversa (Ghaderi, Nazari, Shahrokhi y Darooneh, 2017; Qian et al., 2019).

Aún continúa abierto el debate sobre si estas diferencias representan anormalidades cerebrales específicas características del TDAH, o se deben a un retraso en el desarrollo madurativo. Sin embargo, lo que sí queda claro es que hay diferencias tanto estructurales como funcionales entre las presentaciones del trastorno y que estas se encuentran a la base de su sintomatología, su conducta y su rendimiento funcional.

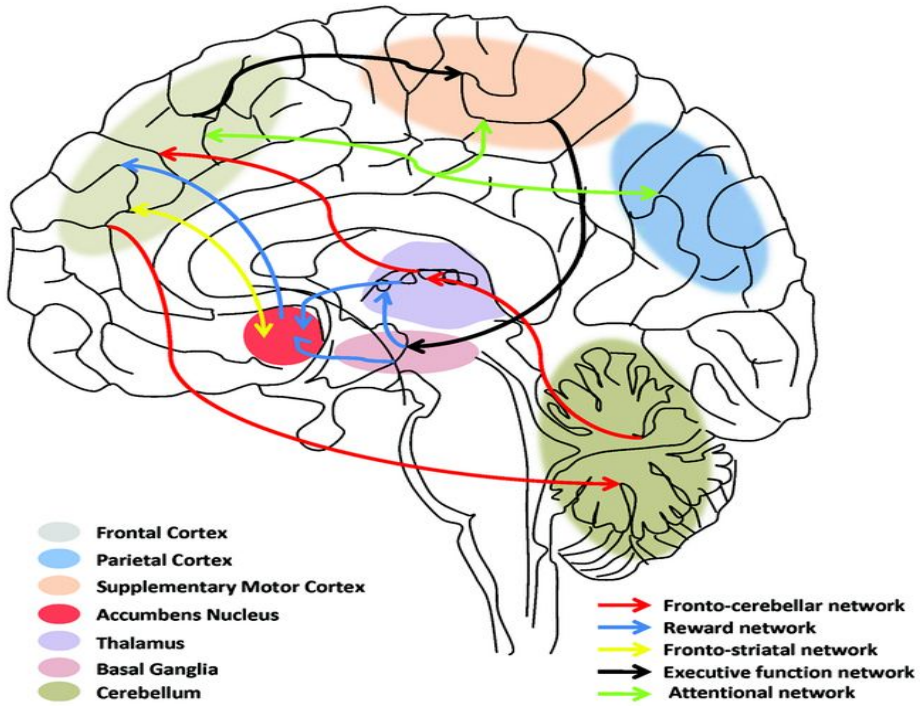

Figura 1. Representación esquemática de los circuitos funcionales implicados en la patofisiología del TDAH. Red fronto-cerebelar (rojo), red de recompensa (azul), red fronto-estriatal (amarillo), red de función ejecutiva (negro) y red atencional (verde). Recuperado de: https://www.nature.com/articles/pr9201196/figures/1

Rendimiento cognitivo en los niños con TDAH

Fue en la tercera edición del DSM cuando se establecieron los criterios explícitos para el diagnóstico del TDAH enfatizando tanto la falta de atención como la hiperactividad (APA, 1980). Sin embargo, hasta 1997 no se propuso una teoría

integradora del TDAH en la que exponía que el control inhibitorio era el déficit central que interrumpe de manera secundaria otros procesos de las funciones ejecutivas (FE) (Barkley, 1997). Este paradigma, aunque dominante, tuvo varios modelos alternativos: el modelo de aversión al retraso (Sonuga-Barke, Houlberg y Hall, 1994), el modelo de inhibición/activación del comportamiento (Quay, 1993), el modelo de función ejecutiva (Pennington y Ozonoff, 1996) y el modelo cognitivo-energético (Sergeant, Oosterlaan y Meere van der, 1999).

La llegada posterior del modelo dual surgió como una conciliación de las teorías previas, proponiendo que los pacientes con TDAH podrían tener un déficit primario en la función ejecutiva o un déficit en los procesos de refuerzo relacionados con la recompensa y la motivación que producen una aversión al retraso (Sonuga-Barke, 2003). Durante el desarrollo de las teorías explicativas del TDAH se ha ido generando un gran crecimiento de la literatura científica focalizada en comprender la neuropsicología del trastorno.

En general, los niños con TDAH muestran un peor rendimiento cognitivo que los niños sin el trastorno (Mayes, Calhoun, Chase, Mink y Stagg, 2009; Taddei y Contena, 2017; Willcutt, Doyle, Nigg, Faraone y Pennington, 2005) y eso podría ser el resultado de una activación cerebral atípica. Por un lado, se encuentran los deterioros en las FE, incluyendo la memoria de trabajo (verbal y espacial), la planificación, la vigilancia, el control de respuesta y la velocidad de procesamiento (Fried et al., 2017; Martinussen, Hayden, Hogg-Johnson y Tannock, 2005; Moreno-García, Delgado-Pardo y Roldán-Blasco, 2015; Willcutt et al., 2005). Por otro lado, algunas funciones no ejecutivas también se han visto afectadas en los niños con TDAH, como son la motivación (Sagvolden, Johansen, Aase y Russell, 2005), la activación, el esfuerzo

(Sergeant, 2005) y el reconocimiento espacial, entre otras (Rhodes, Coghill y Matthews, 2006).

En cuanto a la inteligencia, los resultados de los estudios han sido contradictorios. Mientras algunos estudios han indicado la existencia de menores puntuaciones en CI en los niños con TDAH en comparación con los niños sin el trastorno (véase revisión de Frazier, Demaree y Youngstrom, 2004), otros autores lo han asociado también con altas capacidades intelectuales (ver revisión de Rommelse et al., 2016).

Si bien es conocida la heterogeneidad sintomática del trastorno, son pocos los estudios que han examinado los déficit cognitivos en el TDAH según su presentación (v.gr. Mayes et al., 2009). De hecho, en muchos estudios no se ha tenido en cuenta la diferenciación entre las presentaciones para el análisis de los procesos cognitivos (Barber et al., 2015; Cornoldi, Giofrè, Calgaro y Stupiggia, 2013), por lo que no queda claro si el deterioro en un área cognitiva específica es más característico de una presentación o de otra. A este respecto, no existe una revisión actualizada sobre el rendimiento cognitivo en los niños con TDAH según su sintomatología dominante, lo que podría aportar claridad a la heterogeneidad entre las diferentes presentaciones del trastorno y ayudar a delimitar la etiología de sus diferencias en el comportamiento.

Rendimiento académico en los niños con TDAH

Según lo expuesto previamente (ver sección *TDAH: estructura y función cerebral atípica*), el cerebro de los niños con TDAH muestra diferencias tanto estructurales como funcionales no solo con respecto a los niños sin el trastorno, sino

también entre las diferentes presentaciones del mismo. Estas diferencias están en la base de su sintomatología y rendimiento cognitivo, dos factores que podrían repercutir negativamente en su rendimiento académico (Daley y Birchwood, 2010). De hecho, está ampliamente documentado que el TDAH se asocia con un bajo rendimiento académico (ver revisiones de Arnold, Hodgkins, Kahle, Madhoo y Kewley, 2015; Baweja et al., 2015). Sin embargo, no se conoce hasta qué punto los déficit neuropsicológicos tempranos, la sintomatología propia del TDAH u otros factores relacionados indirectamente con el trastorno son predictivos del bajo rendimiento (Coghill, Hayward, Rhodes, Grimmer y Matthews, 2014).

Por un lado, en algunos estudios se ha demostrado que los déficits en las FE y la variabilidad en el tiempo de reacción pueden influir en el bajo rendimiento académico de estos niños (Rogers, Hwang, Toplak, Weiss y Tannock, 2011; Sjöwall y Thorell, 2014). Por otro, también se ha observado que los síntomas de inatención e hiperactividad pueden contribuir a las dificultades académicas en lectura (Martinussen, Grimbos y Ferrari, 2014; Willcutt et al., 2010), matemáticas (Massetti et al., 2008) y fluidez y precisión en la composición escrita (Kim, Al Otaiba, Sidler y Gruelich, 2013).

Teniendo en cuenta las presentaciones del trastorno, se ha indicado que los niños con TDAH-I tienen peor rendimiento en la adolescencia comparados con los niños con TDAH-C y aquellos sin el trastorno (Massetti et al., 2008). En contraste con estos resultados, recientemente se ha indicado que los síntomas de TDAH se asocian con problemas de conducta y funcionamiento global, pero no con el rendimiento académico (Simone, Marks, Bédard y Halperin, 2018). Los resultados a este respecto son, por tanto, poco concluyentes.

La existencia de múltiples variables moderadoras entre el TDAH y el rendimiento escolar pueden dificultar la identificación exacta de cómo este trastorno repercute en los aspectos académicos (ver Baweja et al., 2015). De hecho, los individuos con TDAH tienen dificultades asociadas como los problemas de sueño (Díaz-Román, Hita-Yáñez y Buela-Casal, 2016; Hvolby, 2015). Sin embargo, son pocos los estudios que han analizado el papel moderador del sueño en el rendimiento académico del TDAH (ver revisión de Chaput et al., 2016; Cusick, Isaacson, Langberg y Becker, 2018).

En definitiva, existe un consenso sobre el bajo rendimiento académico de los niños con TDAH en comparación con su grupo de iguales. Sin embargo, en algunos estudios se defiende que la causa de este bajo rendimiento son los problemas cognitivos derivados del trastorno y, en otros, que la causa es la propia sintomatología. El papel modulador de otros factores como el sueño aún está por dilucidar, ya que existen limitaciones metodológicas que impiden conocer de manera precisa hasta qué punto esos factores modulan e influyen en el rendimiento diurno (véase sección *Relación entre el sueño y el rendimiento cognitivo y escolar en los niños con TDAH).*

El sueño en los niños con TDAH

Con frecuencia, una amplia variedad de trastornos concurrentes contribuyen al estado psicopatológico de los niños con TDAH, afectando a la presentación de los síntomas, aumentando su gravedad y llevando a un mayor deterioro funcional. Algunos de estos son los ya mencionados problemas de sueño, que afectan a más del 70% de estos niños (Sung, Hiscock, Sciberras y Efron, 2008).

De manera específica, el sueño en los niños con TDAH se caracteriza por una peor calidad y eficiencia que en los niños sin el trastorno. Además, pueden presentar problemas respiratorios, movimientos periódicos de las piernas, un sueño más fragmentado y mayores niveles de somnolencia diurna (ver revisiones de Cortese, Faraone, Konofal y Lecendreux, 2009; Díaz-Román et al., 2016). Existen también algunas evidencias de que los niños con TDAH pueden presentar un porcentaje significativamente mayor de anomalías epilépticas nocturnas (v.gr. Bakke, Larsson, Eriksson y Eeg-Olofsson, 2011).

Los hábitos de sueño poco saludables, la edad, el ejercicio físico, la presencia de otras enfermedades comórbidas, así como el consumo de la medicación específica son moderadores de la asociación sueño-TDAH (Becker, Froehlich y Epstein, 2016; Sadeh, Pergamin y Bar-Haim, 2006; Santisteban, Stein, Bergmame y Gruber, 2014). Además, la sintomatología propia del trastorno también puede aportar información relevante a este respecto, aunque son pocos los estudios que han tenido en cuenta la diferenciación de las presentaciones de TDAH en los análisis del sueño.

En algunos estudios se indica que no existe ninguna diferencia en las características de sueño en las diferentes presentaciones del TDAH (Virring, Lambek, Thomsen, Møller y Jennum, 2016; Wiggs, Montgomery y Stores, 2005). En otros, sin embargo, se ha observado una mayor presencia de ronquidos crónicos y unas latencias de sueño más cortas para el TDAH-H/I que para el TDAH-C así como un sueño más fragmentado para el TDAH-H/I que en las otras dos presentaciones (LeBourgeois, Avis, Mixon, Olmi y Harsh, 2004; Ramos, Vela, Espinar y Kales, 1990). Además, los síntomas de hipersomnia, las siestas involuntarias, las latencias más cortas de inicio del sueño, así como la somnolencia diurna, se han asociado más con el grupo TDAH-I

(Chiang et al., 2010; LeBourgeois et al., 2004; Lecendreux, Konofal, Bouvard, Falissard y Mouren-Simeoni, 2000; Mayes et al., 2009).

Con respecto a la metodología de estudio, en algunas investigaciones se ha recogido la información de sueño a través de medidas objetivas (v.gr. polisomnografía y actigrafía) mientras que otros han utilizado cuestionarios basados en los informes de los padres o autoinformes (ver revisión de Cortese et al., 2009). Son pocos los estudios que han utilizado medidas tanto objetivas como subjetivas para evaluar el sueño de estos niños (Huang et al., 2004; Wiebe, Carrier, Frenette y Gruber, 2013; Wiggs et al., 2005), lo que puede estar a la base de las discrepancias en los resultados (ver revisiones de Cortese et al., 2009; Díaz-Román et al., 2016).

El consumo de psicoestimulantes (la primera opción farmacológica para el TDAH) también puede ejercer un impacto sobre los niveles de alerta y en la arquitectura de sueño (Cortese et al., 2013). Además, hay evidencia de que los medicamentos para el TDAH pueden afectar a los ritmos circadianos (v.gr. Baird, Coogan, Kaufling, Barrot y Thome, 2013). Sin embargo, se necesitan más estudios sobre los efectos de la medicación a largo plazo para determinar la influencia real que esta ejerce sobre el sueño en estos niños.

En conclusión, los niños con TDAH muestran más problemas de sueño que los niños sin el trastorno; sin embargo, aún quedan limitaciones metodológicas por superar para entender cómo estos problemas pueden diferir según la presentación del trastorno, el informante y la relación que tienen con otras áreas de funcionamiento. Entre estas limitaciones metodológicas podrían incluirse la coherencia en el rango de edad de los niños, la diferenciación de las presentaciones y el uso de medidas tanto objetivas como subjetivas de sueño.

Spindles: definición y su relación con el TDAH

Los *spindles* son oscilaciones cerebrales que se observan durante el sueño No-REM. Fueron los primeros eventos del sueño observados en la señal EEG y sus mecanismos neurofisiológicos se dilucidaron a principios de los años treinta del siglo XX (Berger, 1929; Loomis, Harvey y Hobart, 1935). Estas oscilaciones se generan por una cascada de señales inhibitorias y excitatorias entre el núcleo reticular, las células tálamo-corticales y las neuronas corticales (véase revisión de Clawson, Durkin y Aton, 2016).

Los *spindles* se observan en la frecuencia sigma de 11–16 Hz, por lo que predominan en N2, encontrándose también en el sueño de onda lenta (SOL) (Iber, Ancoli-Israel, Chesson y Quan, 2007; Lüthi, 2014). Tienen una duración de entre 0,5—2 seg. y según su frecuencia, se pueden dividir entre lentos (11—14 Hz, predominan en las áreas frontales) y rápidos (14—16 Hz, predominan en las áreas centrales y parietales) (ver revisión de De Gennaro y Ferrara, 2003). Los *spindles* sufren cambios durante el desarrollo en términos de densidad (número de *spindles*/min de sueño No-REM), duración, amplitud (distancia entre pico y pico, reflejando el voltaje) y frecuencia (número de ondas por seg.) (Scholle, Zwacka y Scholle, 2007). Además, los dos tipos de *spindles* muestran diferentes patrones de maduración, lo que sugiere que su desarrollo está asociado con cambios en las estructuras tálamo-corticales y con la maduración de los sistemas fisiológicos que los producen (De Gennaro y Ferrara, 2003; Purcell et al., 2017; Shinomiya, Nagata, Takahashi y Masumura, 1999). Es por esto que han sido considerados no solo como una “huella” electrofisiológica (De Gennaro,

Ferrara, Vecchio, Curcio y Bertini, 2005), sino como un marcador de maduración biológica (Scholle et al., 2007; Shinomiya et al., 1999).

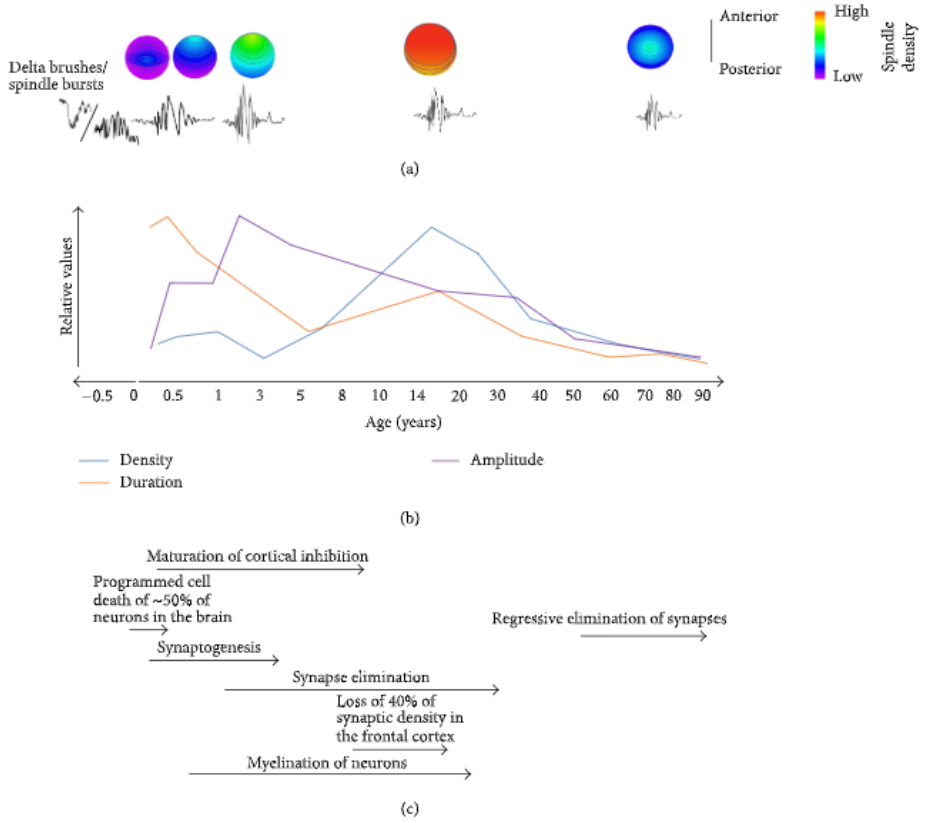

Figura 2. Cambios en los *spindles* a los largo de la vida. (a) Los mapas de calor representan la densidad topográfica del *spindle* durante el desarrollo temprano, la adolescencia y el envejecimiento. Los *spindles* se encuentran inicialmente sobre áreas centrales del cerebro y se desarrollan gradualmente sobre áreas frontotemporales durante el primer año de vida (Hagne, 1972). Durante la adolescencia, la densidad alcanza un máximo relativo con una distribución equitativa a través de las zonas frontales, centrales y parietales. En el envejecimiento, hay un retorno al mismo patrón observado anteriormente en el desarrollo, con la mayor densidad en la zona central (Martin et al., 2013). Debajo de los mapas de calor hay representaciones de la morfología del *spindle* a estas edades. (b) Densidad del *spindle* (*azul*) Aumenta a lo largo del desarrollo temprano, alcanzando su punto máximo durante la pubertad y disminuyendo constantemente desde la adolescencia hasta la vejez (Louis, Zhang, Revol, Debilly y Challamel, 1992; Nicolas, Petit, Rompre y Montplaisir, 2001). La duración del *spindle* (*naranja*), por otro lado, alcanza su punto máximo al principio de la vida y luego disminuye en general a lo largo de la vida. La amplitud del *spindle (púrpura*) es relativamente pequeña al principio del desarrollo, aumentando a valores máximos durante el primer año de vida y luego disminuye constantemente hasta la vejez (Crowley, Trinder, Kim, Carrington y Colrain, 2002). (c) Indicadores del desarrollo neurológico. Recuperado de: https://www.hindawi.com/journals/np/2016/6936381/fig2/

Una fuerte evidencia empírica ha permitido dilucidar el papel que los *spindles* desempeñan; estos facilitan el aprendizaje y la formación de la memoria, además de cumplir un rol protector del sueño (Cote, Epps y Campbell, 2000; Lüthi, 2014; Ulrich,

2016). Por esta razón, su estudio ha sido de gran importancia en los trastornos del neurodesarrollo.

Como se ha contemplado en apartados anteriores, los niños con TDAH muestran déficit cognitivos y problemas de sueño, por lo que el impacto de la generación disfuncional de *spindles* podría amplificarse en este caso. En la escasa literatura científica que se ha focalizado en el estudio de los *spindles* en los niños con TDAH se han encontrado hallazgos contradictorios. En la década de los ochenta del siglo XX, Kiesow y Surwillo (1987) no observaron diferencias significativas en el número de *spindles* entre niños hiperactivos y no hiperactivos. Sin embargo, Khan y Rechtschaffen (1978) indicaron una menor frecuencia de los *spindles* en los niños hiperactivos (aunque notaron un aumento de estos tras la administración de metilfenidato en tres de los cinco niños de la muestra clínica). Por su parte, Poitras, Bylsma, Simeon y Pivik (1981) reportaron más *spindles* en niños hiperactivos comparados con niños sin el trastorno. Cabe señalar que las diferencias metodológicas entre los tres estudios anteriores dificultan la comparación directa de sus resultados, ya que mientras que dos estudios registraron el sueño durante la noche (Khan y Rechtschaffen, 1978; Poitras et al., 1981), el otro lo registró durante el día y utilizó el hidrato de cloral para inducir el sueño (Kiesow y Surwillo, 1987).

Lo mismo sucede con los estudios más recientes. Por una parte, no se han observado diferencias significativas en número, densidad, amplitud y duración de los *spindles* entre los niños con TDAH con respecto a los controles (Prehn-Kristensen et al., 2011; Tong, 2011). Por otra, sí que se han observado diferencias (en actividad sigma/*spindles*) aunque reflejando resultados contradictorios. Salentin, Coon y Carskadon (2017) han indicado que existe una disminución selectiva de potencia en la

banda sigma para el grupo de TDAH. Estos resultados han sido parcialmente apoyados por De Dea, Zanus, Carrozzi, Stecca y Accardo (2018) que han reportado mayores valores en los niños controles que en los niños con TDAH en casi todas las bandas espectrales de potencia en el hemisferio izquierdo antes, durante y después de los *spindles*. A este respecto, Merikanto et al. (2019) también han mostrado que un aumento de la sintomatología de TDAH se asocia con un decremento en los *spindles* rápidos. Por el contrario, Saito et al. (2019) han observado que la potencia relativa de los *spindles* frontales en niños con TDAH es superior a la de los controles.

En conclusión, la información referente a las características de los *spindles* de los niños con TDAH en comparación con los controles es poco concluyente debido al uso de metodologías de estudio diferentes. Además, la información referente a las características de los *spindles* en niños con las diferentes presentaciones del TDAH aún no ha sido reportada. Si bien está establecido que los *spindles* representan una huella electrofisiológica y un buen indicador de la maduración biológica, el análisis de las características de los *spindles* en las diferentes presentaciones del TDAH podría aportar una mejor comprensión de los diferentes perfiles de desarrollo cerebral en estos niños.

Relación entre el sueño y el rendimiento cognitivo y escolar en los niños con TDAH

La asociación entre el sueño y el funcionamiento diurno se ha reportado previamente tanto en adultos (v.gr. Almondes, Costa, Malloy-Diniz y Diniz, 2016) como en niños (ver revisión de Araújo y Almondes, 2014). En el TDAH, esta relación se ha demostrado también a través de cuestionarios y medidas objetivas de sueño (ver revisiones de Davidson, Rusak, Chambers y Corkum, 2018; Dewald, Meijer, Oort,

Kerkhof y Bögels, 2010), así como en investigaciones en las que el sueño ha sido manipulado experimentalmente (v.gr. Astill, Van der Heijden, Van IJzendoorn y Van Someren, 2012).

Con respecto al rendimiento cognitivo, diversos estudios usando medidas objetivas de sueño han reportado que la duración, la eficiencia de sueño, N2, SOL, MOR, los movimientos periódicos de las piernas y el sueño fragmentado están asociados con el rendimiento en diversas áreas como las FE, la atención y la memoria (Kirov, Brand, Banaschewski y Rothenberger, 2017; Lee et al., 2014; Moreau, Rouleau y Morin, 2013; Prehn-Kristensen et al., 2013; Um et al., 2016; Waldon, Vriend, Davidson y Corkum, 2018). Sin embargo, en algunas investigaciones en las que se ha evaluado el sueño mediante cuestionarios, se ha sugerido que los problemas en FE no se atribuyen a problemas de sueño (Schneider, Lam y Mahone, 2016), generando así resultados contradictorios.

En relación al rendimiento escolar, dos meta-análisis indicaron que la reducción en la duración de sueño está asociada con problemas académicos (Astill et al., 2012; Dewald et al., 2010). Además, a través del uso de cuestionarios y autoinformes, se ha reportado que las conductas problemáticas del sueño se asocian significativamente con rendimiento académico disfuncional y que la somnolencia diurna tiene un impacto negativo en el rendimiento académico en diferentes entornos y etapas evolutivas (Langberg, Dvorsky, Becker y Molitor, 2014; Langberg, Dvorsky, Marshall y Evans, 2013; Reynolds, Patriquin, Alfano, Loveland y Pearson, 2017). Respecto a los despertares nocturnos, también se ha demostrado su influencia negativa en el rendimiento en matemáticas (Cusick et al., 2018). Al contrario de estos resultados, en un estudio que utilizó la polisomnografía no se observó ninguna relación entre el sueño

y el rendimiento académico en niños con sintomatología de TDAH (Mayes, Calhoum, Bixler y Vgontzas 2008).

A pesar de los novedosos avances en la literatura científica centrada en el sueño y el rendimiento cognitivo y escolar en el TDAH, en general los resultados han sido variables y poco concluyentes. El uso de diferentes métodos de evaluación del rendimiento diurno y del sueño, así como la comorbilidad con otros diagnósticos, el uso de medicación y la edad de los participantes pueden estar en la base de estas inconsistencias. Al respecto, se considera que una mayor investigación sobre las complejas asociaciones entre el sueño, el TDAH y el rendimiento cognitivo y escolar permitirá superar limitaciones metodológicas previas para generar un mayor entendimiento del trastorno. De manera específica, conocer los perfiles de sueño y cognitivos de los niños con TDAH, así como la relación existente entre el sueño y el rendimiento diurno de estos niños permitirá plantear mejores intervenciones clínicas y educativas, conduciendo a la consecución de mejores resultados para los niños con TDAH y un incremento en su calidad de vida.

Importancia y finalidad de la presente tesis doctoral

A lo largo de la introducción se han comentado algunas de las cuestiones principales sobre el TDAH en la infancia, el sueño y el rendimiento cognitivo y escolar. Según lo expuesto, la investigación a este respecto aún requiere de mayores esfuerzos para tratar de superar las limitaciones metodológicas de los estudios previos y esclarecer algunas cuestiones pendientes referentes a los perfiles cognitivos y de sueño de las diferentes presentaciones de TDAH.

La realización de la presente Tesis Doctoral surge, por tanto, del principio de la pertinencia, respondiendo a necesidades reales y resolviendo problemas concretos, siendo útil para la comunidad científica y clínica. Los dos aspectos más importantes a la hora de realizar esta Tesis Doctoral han sido enriquecer el conocimiento científico en el área de la Psicología Clínica y de la Salud y generar una aportación práctica que se pueda dirigir a la orientación clínica.

Los datos de la presente disertación permitirán una mejor comprensión de los perfiles de TDAH y arrojarán evidencia sobre la compleja búsqueda de marcadores cognitivos y fisiológicos en las diferentes presentaciones del trastorno.

En definitiva, la presente Tesis Doctoral podrá contribuir a: 1) la comprensión de los perfiles cognitivos y de sueño de los niños con TDAH, así como al conocimiento de la relación entre el sueño y el funcionamiento diurno; 2) el desarrollo de intervenciones específicas que vayan más allá de los síntomas centrales del TDAH para promover y mejorar el sueño y, posteriormente, el funcionamiento diurno de estos niños, 3) la reducción de la sintomatología de TDAH y del riesgo de fracaso académico, con la consecuente mejora de la calidad de vida no solo de los niños con TDAH, sino también de las familias. Así pues, se presentan a continuación los objetivos.

OBJETIVOS

Objetivos

El objetivo general de la presente tesis doctoral es evaluar la relación entre el sueño y el rendimiento cognitivo y escolar de niños con TDAH teniendo en cuenta las diferentes presentaciones (TDAH-I, TDAH-H/I, TDAH-C).

Partiendo del objetivo general, a continuación se derivan los objetivos específicos que plantean los siguientes estudios independientes y sucesivos:

1. Revisar la literatura científica existente sobre el rendimiento cognitivo en los niños con TDAH

- Estudio 1. *Cognitive performance in children with attention deficit hyperactivity disorder: Meta-analysis*

2. Examinar los patrones de sueño subjetivos y objetivos en niños con TDAH diferenciando entre sus presentaciones.

- Estudio 2. *Sleep among presentations of attention-deficit/hyperactivity disorder: Analysis of objective and subjective measures*

3. Analizar las características de los *spindles* en niños con TDAH diferenciando entre sus presentaciones.

- Estudio 3. *Spindles characteristics in children with attention-deficit/hyperactivity disorder*

4. Analizar la influencia del sueño en el rendimiento cognitivo y escolar en los niños con TDAH.

- Estudio 4. *Sleep, academic achievement, and cognitive performance in children with attention-deficit/hyperactivity disorder: A polysomnographic study*

ESTUDIO 1

Cognitive performance in children with attention deficit/hyperactivity disorder: Meta-analysis

Abstract

Objective: To update previous meta-analyses on cognitive performance in school-aged children with attention deficit/hyperactivity disorder (ADHD) (7—12 years), including both executive and non-executive domains, and separating among presentations. **Method**: A comprehensive search through Cochrane, Web of Science, PsycINFO, Scopus, and PubMed was conducted, which included 116 studies (with 127 independent samples). A meta-analysis of standardized mean differences was carried out reporting data on 21 different cognitive domains in children with ADHD compared to a control group. **Results**: Differences were observed in 17 of the 21 variables analysed. Children with the combined presentation were those who present the greatest cognitive deficits, although children with the inattentive presentation were those who show the more particular cognitive profile. Concerning the hyperactive/impulsive presentation, not enough data were available for drawing conclusions. **Conclusion:** These results facilitate the understanding of ADHD profiles, clarifying contradictory results from previous studies.

Keywords: Attention deficit hyperactivity disorder, ADHD, presentation, cognitive performance, children.

Introduction

Attention deficit/hyperactivity disorder (ADHD) is a neurodevelopment disorder characterised by symptoms of hyperactivity, impulsivity, and inattention in childhood. This is one of the most common disorders in childhood, with a global prevalence estimated at about 5% in children (see Ramos-Quiroga, Montoya, Kutzelnigg, Deberdt, & Sobanski, 2013, for a review). According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5; American Psychiatric Association, 2013), ADHD can be classified into three clinical presentations: Inattentive (ADHD-I), hyperactive/impulsive (ADHD-H), and combined (ADHD-C). This disorder has a remission rate ranging from 55% to 80%, depending on the stage of adulthood (see Sudre, Mangalmurti, & Shaw, 2018, for a review), and it is related to other prevalent conditions, such as autism spectrum disorders (Romero et al., 2016), oppositional defiant disorder (Biederman et al., 2008), sleep problems (Díaz-Román, Hita-Yáñez, & Buela-Casal, 2016), substance abuse (Miranda, Colomer, Berenguer, Roselló, & Roselló, 2016), and obesity (see Hanć & Cortese, 2018, for a review).

Furthermore, ADHD is frequently associated with difficulties related to cognitive function and academic performance in children with this disorder (Fleming et al., 2017). In fact, a distinctive cognitive style of these children has been revealed in research, and it is characterised by poorer performances in multiple executive and nonexecutive domains (Mayes, Calhoun, Chase, Mink, & Stagg, 2009; Taddei & Contena, 2017; Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005). These difficulties have been widely associated with structural and functional dysfunctions in different brain areas, as well as with differences in electrical activation patterns (Aldemir et al., 2017; Ercan et al., 2016; Semrud-Clikeman, Goldenring, Bledsoe, & Zhu, 2017).

With respect to cognitive impairments, executive functioning has largely been considered as one of the most impaired areas in ADHD, as denoted by the results of numerous studies and meta-analyses performed over the years. For instance, more than two decades ago, Pennington and Ozonoff (1996) conducted a meta-analysis that revealed that ADHD is associated with impairments in at least one subset of executive functions (EF). Since then, the meta-analysis of Willcutt et al. (2005) also verified the existence of impairments in attention (vigilance) and working memory (WM) domains, the latter capturing the interest of numerous investigations (see reviews of Fried et al., 2017; Martinussen, Hayden, Hogg-Johnson, & Tannock, 2005). Recently, other studies have been conducted to further explore the executive, academic, intellectual, and social functioning of these children, and similar results were obtained (Berenguer et al., 2017; Lambek et al., 2017; Murray, Robinson, & Tripp, 2017).

Nevertheless, when examining memory impairments in children with ADHD when compared with controls, some authors have suggested that these impairments might be the consequence of their attention deficits (Barnett, Maruff, & Vance, 2005). In this respect, attention is considered a key factor for the cognitive functioning in children with ADHD. In effect, Konrad, Neufang, Hanisch, Fink, and Herpertz-Dahlmann (2006) observed a deviated brain-activation pattern in these children, and it affected three attentional networks: *Alerting, orienting,* and *executive* (see Posner & Petersen, 1990, for a review). These data have been recently confirmed by other studies that showed an atypical activation in brain areas associated with sustained attention and vigilance in ADHD (Barber et al., 2015; Christakou et al., 2013). Moreover, types of attention deficit have been associated with these children's poorer educational achievements (see Baweja, Mattison, & Waxmonsky, 2015, for a review), which extend

far beyond their intelligence quotients, as findings in this respect have been contradictory. Specifically, there is evidence of either an underperformance of children with ADHD on intelligence-related tasks (Patros, Alderson, Hudec, Tarle, & Lea, 2017), or a link between this disorder and a high intellectual capacity (see Rommelse et al., 2016, for a review). Problems in attention, memory, or other EFs, seem also affect the performance of children with ADHD in intelligence tasks (Kubo et al., 2018; Lahat, Van Lieshout, Saigal, Boyle, & Schmidt, 2014; Roberts, Martel, & Nigg, 2017).

In summary, children with ADHD underperform in cognitive functions when compared with children without ADHD, and these problems could be the result of their brain atypical activation (Aldemir et al., 2017; Altinkaynak et al., 2018; Semrud-Clikeman, et al., 2017). In this regards, some inconsistencies in results of previous studies on cognitive deficits in children with ADHD compared to their peers, might be derived from brain changes associated to development (see Franke et al., 2018 for a review; Hong, Park, Cho, & Park, 2017). In effect, significant changes occur in the symptomatology of ADHD during children's development (Francx et al., 2015). This underlines the importance of appropriately delimiting age ranges when studying cognitive performance in children with ADHD, in order to prevent the influence of these developmental brain changes on their performance. Furthermore, structural or functional brain differences among ADHD presentations have been also reported in some studies (Aldemir et al., 2017; Ercan et al, 2016; Rossi et al., 2018; Semrud-Clikeman et al., 2017), but a differentiation between presentations has not always been conducted in studies on cognitive performance (Barber et al., 2015; Cornoldi, Giofrè, Calgaro, & Stupiggia, 2013).

Therefore, the main purpose of this study was to update previous meta-analyses on cognitive performance in children with ADHD, including both executive and non-executive functions and restricting the age range. Specifically, our systematic review and meta-analysis was aimed to analyse and compare the performance of school-aged children (7—12 years) with and without ADHD in the following cognitive domains: Categorisation, decision making, flexibility, response inhibition, planning, EF global index, numerical WM, verbal WM, visuospatial WM, unspecified WM, short-term verbal memory, short-term visuospatial memory, alerting, executive, and orienting attentional networks, verbal comprehension, verbal IQ, perceptual reasoning (PR), performance IQ, processing speed (PS), and full-scale IQ (FSIQ). It was decided that these cognitive domains would be analysed separately, despite their overlapped relationships, because these domains are individually important within the study of ADHD, apart from children's other EFs less commonly explored. Moreover, we also pretended to explore potential differences between presentations in these cognitive domains when reported in the studies included, in order to facilitate a better understanding of ADHD profiles.

The initial hypothesis was not only focused on the underperformance of school-aged children with ADHD in comparison with their peers, both in executive and non-executive domains, but also on the cognitive deficits associated with the different presentations. We hypothesized that every ADHD presentation would show a differentiated cognitive profile, especially the ADHD-I and ADHD-C, as the ADHD-H/I presentation is rarely diagnosed in clinical settings (Willcutt et al., 2012). In particular, we expected to find more or less cognitive deficits in children with each presentation, and differences between the three presentations, depending on their core

ADHD symptoms themselves. Therefore, as children with ADHD-C present both attention and hyperactivity-impulsivity symptoms, we assumed that children with ADHD-C would show overall worse performance, suggesting greater cognitive deficits associated with this presentation. We also expected our results to reveal a stronger relationship between the ADHD-I presentation and impairments in those most attention-related cognitive domains (i.e., alerting, orienting, executive, working memory and processing speed; Barkley, 1997; Kubo et al., 2018; Mayes et al., 2009; Posner & Petersen, 1990).

Method

Type of study

To pursue the objectives of this study, PRISMA recommendations were followed (Moher et al., 2015; Urrútia & Bonfill, 2013), as well as those proposed by Botella and Gambara (2006), Sánchez-Meca (2010), and Perestelo-Pérez (2013).

Search of the studies

As the first step, we searched for similar reviews using Cochrane but found none. Next, the Web of Science, PsycINFO, Google Scholar, and Scopus databases and the PubMed search engine were used to locate all articles that covered any area of cognitive functioning in relation to ADHD and were available until April 2017. The following search equation was used: (((“Cognitive performance” OR Memor* OR Recov* OR Evocat* OR “Executive function” OR Vocab* OR Intelligen* OR IQ*)) AND ((ADHD OR “attention deficit” OR hyperact*)) AND ((Child* OR Adolesc* OR Teen* OR Pubert*))); however, this equation was slightly adapted to the particular

specifications of each database. Once the articles were excluded according to their titles and abstracts, 1,016 references remained to be screened in full-text form.

Inclusion and exclusion criteria

Several explicit criteria were used to determine the inclusion of the articles in the final database (Sánchez-Meca, 2010):

- They had to be written in English or Spanish, including samples from any country and published in any geographic region.
- Only observational, quasi-experimental, and experimental articles were included. Reviews, meta-analyses (references from these papers were traced to articles that met the criteria for inclusion in this study), single case studies, and conference papers were excluded.
- Studies had to include at least one group of children with ADHD (with no associated comorbidity) and a control group (without any psychological disorders), and the participants had to be between 7 and 12 years old.
- Articles must include means and standard deviations for both groups or enough data that could allow the effect sizes to be estimated.

When pre- and posttreatment means were provided for both groups, the pretreatment means were always selected. The decision to exclude samples including both ADHD and comorbidities was made in order to control the potential confounding effects of these comorbidities in children's cognitive performance.

Cohen's *d* was used as the effect size measure for mean comparisons. When data from the same sample were available in relation to two or more cognitive variables of the same domain, only those data corresponding to the variable with the largest effect size were retained. In these situations, we first checked whether the use of one effect

size or another produced substantial differences in our results, in order to prevent an inflation of the effect size estimates. In any case, substantial differences were observed.

Selection of studies

On the basis of the inclusion and exclusion criteria, the studies were screened in phases and first selected according to their titles and abstracts; the final inclusion was based on the full texts. A coding guide was compiled, and it described the variables to be extracted from each of the papers. On the basis of this document, two of the researchers independently codified 20 articles to obtain an index of agreement between judges. The kappa index was used for categorical variables, and the intraclass correlation was used for continuous variables. In all cases, the rates ranged from good to very good. A summary of the selection process is shown in Figure 1.

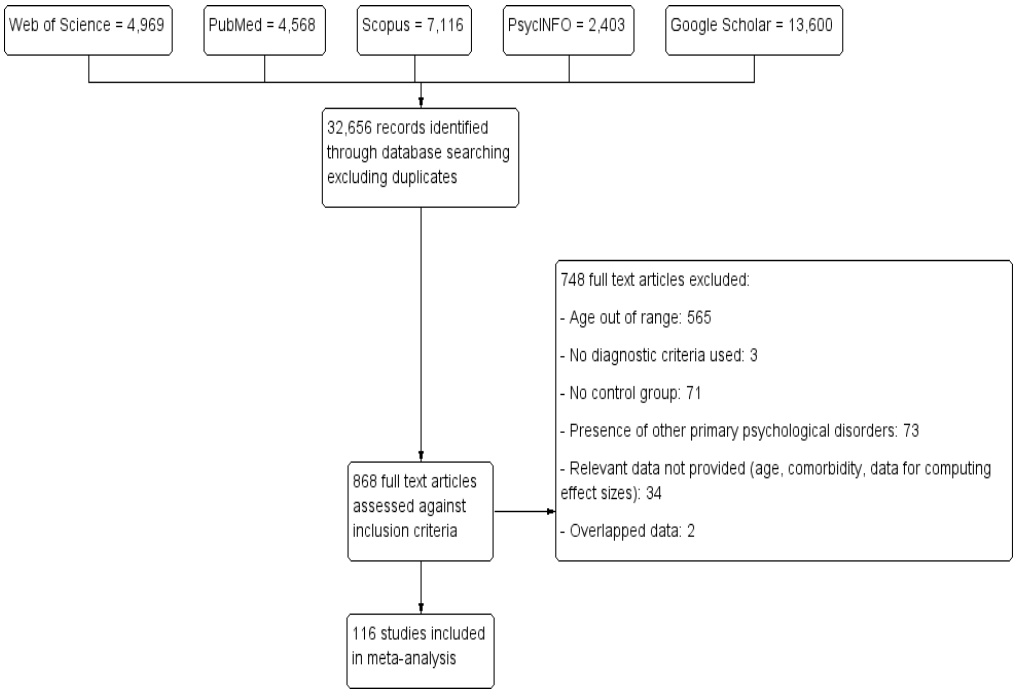

Figure 1. Selection process of the studies included in the meta-analysis.

Data extraction

The following measures were coded for each of the selected articles: (a) study identification data: authors, year of publication, and type of document; (b) sample data: country of sample, age range of participants, percentage of women, and whether the sample was in school; (c) clinical data (a summary is presented in Appendix 1): presentation of ADHD and presence or absence of a clinical diagnosis or diagnostic criteria for ADHD; (d) data for computing the effect sizes: dependent variable, method of assessment of the dependent variable (and whether it was standardised or not), the means and standard deviations of the ADHD group (when an intervention or treatment was performed, the premeans were extracted), the means and standard deviations of the control group, effect sizes reported by the authors, or any other statistical data (*t* student or *F* values and degrees of freedom) that allowed the effect size to be estimated when means and standard deviations were not available; (e) data for evaluating methodological quality: As the studies had different methodologies, the use of a single scale for assessing methodological quality made no sense, so variables such as the number of cases of each group, the diagnostic criteria employed, and the use or not of standardised scales for participants' cognitive assessment were used to control that the included studies had enough scientific quality.

Statistical analysis

Cohen's *d* was the statistic used to conduct the comparison between children with ADHD and controls. The DerSimonian and Laird estimation method was used because it was adequate for taking continuous measurements of such things as Cohen's *d*, provided that a random effects model was assumed. In this case, because of the number of studies and the fact that they were performed in different countries,

variability was assumed among them. In addition, in most of the analyses, *Tau* and I^2 statistics indicated that it was appropriate to follow a random effects model. The moderators were analysed with the sample subgroup as a variable. The statistical software *R* and its *metafor* package were used for the analyses (Viechtbauer, 2010).

Results

Studies included in the meta-analysis

The literature search provided 32,656 records, from which 868 studies were full-text screened against the inclusion and exclusion criteria, after 31,788 records were removed according to their titles and abstracts. One hundred sixteen articles with 127 independent samples of children with ADHD were finally included in the systematic review and meta-analysis. A summary of the selection process, including the records retrieved through each database and reasons for the exclusion of studies assessed in full text, is shown in Figure 1.

Study characteristics

About 47% of the studies included in the meta-analysis had been published from 2010 onwards. The total sample provided by these studies was 10,040 participants, with an average of 79.68 participants per study (*SD* = 112.63; lower sample = 17; higher sample = 1,156). The total ADHD sample comprised 4,566 participants, and the total control sample comprised 5,474 participants. Participants' ages ranged from 7 to 12 years, and the percentage of females varied between 0% and 67.96%, although sex distribution was not reported in some studies. Children with ADHD were medication-free in 85 of the included studies, whereas other children with ADHD were using medication in five studies, and this information was not reported in 23 studies. Children

were diagnosed with ADHD following the DSM-IV and DSM-5 criteria in most of the included studies (k = 82). Distribution of ADHD presentations among participants was as follows: 3.42% ADHD-I, 5.08% ADHD-H, and 25.93% ADHD-C. The remaining 64.55% corresponded to children who had ADHD but no appropriately specified presentation or to those whose cognitive performances were not analysed on the basis of their presentations. Further descriptions of the study characteristics are provided in the Supplemental material 1. References of these studies are listed in the Supplemental material 2.

Cognitive performance in children with ADHD

Table 1 shows the results obtained in the meta-analysis of cognitive functions in children with ADHD. Regarding the comparison of the ADHD vs. control group, there were significant results in decision making, flexibility, response inhibition, planning, overall EF index, and WM when the total sample of children with ADHD was analysed compared to a control group. However, differences between groups in categorisation were not significant. The number of included studies was appropriate for flexibility, response inhibition, and planning, whereas this was lower for categorisation, decision making, and global index. The heterogeneity tests showed high heterogeneity in all variables (I^2 range = 77%–89%, p < .01), except for decision making (I^2 = 33%, p = .20).

Similarly, significant results that revealed large impairments in the total sample of children with ADHD compared with the controls were found for short-term memory variables. The heterogeneity test showed a high heterogeneity between studies in all variables (I^2 range = 63%–86%, p < .001), except for one (short-term verbal memory) with medium heterogeneity (I^2 = 55%, p = .01).

There were significant differences between total ADHD and control groups in each attentional network proposed, thereby confirming attention impairments in children with ADHD. The number of studies examined was sufficient for every variable. The heterogeneity analyses revealed high-heterogeneity values in executive and orienting variables (I^2 = 83%, p < .001, and I^2 = 79%, p < .001, respectively). However, alerting heterogeneity analysis did not show statistical significance (I^2 = 11%, p = .32).

Last, the area for which more studies were available to be analysed was the FSIQ, followed by the performance IQ and verbal comprehension areas. In contrast, fewer studies were available to analyse the PR and PS areas. Significant results confirming a worse performance for the ADHD group with respect to controls were obtained for verbal IQ, performance IQ, and FSIQ. The heterogeneity analyses showed a high variability in FSIQ (I^2 = 76%, p < .001), verbal comprehension (I^2 = 78%, p < .001), PR (I^2 = 88%, p = < .001), and PS (I^2 = 76%, p = < .001). Medium heterogeneity was also observed in verbal IQ (I^2 = 58%, p = .01), and no heterogeneity was revealed for performance IQ (I^2 = 16%, p = .28).

When comparing cognitive performance distinguishing among ADHD presentations (Table 1), significant results were observed in the ADHD-I presentation only in the FSIQ variable. With respect to the ADHD-H/I presentation, no studies were available to analyse differences between these children and the controls in the majority of variables, and results were non-significant. However, for the ADHD-C presentation, there were significant results for the majority of the variables assessed, excepting for decision-making, planning, verbal comprehension, and perceptual reasoning. Marginal results were obtained for the executive attentional network (p = .07).

Table 1

Meta-Analysis of Cognitive Performance in Children with ADHD

Variable	ADHD-I	ADHD-H/I	ADHD-C	Total[c]
Categorisation[a]				
k				2
d				-0.34
SD				0.49
p				.493
Decision Making				
k			2	3
d			0.47	0.53
SD			0.35	0.22
p			.173	.018
Flexibility[a]				
k	2		7	18
d	-0.07		0.85	0.59
SD	0.58		0.31	0.19
p	.907		<.001	.002
Response Inhibition				
k	2		9	50
d	0.48		0.84	0.69
SD	0.40		0.19	0.08
p	.233		<.001	<.001
Planning				
k	3		8	20
d	0.42		0.31	0.38
SD	0.32		0.20	0.12
p	.19		.108	<.001
EF Global Index				
k				5
d				1.01
SD				0.25
p				<.001
Unspecified WM[b]				
k	2		8	21
d	0.27		0.87	0.87
SD	0.53		0.27	0.15
p	.616		<.0001	<.001
Numerical WM				
k		2	7	21
d		-0.30	-0.75	-0.57
SD		0.26	0.15	0.09

p		.256	<.001	<.001
Verbal WM				
k			9	19
d			-0.84	-0.85
SD			0.21	0.14
p			<.001	<.001
Visuospatial WM				
k			11	29
d			-0.79	-0.90
SD			0.17	0.10
p			<.001	<.001
Short-term verbal memory				
k			6	11
d			-0.83	-0.83
SD			0.17	0.12
p			<.001	<.001
Short-term visuospatial memory				
k			5	13
d			-1.02	-1.01
SD			0.26	0.16
p			<.001	<.001
Alerting				
k			5	18
d			0.41	0.58
SD			0.11	0.07
p			<.001	<.001
Executive				
k			6	14
d			0.50	0.79
SD			0.28	0.18
p			.070	<.001
Orienting				
k			3	14
d			0.64	0.82
SD			0.31	0.13
p			.03	<.001
Verbal comprehension				
k		2	6	16
d		-0.12	0.30	0.24
SD		0.36	0.22	0.13
p		.73	.17	.068
Verbal IQ				
k				11
d				0.4

SD				0.11
p				<.001
Perceptual reasoning				
k		2	3	9
d		0.17	-0.63	-0.05
SD		0.45	0.37	0.2
p		.71	.09	0.80
Performance IQ[a]				
k			3	14
d			-0.70	-0.39
SD			0.15	0.07
p			<.001	<.001
Processing speed				
k				11
d				0.25
SD				0.14
p				0.08
FSIQ[a]				
k	8		17	73
d	-0.61		-0.71	-0.61
SD	0.20		0.13	0.06
p	<.001		<.001	<.001

Note. Data reflect the meta-analysis for each of the exposed variables: Categorisation, decision-making, flexibility, response inhibition, planning, EF global index, unspecified working memory (WM), numerical WM, verbal WM, and visuospatial WM, short-term verbal memory, short-term visuospatial memory, alerting, executive, orienting, verbal comprehension, verbal IQ, perceptual reasoning, performance IQ, processing speed, FSIQ. Only those presentations in which more than one sample was included are shown. Total = size of the total effect of the variable; *k* = number of articles; *d* = effect size; *SE* = standard error; ADHD-I = attention deficit hyperactivity disorder, inattentive presentation; ADHD-H/I = attention deficit hyperactivity disorder; hyperactive/impulsive presentation; ADHD-C = attention deficit hyperactivity disorder, combined presentation; EF = executive function; WM = working memory; IQ = intelligence quotient; FSIQ = full scale intelligence quotient.

[a] A negative value means that children with ADHD performed worse than controls in this variable.

[b] Positive values of *d* indicate worse performance for the ADHD group.

Moderator analyses

After verifying the existence of medium and high effect sizes in the dependent variables and high heterogeneity, the possible causes of heterogeneity were explored for the total ADHD sample. The influence of mean age, the percentage of girls in the sample, the clinical guidelines used to make the diagnosis, and the pharmacological treatment of the sample were analysed as possible moderator variables. No analysis was

performed for the executive functions variables because of the reduced number of studies. The results showed that there was no influence of sex on any variable ($p \geq .15$), except for short-term verbal memory ($p = .002$). In the case of age, there was only an influence on performance IQ ($p = .005$ and $p \geq 12$ in the rest of the dependent variables). The diagnostic criteria used had an effect on numerical WM ($p = .04$) and visuospatial WM ($p = .02$), with $p \geq .25$ in the rest of variables. Medication influenced performance IQ ($p = .003$) but showed no other significant results ($p \geq .12$).

Methodological quality and risk of bias

First, we analysed the possible existence of publication bias with the Egger test, and significance values lower than .07 were not obtained in any of the variables explored. Simultaneously, the Rosenthal test's values were higher than 28 in perceptual reasoning and 200 in the rest of variables. Subsequently, the influence of individual studies on the mean effect sizes, as well as on the rest of the tests, was analysed. It was not possible to perform any sensitivity analysis for categorisation, decision making, and global index because of the low number of studies. In each one of the variables, one different study was found to have a significant influence. These influential studies were then eliminated, although this did not change the significance of the mean effect size in any case. The sensibility analysis was replicated after influential studies being removed, and we did not find new studies whose elimination affected the results.

Discussion

The objective of the present study was to update previous meta-analyses focused on cognitive performance in children with ADHD, by expanding the number of cognitive domains studied up to date and limiting the age range to school-aged children

(7—12 years). We explored cognitive performance while distinguishing among the ADHD presentations when possible. In most of the 21 variables included, all children with ADHD showed a worse performance than their comparison group (except for the categorisation, verbal comprehension, PR, and PS variables). Concerning ADHD presentations, we expected that every ADHD presentation would show a differentiated cognitive profile, with greater cognitive deficits in the ADHD-C group, and more attention-related deficits in the ADHD-I group. In this regards, different cognitive profiles were observed among ADHD presentations, but the number of studies for each specific presentation was not enough to conduct separate analyses for every variable and, thus, to completely confirm our hypotheses.

Children with ADHD showed deficits in decision making, flexibility, response inhibition, planning, EF global index, and WM compared to their peers. These deficits are consistent with previous scientific literature (Barkley, 1997; Berenguer et al., 2017; Martinussen et al., 2005; Pievsky & McGrath, 2018; Roberts et al., 2017), and they replicate and extend the findings of Pennington and Ozonoff (1996) and Willcutt et al. (2005), though the role of categorisation in children with ADHD remains unclear. Moreover, when the ADHD presentations were compared, these deficits could only be confirmed in the ADHD-C group (in flexibility and response inhibition), but not in the other groups. Specifically, children with the ADHD-I only showed marginal differences in planning, when compared to controls, and no specific executive profile could be confirmed in the ADHD-H group because of the sparse number of studies.

The results of this study confirm underperformance of children with ADHD in verbal, numerical, and visuospatial short-term memory tasks. Therefore, on the basis of these results, we can assume that children with ADHD have not only WM deficits but

also short-term memory deficits when compared with a control group. Interestingly, these memory deficits do not seem to be specifically related to inattention or hyperactivity symptoms separately, because they were observed in the ADHD-C group but not in the ADHD-I or ADHD-H groups. Nevertheless, these results might be explained not only by the fact that every variable could not be analysed in each presentation but also by the differences among the methodologies employed in clinical and laboratory settings for assessment (Tarle et al., 2017).

Regarding the three attentional networks, a lower performance was observed in children with ADHD when compared with controls (Ortega et al., 2013; Willcutt et al., 2005). In regard to ADHD presentations, our results confirmed significant deficits in children with ADHD-C in terms of the alerting and orienting networks, confirming that attention problems are common to the three presentations (Willcutt et al., 2012). In addition, differences between these children and controls in the executive network, despite marginal significance, showed a medium effect size. Unfortunately, we could not confirm whether children with ADHD-I or ADHD-H have more deficits in a specific attention network, because the studies available were not enough to compare these children and the controls.

Last, according to the results for the intelligence variables, children with ADHD, regardless of their presentation, scored lower than the control children, as noted in prior research (see Kuntsi et al., 2004, for a review). By comparing among the presentations, we found similar results: Both children with ADHD-C and ADHD-I had lower scores than the controls. Unfortunately, the number of studies available for the analysis of intelligence within the ADHD-H presentation was insufficient, which prevented us from confirming these results of this group. However, it is still not clear whether ADHD is

actually linked to lower intelligence levels or only to lower scores in cognitive tests, the latter of which might be due to deficits in other areas (see Lee & Olenchak, 2015, for a review). In this connection, according to studies that associate ADHD with high intelligence scores in childhood, these children may be using compensatory strategies that mitigate their real cognitive deficits (Rommelse et al., 2016). Therefore, the lack of these compensatory strategies might be a plausible explanation for our results of these children even more than their actual intelligence capacities.

This meta-analysis represents an important step forward in the study of ADHD. The large number of studies included makes this the most extensive meta-analysis of cognitive performance in ADHD reported to date. The results replicate and amplify the findings of previous research with an updated sample of studies, covering a wider range of cognitive domains and introducing the novelty of presenting multiple memory domains. However, our work was hampered by the lack of agreement in research on how to report ADHD profiles. Thus, many of the included studies were focused on children with ADHD without any appropriately specified clinical presentation. It might be inferred that they were part of the ADHD-C group in some studies (e.g., Schachar et al., 2000; Wu et al., 2014), according to the methodology used and the results obtained, but no separated analyses were advisable. Another limitation was the difficulty in deciding which domain assessed each task, because these tasks do not uniquely measure a single neurocognitive function; multiple neurocognitive processes are involved in almost every cognitive task. In effect, the classification used in this manuscript was performed to facilitate the presentation and interpretation of the results.

Conclusion

The results obtained in this meta-analysis support the existence of cognitive deficits in children with ADHD, and they suggest a different cognitive profile for each presentation of ADHD. In particular, our results indicate that more generalised deficits exist in children with the ADHD-C presentation, especially in terms of executive functioning and memory, than in children with the other presentations. However, these results should be interpreted with caution, since only a low percentage of the studies included in this meta-analysis reported data for every ADHD presentation separately. To confirm and extend our findings, more studies that investigate cognitive performance in children with ADHD while distinguishing among presentations are needed. Furthermore, it would be convenient to take into account other variables that can influence performance such as motivation (Martinelli, Mostofsky, & Rosch, 2017) or the implementation of compensatory strategies (Zamorano et al., 2017). In addition, the plausible presence of a hierarchical order of deficits that could explain performance in higher cognitive domains, in relation to the use or not of compensatory strategies, is still a subject of open debate.

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Supplemental material 1. Sample characteristics of the included studies

Study[a]	Control/ADHD (*n*)	Mean age (SD)	Females (%)	Diagnostic criteria	Presentation[b]	Medication[c]	Meta-analysis[d]
Ackerman (1986) (1)	12/11	9.06 (0.53)	0	DSM-III	3	NR	4
Ackerman (1986) (2)	12/13	10.86 (0.49)	0	DSM-III	3	NR	4
Adams & Snowling (2001)	21/21	9.53 (8–11 y)	19	DSM-IV	1	No	2, 3
Adólfsdóttir (2008)	57/45	10.00 (0.90)	NR	DSM-IV	4	No[c]	3, 4
Alderson (2010)	13/14	9.76 (1.40)	0	DSM-IV	3	No	4
Alloway (2009)	20/46	9.83 (0.95)	23	DSM- IV	3	No	1, 2, 3
Alloway (2010)	10/31	9.68 (1.00)	21.95	DSM-IV	3	No[c]	2
Alloway (2011)	50/50	9.83 (1.00)	27	DSM-IV	3	No[c]	2, 4
Alloway & Cockcroft (2014)	20/52	8.19 (0.77)	42.5	DSM-IV	3	Yes	2, 4
Alloway & Stein (2014)	50/83	9.59 (0.99)	30.6	NR	3	No[c]	2, 4
Antonini (2015)	30/67	8.92 (1.58)	67.96	DSM-IV	4	No	2, 4
Bará-Jiménez (2003) (1)	18/24	9.47 (1.14)	46.8	DSM-IV	2	NR	1, 4
Bará-Jiménez (2003) (2)	18/19	9.42 (1.12)	46.8	DSM-IV	3	NR	1, 4
Barber (2015)	50/50	9.90 (1.16)	42	DSM-III-R, DSM-IV	4	No[c]	1, 3, 4
Bayliss & Roodenrys (2000)	15/15	9.61 (1.01)	NR	DSM-IV	4	NR	1, 4
Benezra & Douglas (1988)	30/30	9.95 (1.63)	0	DSM-IV	4	NR	4
Bental & Tirosh (2007)	23/19	9.75 (0.10)	0	DSM-IV	4	No[c]	1, 2, 3, 4
Bolfer (2010)	23/15	9–12 y	0	DSM-IV	3	No	3
Boucugnani & Jones (1989)	28/28	7~10 y	14.29	DSM-III	4	No[c]	1, 3
Brocki (2008)	34/31	10.11 (1.63)	0	DSM-IV	3	No[c]	2, 3
Bunford (2015)	30/34	9.64 (1.15)	45	DSM-IV-TR	3	No[c]	1, 2, 4
Carter (1995)	19/18	10.61 (1.24)	23.68	DSM-III-TR	4	No[c]	1, 3, 4
Catale (2015) (1)	25/25	9.89 (1.20)	28	DSM-IV	4	NR	1, 2
Catale (2015) (2)	62/62	9.79 (1.09)	39	DSM-IV	4	NR	1, 2
Ceci & Tishman (1984)	19/19	8.00 (0.70)	0	DSM-IV	4	No[c]	2, 4
Chee (1989)	36/14	8.40 (1.53)	0	DSM–III	2	No	1
Collings (2003)	24/35	8.96 (0.74)	0	DSM-IV	3	No[c]	1, 3
Corbett (2009)	18/18	9.48 (1.90)	33.33	DSM-IV	4	Some participants	1, 2, 3, 4
Cornoldi (2013)	58/58	9.54 (0.85)	34	DSM-III	4	NR	2, 4

Craft (1983)	31/31	7–10 y	0	DSM-III	4	No	2, 4
Crippa (2015)	68/11	10.21 (1.99)	35.29	DSM-IV	4	NR	4
De Jong (2009a,b)	26/16	9.12 (1.05)	28.57	DSM-IV	3	No[c]	1, 2, 4
Dirlikov (2015)	133/93	10.20 (1.30)	31.4	DSM-IV	4	No	2, 4
Dos Santos Assef (2007)	29/29	10.35 (8–12 y)	9.68	DSM-IV-TR	4	No[c]	3
Dovis (2015) (1)	20/27	10.94 (0.98)	43.28	DSM-IV-TR	1	No[c]	4
Dovis (2015) (2)	20/70	10.24 (0.49)	30.90	DSM-IV-TR	3	No[c]	4
Fabio & Capri (2015) (1)	14/17	10.38 (0.53)	45.65	DSM-IV-TR	2	No	4
Fabio & Capri (2015) (2)	15/12	9.74 (0.81)	36.59	DSM-IV-TR	3	No	4
Fallgater (2004)	19/16	9.35 (1.25)	0	ICD-10	4	No	1, 3
French (2003)	17/9	9.13 (0.88)	26.92	DSM-IV	4	No	2,4
Gawrilow (2011)	36/43	9.98 (1.25)	0	DSM-IV	2	No[c]	1, 4
Gomarus (2009)	15/15	10.16 (1.25)	26.6	DSM-IV	4	No[c]	3, 4
Gorenstein (1989)	26/21	10.70 (0.90)	34.04	DSM-III-R	3	No	1, 2, 3, 4
Hammer (2015)	17/17	11.27 (0.87)	0	DSM-IV	3	No[c]	2, 4
Healey & Rucklidge (2006)	30/29	9.78 (1.00)	42.37	DSM-IV	4	No[c]	2, 3, 4
Holmes (2010)	50/83	9.78 (0.69)	24.06	DSM-IV	4	No[c]	1, 2, 3
Holmes (2014)	50/83	10.10 (0.84)	28.46	DSM-5	3	Some participants	1, 2, 3, 4
Hooks (1994)	52/40	8.11 (0.67)	0	DSM III-TR	4	No	1, 3
Horn (1989)	31/54	8.11 (1.41)	32	DSM-III-TR	4	No	1, 3, 4
Huang (2016)	203/257	10.19 (0.75)	22.36	DSM-IV	4	No	1, 3, 4
Huang-Pollock & Karalunas (2010) (1)	24/21	10.28 (1.54)	42.02	DSM-IV	2	No[c]	2, 4
Huang-Pollock & Karalunas (2010) (2)	24/32	10.46 (1.24)	48.14	DSM-IV	3	No[c]	2, 4
Huang-Pollock (2014)	33/50	9.96 (1.16)	48.19	DSM-IV	4	No[c]	4
Huang-Pollock (2009)	36/33	9.60 (1.34)	35.86	DSM-IV	2	No	1, 2
Huang-Pollock (2017)	21/46	10.27 (1.95)	38.9	DSM-IV	4	No[c]	1, 4
Hudec (2015)	18/19	9.91 (1.45)	0	DSM-5	4	No[c]	2, 4
Jakobson & Kikas (2007)	102/26	8.58 (1.06)	3.91	DSM-IV	3	No[c]	1, 2
Jennings (1997)	26/40	9.77 (1.23)	0	DSM-III-TR	4	No	1, 4
Joiqsdottir (2005)	15/15	10.50 (1.29)	23.4	DSM-IV	3	NR	2, 4
Kashala (2005)	155/28	8.42 (7–9 y)	59.56	DSM-IV	4	NR	1, 2, 4
Kaufmann & Nuerk (2006,	16/16	10.40	9.38	DSM IV	3	No[c]	1, 2, 4

2008)		(1.30)					
Kibby (2015)	74/88	9.65 (1.37)	50.62	DSM-IV	4	No[c]	2, 4
Kim (2014)	17/17	10.15 (1.55)	14.71	DSM-IV-TR	4	No	2, 3
Kliegel (2006)e	20/20	8.85 (0.54)	0	ICD-10	3	No[c]	0
Konrad (2000)	26/31	10.35 (1.60)	18	DSM-IV	4	No	1, 4
Koschack (2003)	35/35	10.95 (1.25)	24.28	DSM-IV	3	No[c]	1, 3
Kroese et al.(2000)	13/31	9.84 (1.22)	38.64	DSM-IV	4	No[c]	2, 4
Kuntsi (2001)	118/51	8.94 (1.34)	54.72	DSM-III	4	No	1, 2, 4
Kuntsi (2009)	1098/58	8.79 (0.66)	50.26	DSM-IV	1	NR	1, 4
Lee (2014)	32/37	9.00 (2.00)	0	DSM-IV-TR	4	No	1, 4
Loh (2011)	26/14	11.05 (0.75)	30	DSM-IV	4	No[c]	4
Luman (2009)	50/20	9.31 (1.30)	31	DSM-IV	4	No[c]	1, 2, 4
Maehler & Schuchardt (2016)	31/34	8.87 (1.70)	43.07	DSM-IV-TR	4	No	2, 4
Marx (2010)	20/20	9.76 (1.72)	0	DSM-IV	4	No[c]	1, 2, 4
Mary (2015)	31/31	10.34 (0.87)	50	DSM-IV-TR	4	No[c]	1, 3
Marzocchi (2008)	30/35	9.25 (1.37)	9.23	DSM-IV	3	No	1, 2, 4
Matsuura (2014)	19/15	11.14 (1.69)	26.47	DSM-IV-TR	4	No[c]	2, 4
McInnes (2003)	19/21	10.85 (1.01)	0	DSM-IV	4	No[c]	2
Miller (1996)	13/9	8–10 y	0	DSM III-R	4	Yes	1
Mills (2012) (1)	89/70	9.90 (1.25)	23.90	DSM-IV	3	NR	2, 4
Mills (2012) (2)	43/24	8.57 (0.72)	47.76	DSM-IV	4	NR	2, 4
Mioni (2016)	24/23	10.89 (0.97)	25.53	DSM-5	4	NR	2
Munkvold (2014)	160/50	9.45 (0.95)	39.05	DSM-IV	4	NR	4
Newcorn (1989)	68/6	9.10 (1.50)	50.58	DSM-III-R	4	No	1, 3
Nyman (2010)	30/30	8.65 (0.76)	15	DSM-IV	3	No[c]	1, 2, 4
O'Dougherty (1984)	17/11	8.68 (1.80)	38.96	DSM-III	1	No	1
Ortega (2013)	30/30	10.85 (1.40)	26.67	DSM-IV	3	No[c]	3, 4
Passolunghi (2005)	10/10	9.83 (0.49)	NR	DSM–IV	4	NR	2
Pastura (2016)	16/17	8.50 (1.25)	54.5	DSM-IV-TR	4	No	4
Patros (2017)	17/15	9.88 (1.50)	0	DSM-5	4	No	2, 4
Pennington (1993)	23/16	8.70 (0.07)	0	DSM-III-R	4	NR	1, 3, 4
Pineda (1998, 1999)	62/62	9.55 (1.65)	0	DSM-III-R	4	No[c]	1, 2, 4

Pliszka (2000)	10/10	11.15 (1.05)	0	DSM-IV	3	No[c]	1
Prehn-Kristensen (2013)	16/16	10.85 (0.95)	0	DSM IV–TR	4	No[c]	4
Purvis & Tannock (2000)	17/17	9.30 (1.50)	20	DSM-III-R	4	No[c]	4
Qian (2013) (1)	55/153	7.90 (0.41)	22.60	DSM-IV	4	No	1, 2, 3, 4
Qian (2013) (2)	100/182	9.36 (0.56)	21.99	DSM-IV	4	No	1, 2, 3, 4
Qian (2013) (3)	62/76	11.35 (0.58)	23.91	DSM-IV	4	No	1, 2, 3, 4
Re (2014)	19/19	9.91 (0.84)	15.78	DSM-5	4	NR	2
Rennie (2014)	34/17	9.74 (1.01)	51	DSM-5	4	NR	1, 2, 4
Rodriguez (2014)	41/91	9.72 (1.39)	38.64	DSM-IV-TR	4	No	3, 4
Rubio (2011)	11/6	9.17 (2.14)	NR	DSM-IV	3	No[c]	3
Sadeh (1996)	20/30	9.43 (8–10 y)	26	DSM-III-R	4	No	2
Saydam (2015) (1)	18/37	9.61 (1.69)	15.06	DSM-IV-TR	2	No	1, 2, 3, 4
Saydam (2015) (2)	18/37	9.14 (1.63)	16.43	DSM-IV-TR	3	No	1, 2, 3, 4
Schachar & Tannock (1995)	16/22	9.11 (1.28)	0	DSM-III-R	4	No[c]	1, 4
Schachar (1995)	22/14	9.01 (0.75)	0	DSM-III-R	4	No[c]	1
Schachar (1998)	15/18	8.77 (1.48)	0	DSM-III	4	No	1
Schachar (2000)	33/72	9.09 (1.43)	NR	DSM-III	4	No[c]	1, 4
Scheres (2001)	41/24	10.20 (1.56)	64	DSM-IV	4	No[c]	1, 4
Shallice (2002) (1)	16/10	7.65 (0.49)	NR	DSM-IV	4	NR	1, 4
Shallice (2002) (2)	17/21	10.02 (1.09)	NR	DSM-IV	4	NR	1, 4
Shapiro (1993)	38/67	8.95 (1.26)	20.95	DSM-IV	4	NR	4
Shimoni (2012)	25/25	9.17 (0.84)	0	DSM-IV	4	NR	1
Shue & Douglas (1992)	24/24	10.30 (1.55)	NR	DSM-IV	4	No[c]	1, 3, 4
Simone (2016)	51/63	8.55 (0.30)	31.63	DSM-5	4	No	2
van der Stelt (2001)	24/24	9.20 (1.35)	0	DSM-IV-TR	3	No	3
Wiers (1998)	34/28	9.05 (1.35)	0	DSM-IV	3	No	1, 2, 4
Williams (2013)	18/14	10.16 (1.35)	43.56	DSM-IV	3	No[c]	3, 4
Wu (2014)	12/11	9.17 (1.80)	21.74	DSM-IV	4	No[c]	2, 3
Yanez-Tellez (2005)	13/19	7–12 y	0	DSM-IV	4	NR	1, 2, 3, 4
Yanez-Tellez (2012)	25/26	8.80 (1.70)	0	DSM-IV	4	NR	1
Zambrano-Sanchez (2013) (1)	37/39	≈ 8.42 (1.29)	NR	DSM-IV-TR	1	No	2, 4

Zambrano-Sanchez (2013) (2)	37/44	≈ 8.42 (1.29)	NR	DSM-IV-TR	2	No	2, 4
Zambrano-Sanchez (2013) (3)	37/73	≈ 8.42 (1.29)	NR	DSM-IV-TR	3	No	2, 4
Zarafshan (2015)	30/30	9.74 (1.46)	25	DSM-IV-TR	4	NR	2, 4
Zarghi (2012)	50/50	10–12 y	50	DSM-5	3	Yes	2

ADHD = attention deficit hyperactivity disorder; y = years; NR = not reported; DSM-III = Diagnostic and Statistical Manual of Mental Disorders, third edition; DSM-III-R = DSM, third edition revised; DSM-IV = DSM, fourth edition; DSM-IV-TR = DSM, fourth edition (text revised); DSM-5 = DSM, fifth edition; ICD-10 = International Classification of Diseases, 10th edition. [a]Numbers indicate that different samples were reported in some study. [b]1 = inattentive presentation; 2 = hyperactive-impulsive presentation; 3 = combined presentation; 4 = mixed or non-specified. [c]Medication was removed prior cognitive assessment. [d]1 = executive function; 2 = memory; 3 = attention; 4 = intelligence. [e]Data provided in this study were not meta-analysed because they were not reported in any other study.

Supplemental material 2. List of references of included studies

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ESTUDIO 2

Sleep among presentations of Attention-Deficit/Hyperactivity Disorder: Analysis of objective and subjective measures

Noelia Ruiz-Herrera, Alejandro Guillén-Riquelme, Amparo Díaz-Román, Nicola Cellini y Gualberto Buela-Casal

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Abstract

Objective*:* To examine subjective and objective sleep patterns in children with different attention-deficit/hyperactivity disorder (ADHD) presentations. **Method:** We assessed 92 children diagnosed with ADHD (29 ADHD-Inattentive [ADHD-I], 31 ADHD-Hyperactive/Impulsive [ADHD-H/I], and 32 ADHD-Combined [ADHD-C)]) aged 7–11 years. The Pediatric Sleep Questionnaire (PSQ), Pediatric Daytime Sleepiness Scale (PDSS), and a sleep diary were used as subjective sleep measures, and polysomnography was used to objectively assess sleep quantity, quality, and fragmentation. **Results:** Subjective data showed impaired sleep in 12.7% of the sample. No significant differences were found between ADHD presentations in any objective and subjective sleep variable. Nevertheless, data on sleep fragmentation suggested a worse sleep continuity for the ADHD-H/I group, and correlation analyses confirmed that sleep is affected by age. **Conclusions:** Children with ADHD may suffer from sleep breathing problems and daytime sleepiness, as reported by their parents, even when their total sleep time and sleep efficiency are not affected. It seems that sleep in this population does not largely vary as a function of the ADHD presentation. Sleep in children with ADHD evolves with age.

Keywords: ADHD, Sleep, Polysomnography, Children, *Ex post facto* study.

Introduction

Attention deficit hyperactivity disorder (ADHD) is one of the most prevalent neurodevelopmental disorders in children, affecting about 3.4% of the world population (Polanczyk, Salum, Sugaya, Caye, & Rohde, 2015). It can be classified into three clinical presentations: Inattentive (ADHD-I), hyperactive/impulsive (ADHD-H/I), and combined (ADHD-C) (American Psychiatric Association, 2013), which can be detected through the combined use of different assessment measures (see Morales-Hidalgo, Hernández-Martínez, Vera, Voltas, & Canals, 2017; Rodríguez, Areces, García, Cueli, & González-Castro, 2018). This disorder has been associated with numerous comorbid conditions (Barkley, 2006; Tung et al., 2016), including sleep problems (see reviews of Díaz-Román, Hita-Yáñez, & Buela-Casal 2016; Hvolby, 2015), as well as with deficits in executive functioning (Krieger, Amador-Campos, & Peró-Cebollero, 2019). According to previous studies, sleep in children with ADHD is characterized by a lower sleep quality and lower sleep efficiency than healthy children. These children may also present sleep breathing disorders and periodic limb movements, sleep fragmentation, and higher levels of daytime sleepiness compared to children without ADHD (see reviews of Cortese, Faraone, Konofal, & Lecendreux, 2009; Díaz-Román et al., 2016).

Sleep problems in children with ADHD are associated with a worse neurocognitive functioning (Frye et al., 2018) and with emotional and behavioral conditions, such as oppositional defiant disorder and depressive symptoms (Becker, Cusick, Sidol, Epstein, & Tamm, 2018). Consequently, investigating their sleep characteristics may help to improve the neurocognitive functioning and mental health of these children, thus preventing potential emotional and behavioral problems already noted in general populations (Kazdin et al., 2018; Teismann et al., 2019). In this

relation, sleep problems have been explored focusing on factors such as sex, age, comorbidity with other disorders, and pharmacological treatment (Becker et al., 2018; Vigliano et al., 2016). Nevertheless, the results of these studies have been inconsistent (see Cortese et al., 2009; Díaz-Román et al., 2016, for reviews).

Discrepancies in previous findings on sleep in ADHD should be interpreted in the light of some differences across studies. Firstly, while some studies have recorded sleep information through objective measures (i.e., Polysomnography [PSG] and actigraphy), other have used questionnaires based on parent or child reports and self-reports (see Cortese et al., 2009, for a review). Only few studies have used both objective and subjective measures to assess sleep in this population (Huang et al., 2004; Wiebe, Carrier, Frenette, & Gruber, 2013; Wiggs, Montgomery, & Stores, 2005), even if the use of a single instrument may be not enough to achieve a full understanding of the complex interactions between sleep and ADHD (Hvolby, 2015). Secondly, the notable heterogeneity within the disorder remarks the importance of investigating sleep problems accounting for the different ADHD presentations, but there are few studies in this regards and their results are inconsistent. Some studies have reported differences in some sleep features as a function of the presentation, such as more presence of chronic snoring for ADHD-H/I than ADHD-C, shorter sleep latencies, and more fragmented sleep for ADHD-H/I than in other two presentations (LeBourgeois, Avis, Mixon, Olmi, & Harsh, 2004; Ramos, Vela, Espinar, & Kales, 1990). In addition, greater daytime sleepiness (LeBourgeois et al., 2004; Mayes et al., 2009) or hypersomnia symptoms like daytime inadvertent napping (Chiang et al., 2010) and shorter sleep-onset latencies (Lecendreux, Konofal, Bouvard, Falissard, & Mouren-Simeoni, 2000) have been found to be grater in ADHD-I than in the other presentations. However, other studies have

failed to show any difference in sleep characteristics between ADHD presentations (Virring, Lambek, Thomsen, Møller, & Jennum, 2016; Wiggs et al., 2005). Therefore, the goal of this study was to examine sleep characteristics in three different groups of children with ADHD (ADHD-I, ADHD-H/I, ADHD-C) through objective (i.e PSG) and subjective (i.e., sleep diary and questionnaires) measures. Considering previous findings (LeBourgeois et al., 2004), we expected to find higher scores in snoring variable for the ADHD-H/I group and a higher daytime sleepiness for the group ADHD-I in parents' questionnaires. We also expected to observe more fragmented sleep and less sleep efficiency in the ADHD-H/I group compared to the other two groups (Ramos et al., 1990).

Method

Participants

The sample consisted of 92 children with ADHD from Granada, Spain (29 ADHD-I, 31 ADHD-H/I and 32 ADHD-C) aged 7-11 years (Table 1). The sample was recruited with the collaboration of public and private schools and with the cooperation of the Child and Youth Mental Health Department of the Virgen de las Nieves Hospital Center, Granada. The parent(s) of each participant gave informed written consent before the start of the study and actively participated by completing questionnaires on the subjective quality of sleep and daytime sleepiness. The study was evaluated and approved by the ethics committee of the University of Granada and the Andalusian Biomedical Research Ethics, Coordinating Committee. The anonymity of the participants and the confidentiality of the data were guaranteed.

The participants had a clinical diagnosis of ADHD as primary disorder, established by a healthcare professional according to the criteria of the *International Classification of Diseases 10th revision* (ICD-10*;* World Health Organization, 1992). Psycho-educational reports provided by the educational psychologist of children' school were considered equivalent to clinical diagnosis when children had been registered as children with ADHD into the SENECA platform of the Spanish Ministry of Education and Science (Spanish Organic Law 8/2013, 9th December, for the improvement of the educational quality [Ley Orgánica 8/2013, de 9 de diciembre, para la mejora de la calidad educativa]). Specifically, children with ADHD can be considered children with 'specific educational support needs' with no significant curricular adaptation. Eighty-eight percent of the participants had a clinical diagnosis, and the rest of children were registered into SENECA as meeting criteria for ADHD in school environment, waiting for clinical assessment. We did not include any child with a total score less than 70 in the Wechsler Intelligence Scale for Children–Four Edition (WISC-IV; Wechsler, 2010), so three children were excluded from the sample. This score was not obtained for two children but they remained in the study since it was explicitly reported that they have no significant curricular adaptation for intellectual disability. Other exclusion criteria were having been diagnosed with any severe organic disease with sleep impairment (including severe respiratory-related diseases); having sensory deficits and/or generalized developmental disorders; having a body mass index > 30.

Instruments and measures

Socio-demographic data was obtained through a non-structured interview for parents. Data related to exclusion criteria, age, gender, diagnosis, and medical consume were obtained in this interview.

Pediatric Sleep Questionnaire (PSQ). The PSQ (Tomás, Miralles, & Beseler, 2007) is a questionnaire compiled by parents and it allows detecting sleep-disordered breathing (α = .81), sleepiness (α = .63), and behavioral problems (α = .86). It consists of 22 items divided into three parts and its response format into the first two parts (α part A = .81; α part B = .63) is *yes/no/do not know* and the third part (α part C = .86) from 0 (*never*) to 3 (*most of the time*). A higher PSQ score means worse sleep quality, and it has been clinically validated (cutoff score ≥ .33 reflects clinical problems; Chervin, Hedger, Dillon, & Pituch, 2000).

Pediatric Daytime Sleepiness Scale (PDSS). The PDSS is a questionnaire filled in by parents to assess the child's level of daytime sleepiness and related school outcomes (α = .80). It consists of 8 items with a response scale from 0 (*never*) to 4 (*always*). The last item is inverse and the global score goes from 0-32 (higher score, higher levels of sleepiness). A score > 20 indicates clinical levels of excessive daytime sleepiness (Drake et al., 2003).

Sleep diary. An 8-items sleep log was compiled by children's parents during seven days to collect sleep habits of the child. Specifically, we collected information about bedtime and wake time, total sleep time (TST), number of awakenings and sleep efficiency.

PSG. A PSG recording was performed at the children's home, using SomnoScreen® Plus. The recording electrodes were placed following the 10-20

International System: Electroencephalography (five channels: Two frontals (Fpz, Fz), one central (Cz), one parietal (Pz), one occipital (Oz)) and the left auricular as a reference (A1); electrooculogram (from the left and right outer canthi of the eye); electromyogram (EMG) in submentalis muscle; EMG of the right and left anterior tibial muscles. We recorded the sleep breathing pattern with nasal airflow thermistors and thoracic and abdominal respiratory effort calibrator. Oxygen saturation was also evaluated with pulse oximetry. Signals were sampled at 256 Hz and stored for further analysis with DOMINO light version 10.04, and the sleep phases were scored in 30-second epochs following the criteria of Rechtschaffen and Kales (1968). Two trained researchers performed the sleep scoring independently.

The following sleep parameters were computed: Time in bed (TIB, time from lights off to lights on), sleep period time (SPT, time from sleep onset to final awakening), TST (total time spent in a sleep stage), sleep onset latency (time from wakefulness to stage 1 sleep), sleep efficiency (TST/TIB x 100), proportion of the TST spent in each sleep stage (including slow wave sleep (SWS), i.e. stages 3+ 4 sleep), REM latency (time spent from the start of sleeping and the start of REM sleep), arousal index (frequency of arousals per hour of sleep; number of rapid changes in the electroencephalography frequency of 3 or more seconds and preceded by a minimum of 10 continuous seconds of sleep), and index of periodic limb movements (number of periodic limb movements per hour of sleep). In addition, we extracted information about sleep continuity (number of awakenings/hour < 2 min), sleep stability (number of stage shifts, considering stages 3 and 4 sleep as a single stage), and sleep organization (number of sleep cycles, not interrupted by periods > 2 min of wake/stage 1 sleep) (see Conte et al., 2014, for further information about these constructs).

Epochs containing technical artifacts or extremely high muscle activity causing saturation of amplifiers were carefully detected and marked for their exclusion from the analysis.

Procedure

Firstly, parents gave written consent for their children to participate in the study, conducted the interview on sociodemographic data and were administered questionnaires on subjective sleep quality and daytime sleepiness. The intelligence test was carried out as long as it was not already available (maximum two years before). This first phase of the procedure was used to assess the inclusion criteria of participants.

In the second phase, we performed the PSG recordings at the participants' home. Consumption of stimulant beverages (i.e. caffeinated) during the day of the PSG was not allowed. Consume of methylphenidate, atomoxetine, guanfacine, and lisdexamphetamine was controlled as specific medication for ADHD (and it was withdrawn 36 hours before the sleep study).

Statistical analysis

The sample size was estimated using $d = 0.34$ (it corresponded to $t = 3.3$; Mayes et al., 2009), $\alpha = .05$, power = .80. Based on these data, the required estimated sample was 87 participants.

Analysis of variance (ANOVA) and chi-square test were performed for age and sex (respectively) group comparisons. T-student analyses were performed to compare possible differences in sleep variables between children with and without medication. Scores on PSQ and PDSS, and sleep parameters measured through PSG were compared with one factor ANOVA. Independence of observations was verified through Durbin-Watson statistic, the normality of the distribution by Kolmogorov-Smirnov, and the

homogeneity of the variances using the Levene Test. No significant violations were observed in any of the variables. Also, Mahalanobis distance was used, not detecting any outlier. Whenever statistically significant differences were observed in any analysis, other comparisons were made with *Fisher's least-significant difference* (LSD) test.

Furthermore, using a Bayesian approach (Wagenmakers, 2018), we estimated the probability that the alternative hypothesis (Pr (H1|D) be true as a function of the approximate Bayes Factor (BF_{10}), with largeBF_{10} values supporting the alternative hypothesis (H1), and small BF_{10} values supporting the null hypothesis (H0). The Bayesian analysis was implemented using JASP 0.9. (2018).

Results

Sample description

Table 1 presents the demographics and medication data for the three groups. A higher proportion of males were noted in the three ADHD presentations ($p < .05$). There were no statistical differences in age and full-scale IQ. There were significant differences in the medication use ($p < .05$) between the three groups, with a higher medication use among children with the ADHD-C presentation. However, when compared children with and without medication, no significant results were found in any sleep variable (all *p*-values ≥ .09).

Table 1

Sociodemographic Data of the Total Sample (N = 92)

	ADHD-I (n = 29)	ADHD-H/I (n = 31)	ADHD-C (n = 32)	F/X^2	*p*
Gender (No. girls)	12	3	3	6.84	.002
Age, years (mean, SD)	9.14 (1.19)	9.10 (1.45)	8.90 (1.37)	0.27	.766
*FSIQ; WISC-IV)	95.43 (17.92)	98.43 (17.65)	95.97 (16.57)	0.25	.779
Medication (yes/no)	16/13	18/13	28/4	4.11	.020

Note. ADHD-I = attention deficit hyperactivity disorder inattentive presentation; ADHD-H/I = attention deficit hyperactivity disorder hyperactive/impulsive presentation; ADHD-C = attention deficit hyperactivity disorder combined presentation; FSIQ = Full Scale Intelligence Quotient; WISC-IV = Wechsler Intelligence Scale for Children.
*Scores in FSIQ WISC-IV were no obtained for one ADHD-I and one ADHD-C children.

Sleep description

Subjective measures. Table 2 summarizes the subjective measures data analysis. Data obtained with PSQ questionnaire revealed no significant differences in snoring, daytime sleepiness, ADHD symptomatology, or total score between the three groups, as also shown by the Bayesian analysis (all the posterior probabilities being lower than $Pr(H1|D) \approx 14\%$ and all $BF_{10}s < 0.16$). According to the PSQ snoring scores, 17.7% of the sample presented problems, with the inattentive presentation obtaining the highest percentage (20.8%). In the PSQ sleepiness scores, it was the 17.4% of the sample who exhibited problems, and the ADHD-H/I presentation showed the highest scores (20%). The total score of PSQ in the sample was 12.7%, with the ADHD-H/I presentation showing the higher frequency of sleep problems. No differences between the three ADHD presentations were observed for the PDSS score ($Pr (H1|D) \approx 15\%$ and all $BF_{10} \approx 0.17$). Nevertheless, the ADHD-C presentation showed the higher scores. Similarly, no differences were found in the sleep diary parameters ($Pr(H1|D<21\%$ and

all BF_{10}s < 0.26). Overall, subjective measures did not reveal any difference between ADHD presentations.

PSG sleep parameters.

Quantitative sleep variables. In Table 3, we present the means and *SD*s of the standard quantitative PSG measures of children with ADHD. Significant differences were not observed for any sleep variable. No differences between objective sleep parameters seem to be present between ADHD presentations. These observations were further corroborated by the Bayesian approach, which showed no support for the H1 hypothesis (i.e., all the posterior probabilities being lower than Pr(H1|D) ≈ 34% and all BF_{10}s < 0.52).

Sleep continuity. Overall, no significant differences were observed for sleep continuity variables. However, the data suggests that ADHD-H/I tended to have a more fragmented sleep as indexed by the higher number of awakenings (F2,87 = 2.44, *p* = .093, η2p = .05, Pr(H1|D) ≈ 41%, BF10 = 0.68; Table 4). This effect was mainly driven by the number of short awakenings (less than 2 min; F2,87 = 2.87, *p* = .062, η2p = .06, Pr(H1|D) ≈ 49%, BF10 = 0.96) with a higher number of awakenings in the ADHD-H/I group compared to the ADHD-C (*p* =.018, BF10 = 1.73) and, not significantly, to the ADHD-I (*p* = .243, BF10 = 0.34). Instead, no differences were observed for the number of long awakenings (longer than 2 min; F2,87 = 1.36, *p* = .263, η2p = .03, Pr(H1|D) ≈ 22%, BF10 = 0.29) and for the average duration of the awakenings F2,87 = 1.71, *p* = .187, η2p = .04, Pr(H1|D) ≈ 28%, BF10 = 0.38).

Table 2

Total Scores and Subscale Scores on PSQ, PDSS, and Sleep Diary Completed by Parents in the ADHD-I, ADHD-H/I and ADHD-C Groups (N = 85)

Sleep variable	ADHD-I (n = 25)	ADHD-H/I (n = 29)	ADHD-C (n = 31)	*F/ χ2*	*p*
PSQ Snoring	0.197 (0.21)	0.183 (0.25)[c]	0.16 (0.18)	0.24	.791
PSQ Sleepiness	0.167 (0.18)	0.167 (0.18) [c]	0.208 (0.18) [c]	0.42	.661
PSQ ADHD	2.02 (1.07) [b]	1.72 (0.62) [b]	2.16 (0.69) [b]	1.83	.168
PSQ Total Score	0.178 (0.14)	0.176 (0.20) [c]	0.175 (0.15)	0.002	.998
Prevalence of sleep problems (%)[a]	8	19.2	10.7	1.602	.449
PDSS Total Score	11.44 (5.50)	10.97 (5.43)	12.00 (5.35)	0.28	.759
Sleep diary[d,e,f]					
Time in bed (min)	600.46 (53.8)	595.32 (42.7)	589.35 (32.77)	0.38	.683
Total sleep time (min)	568.10 (40.95)	551.09 (39.74)	559.86 (34.33)	1.05	.356
No.of awakenings	0.52 (1.1)	0.23 (0.31)	0.44 (0.68)	1.06	.352
Sleep efficiency (%)	95.13 (5.71)	93.94 (5.36)	94.77 (3.64)	.317	.730

Note. ADHD-I = attention deficit hyperactivity disorder, inattentive presentation; ADHD-H/I = ADHD hyperactive/impulsive presentation; ADHD-C = ADHD combined presentation; PSQ = Pediatric Sleep Questionnaire; PDSS = Pediatric Daytime Sleepiness Scale. Data are presented as mean and (standard deviation).

[a] As reported by children's parents in the PSQ.

[b] ADHD-I sample for PSQ ADHD was 24, ADHD-H/I sample was 26, ADHD-C sample was 23.

[c] ADHD-H/I sample for Snoring values was 27, for sleepiness was 26 and 27 for the total score; ADHD-C sample for the sleepiness score was 23.

[d] ADHD-I sample for Time in bed was 20, for Total sleep time 20, for No. of awakenings was 29, and for Sleep efficiency was 18.

[e] ADHD-H/I sample for Time in bed was 25, for Total sleep time 22, for No. of awakenings was 28, and for Sleep efficiency was 21.

[f] ADHD-C sample for Time in bed was 26, for Total sleep time 22, for No. of awakenings was 28, and for Sleep efficiency was 21.

Sleep stability. No significant differences were observed for sleep stability. However, again the ADHD-H/I showed, although not significantly, a higher number of state transitions ($F_{2,87} = 2.13$, $p = .125$, $\eta 2p = .05$, $Pr(H1|D) \approx 35\%$, $BF10 = 0.54$, Table 4).

Sleep organization. No significant differences were observed for sleep organization variables. Sleep cycles, here operationalized as an interrupted sequence (interleaved by a maximum of 2 continuous min of wake) of NREM-REM epochs

lasting at least 10 min each max, were 3.8±1.05 and lasted on average 112.66±29.90 min (Table 4).

Exploratory correlations.

Sleep diary vs PSG. Significant associations were observed for the TIB score obtained by both PSG and diary (r = .83, p < .001, n = 71) suggesting that both measures are efficient for estimate this. Also, we found correlation between number of awakenings and sleep efficiency obtained with the sleep diary (r = -.26, p < .04, n = 63). However, we found no associations between the number of awakenings measured with the sleep diary and the time spent awake (r = -.41, p = .71, n = 84) or the number of long awakenings measured with the PSG (r = .09, p = .38, n = 84), and between sleep efficiency obtained through both measures (r = -.08, p = .52, n = 64), suggesting that sleep diary can provide limited information about the sleep quality of the children of the current study.

Age and sleep parameters. We confirmed in our sample the inverse relationship between age and the proportion of SWS (r = -.23, p = .003, n = 90). Interestingly, with increase age we also observed an increment of the number of awakenings (r = .22, p = .032, n = 90), again driven by the number of short awakenings (r = .28, p = .007, n = 90), and a concurrent reduction of their durations (r = .34, p = .001, n = 90).

Table 3

Quantitative Sleep Parameters Obtained by Polysomnography

Sleep variable	ADHD-I (n = 29)	ADHD-H/I (n = 30)	ADHD-C (n = 31)	*F*	*p*
Time in bed (min)	550.78 (58.32)	555.25 (59.11)	554.04 (61.47)	0.04	.957
Sleep period time (min)	531.49 (60.20)	530.48 (56.92)	528.11 (58.59)	0.03	.974
Total sleep time (min)	508.70 (54.87)	501.48 (57.13)	485.42 (105.02)	0.73	.484
Sleep onset latency (min)	15.05 (7.78)	18.65 (10.48)	18.60 (14.35)	0.99	.377
Sleep efficiency (%)	92.39 (3.24)	90.76 (4.62)	90.79 (6.03)	1.11	.334
Wake time (%)	2.72 (2.77)	3.82 (3.73)	4.41 (5.78)	1.18	.312
Stage 1 (%)	2.20 (2.09)	1.95 (1.75)	4.12 (8.00)	1.75	.179
Stage 2 (%)	35.98 (5.99)	36.35 (8.40)	35.44 (8.35)	0.11	.897
Stage 3 (%)	13.83 (5.28)	12.66 (4.62)	13.66 (6.99)	0.36	.699
Stage 4 (%)	22.72 (4.42)	24.61 (7.44)	24.01 (5.16)	0.81	.448
Slow wave sleep (%)	36.56 (8.02)	37.29 (10.00)	37.68 (8.12)	0.00	.995
REM (%)	25.09 (6.40)	24.37 (6.15)	23.47 (5.23)	0.56	.572
REM latency (min)	149.13)63.68)	142.64(48.44)	151.13 (56.99)	0.18	.835
Arousal (index)	0.62 (0.64)	0.53 (0.92)	1.31 (2.54)	2.08	.131
Periodic limb movements (index)	0.64 (1.20)	0.63 (1.24)	0.81 (1.26)	0.21	.812

Note. ADHD-I = attention deficit hyperactivity disorder, inattentive presentation; ADHD-H/I = ADHD hyperactive/impulsive presentation; ADHD-C = ADHD combined presentation; REM = rapid eye movement. Data are presented as mean and (standard deviation).

Table 4

Sleep Continuity, Stability, and Organization

Sleep fragmentation data	ADHD-I (n = 29)	ADHD-H/I (n = 30)	ADHD-C (n = 31)	*F*	*p*
Total awakenings (n)	20.93 (7.80)	23.90 (9.00)	19.39 (7.41)	2.43	.093
Short awakenings (n)	18.55 (7.04)	20.73 (7.91)	16.35 (6.39)	2.87	.061
Long awakenings (n)	1.86 (1.94)	2.80 (2.29)	2.48 (2.39)	1.36	.263
Mean awakening duration (min)	1.40 (0.91)	1.59 (1.13)	2.11 (2.23)	1.71	.187
State transitions (n)	66.28 (16.54)	73.33 (19.49)	64.71 (15.62)	2.13	.125
Sleep cycle (n)	3.93 (0.92)	3.67 (1.09)	3.45 (1.09)	1.59	.209
Mean sleep cycle duration (min)	113.75 (21.67)	107.87 (33.24)	116.27 (33.30)	0.21	.812

Note. ADHD-I = attention deficit hyperactivity disorder, inattentive presentation; ADHD-H/I = ADHD hyperactive/impulsive presentation; ADHD-C = ADHD combined presentation. Data are presented as mean and (standard deviation).

Discussion

The present study investigated whether children diagnosed with attention-deficit/hyperactivity disorder (ADHD) experience different sleep patterns depending on the ADHD symptoms. We observed no differences in any sleep parameter between the three ADHD presentations. Medication did not affect these results, as no significant differences were either found in sleep variables between medicated and non-medicated children.

The lack of sleep differences, as assessed by the PSG, is in line with studies indicating a lack of differences in the sleep architecture between children with different ADHD presentations (Virring et al., 2016; Wiggs et al., 2005). Interestingly, although the study of Lecendreux et al. (2000) reported shorter sleep onset latencies for children with ADHD-H/I, the authors also showed no differences in nocturnal sleep between the groups, in line with the current results. Results on sleep fragmentation also revealed no significant differences for both sleep organization and sleep stability in ADHD presentations. However, the data obtained for sleep continuity indicated a tendency of the ADHD-H/I group to experience more short awakenings than the ADHD-C group, which is consistent with two previous studies (Becker et al., 2018; Ramos et al., 1990). This latter result is also in line with studies linking the presence of hyperactive-impulsive symptoms to more disrupted sleep (Chiang et al., 2010; Mayes et al., 2009).

Regarding to parents' reports, on the one hand the lack of significant differences between ADHD presentations in terms of daytime sleepiness, sleep problems, TIB, TST, number of awakenings, or sleep efficiency are consistent with previous studies reporting no differences in subjective sleep measures between ADHD presentations (Virring, Lambek, Jørgen, Ruge, & Thomsen, 2017; Wiggs et al., 2005). On the other

hand, the PDSS results seem to contradict the previously reported link between sleepiness and ADHD-I (Mayes et al., 2009; LeBourgeois et al., 2004, & Lecendreux et al., 2000). In addition, parents reported a high percentage of sleep-related breathing disorders (17.7%) among these children, as previously noted in research (Cortese et al., 2009), and without meaningful differences between presentations. Finally, our results in terms of general sleep problems are also inconsistent with prior research. Specifically, parents' ratings in the PSQ indicated that 13% of the sample was suffering from sleep problems. Moreover, children with ADHD-H/I showed the highest percentage of sleep problems in our study, though non-significant, whereas the results of the study of Mayes et al. (2009)—including a larger sample of children—pointed to children with ADHD-C as those who have the greatest sleep problems.

The lack of significant differences in sleep patterns between ADHD presentations in our sample might be also explained by commonalities in symptomatology. In this respect, the results of some studies noted a relationship between severity of ADHD symptomatology and sleep disturbances (Hysing, Lundervold, Posserud, & Sivertsen, 2016; Vélez-Galarraga, Guillén-Grima, Crespo-Eguílaz, & Sánchez-Carpintero, 2016). However, no significant differences in severity of ADHD symptomatology, as reported by children's parents using the PSQ, were revealed between the three groups of children in our study. Consequently, the absence of differences in sleep variables might be derived from the similar degree of symptoms between the groups.

Results obtained through correlations indicate a low agreement between measures for assessing sleep in ADHD, which also supports the notion that objective and subjective sleep measures actually assess different constructs and generate a high

inconsistency between their results (Cortese et al., 2009). However, data related to age confirmed that sleep naturally evolves with age also in children with ADHD. Specifically, a decrease in the amount of SWS and an increase in the number of awakenings are observed with age, which is consistent with previous research (Schwarz et al., 2017).

Interestingly, children's subjective and objective sleep efficiency was not affected in our sample (> 90%), in contrast with most of the findings present in research (see Cortese et al., 2009, for a review). In addition, TST of children in this study was within the range suggested as appropriate (7- 12 hours) according to the recommendations of the National Sleep Foundation (Hirshkowitz et al., 2015). Finally, the percentage of sleep problems measured by PSQ (13% of the total sample) was lower that what previously reported (25% to 50%; Corkum, Tannock, & Moldofsky, 1998).

The current results should be interpreted in light of some limitations. Firstly, we collected the sleep diary data for one week instead of 15 days, as recommended by Bioulac, Micoulaud-Franchi, and Philip (2015). Additionally, objective sleep assessment was based on a single night, so it is possible that some differences between ADHD presentations would have not been captured by a single PSG recording (Hvolby, 2015).

In conclusion, there seem to be no differences in subjective or objective sleep variables between ADHD presentations. Discrepancies with respect to previous studies reporting such differences may be due to factors such as age (e.g. LeBourgeois et al., 2004, Lecendreux et al., 2000), or diagnostic criteria (e.g. Ramos et al., 1990). Therefore, further research is needed to disentangle the complex relationship between sleep and ADHD symptoms, and to resolve the discrepancies arisen in this regard.

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ESTUDIO 3

Characteristics of sleep spindles in school-aged children with attention-deficit/hyperactivity disorder

Abstract

Objective. To characterize sleep spindles from a sample of school-aged children with attention deficit/hyperactivity disorder (ADHD) in terms of number, density, duration, amplitude, and intensity. ***Method.*** Spindles information was extracted from an overnight polysomnography in 74 children (27 ADHD-Inattentive, 25 ADHD-Hyperactive/Impulsive, and 22 ADHD-Combined) aged 7–11 years. We obtained data of the frontal (Fz) and parietal (Pz) derivations. ***Results.*** Children with ADHD showed a higher number and density of slow compared to fast spindles, which were more frequent in Fz and N2. Slow spindles lasted longer than fast, and during N2. The spindles amplitude was greater in N3 and Fz, and the intensity was higher in N2 and in Fz. No differences were observed among ADHD presentations for any spindles characteristics. Spindles frequency increased with age, as well as fast spindles density, indicating an age-dependent maturation of different sleep spindles. ***Conclusions.*** Spindles characteristics in children with ADHD follow the same organization as TD children, including topography and frequency, with no marked difference among the presentations. In children with ADHD, the spindles characteristics evolve with age and these associations are mainly driven by ADHD-Combined. There seem to be no associations between the characteristics of spindles and IQ.

Keywords: Attention deficit/hyperactivity disorder, ADHD, presentations, children, sleep spindles.

Introduction

Sleep spindles are one of the neural oscillations identified as an electroencephalographic fingerprint of human sleep (De Gennaro, Ferrara, Vecchio, Curcio, & Bertini, 2005). Sleep spindles characterize non-rapid eye-movement Stage 2 sleep (N2; but they are present also during the sleep stage N3), occur in short burst of about 0.5—2 sec., and appear in the EEG sigma frequency range of 11-16 Hz band. Spindles can be divided into slow (11—13 Hz, predominating in frontal brain regions) and fast (13—16 Hz, predominating in central and parietal brain regions) (see De Gennaro & Ferrara, 2003, for a review; Peter-Derex, Comte, Mauguière, & Salin, 2012), and show age-related changes on the basis of density (number of spindle bursts/min of NREM sleep), duration, amplitude (peak-to-peak difference in spindle size, reflecting voltage), and frequency (number of waveforms per second; Clawson, Durkin, & Aton, 2016; Scholle, Zwacka, & Scholle, 2007). These changes are indicative of the maturation of thalamocortical structures and of the physiological system that generates spindles. Therefore, spindles have been proposed as a valuable neurobiological identifier of neural maturation and plasticity, underlying the manifestation of neurodevelopmental disorders, such as the attention deficit hyperactivity disorder (ADHD; see Gruber & Wise, 2016, for a review; Fogel et al., 2017; Scholle et al., 2007).

As reported by a recent review of the literature (Gorgoni, Scarpelli, Reda, & De Gennaro, 2020), a paucity of studies reported sleep spindles in ADHD and typically developing (TD) children and they yielded inconsistent results partly due to differences in methodology. On the one side, an early study investigating spindles activity in a short daytime nap under Chloral Hydrate (about 8 min of N2) showed no differences between

ADHD and TD children (Kiesow & Surwillo, 1987). More recently, it has been shown a similar spindle density (number of spindles by sleep epochs) in central regions in ADHD and TD children during a nocturnal sleep following a declarative memory task (Prehn-Kristensen et al., 2011). On the other side, some studies have reported a higher (Poitras, Bylsma, Simeon, & Pivik, 1981) or lower number of spindles (Khan & Rechtschaffen, 1978) in unmedicated hyperactive males compared to TD children.

With regard to the associations between spindle/sigma activity and cognitive performance, two studies have not found such correlations in memory performance in children with ADHD (Prehn-Kristensen et al., 2011; Prehn-Kristensen et al., 2013). On the contrary, one study has reported a positive correlation between slow spindle activity and motor learning in children with ADHD, but not in TD children (Salentin et al., 2017), while other have reported a negative correlation between sigma power in N2 and intelligence (IQ) in children with ADHD (Bestmann, Conzelmann, Baving, & Prehn-Kristensen., 2019), thus suggesting that the associations between sigma power and cognitive performance could underlie distinct developmental processes.

These observations seem to indicate that ADHD and TD children do not show different spindle activity, at least in term of density. However, ADHD is a complex disorder, characterized by different presentations: Inattentive (ADHD-I), hyperactive/impulsive (ADHD-H), and combined (ADHD-C). These presentations show distinct neurobiological (Aldemir et al., 2018; Nomi et al., 2018; Qian et al., 2019) and cognitive characterizations (Mayes, Calhoun, Chase, Mink, & Stagg, 2009; Navarro Soria, Fenollar-Cortés, Lavigne Cerván, & Juarez Ruiz de Mier, 2017). Therefore, it is possible that these different ADHD profiles may present distinct sleep spindles characteristics. For example, it has been recently showed that the ADHD

symptomatology (assessed by the Adult ADHD Self-Report Scale, Kessler et al., 2015) was negatively associated with fast spindles duration and amplitude (Merikanto et al., 2019). In particular, higher inattention and hyperactivity symptoms were associated with shorter duration and lower amplitude for fast spindles.

Taking together, sleep spindle intensity (i.e. the product of amplitude and duration) is a suitable marker for brain development, which in turn appears to be associated with ADHD symptom severity. Since ADHD-C is considered as being the most affected ADHD presentation, we expect those patients in comparison to the ADHD-I and ADHD-H groups to display the highest spindle intensity. There are no specific hypothesis of group differences regarding the number/density of fast and slow sleep spindles, nor their occurrence in N2 and N3. Finally, we explore associations between any sleep spindle characteristics and cognitive performance as well as age.

Method

Ethics Statements

The project was approved by the ethics committee of the University of Granada, and the Andalusian Biomedical Research Ethics, Coordinating Committee (Spain). Parents gave written informed consent. The confidentiality of the data and the anonymity of the participants were guaranteed.

Participants

Seventy-eight children took part in this study (age range was 7—11 years), but we had to exclude 4 participants from the spindles analysis due to bad EEG signal. The final sample consisted of 74 children with ADHD (28 ADHD-I, 27 ADHD-H/I, and 23 ADHD-C), and the 87.84% had a clinical diagnosis of ADHD as primary disorder,

established by a healthcare professional according to the criteria of the International Classification of Diseases 10th revision (ICD-10; World Health Organization, 1992). The rest of the children included for being considered as ADHD were under clinical assessment after being assessed by psycho-educational reports based on specific questionnaires and cognitive tests (e.g EDAH [Farré & Narbona, 2013]; attention test d2 [Brickenkamp, 2002]), and being reported to show ADHD symptomatology. More information about the inclusion and exclusion criteria for participants are reported elsewhere (Ruiz-Herrera et al., in press).

Sleep assessment

Overnight PSG recordings were performed using SomnoScreen® Plus (Somnomedics, Randersacker, Germany) and data were recorded at 256 Hz and analyzed with DOMINO light version 10.04 in 30 seconds' epochs following the Rechtschaffen and Kales (1968) criteria. The children were evaluated at home without adaptation night, with a standard PSG montage with 2 EEG channels: (Fz, Pz) and 2 EOG channels referenced to the left mastoid (M1), and a bipolar EMG in submentalis muscle, with a ground placed at Fpz. Further details on the PSG montage and procedure of this sample can be found in Ruiz-Herrera et al. (in press).

The following parameters were obtained: Time in bed, sleep period time, total sleep time (TST), sleep onset latency, sleep efficiency, wake time, proportion of the TST spent in each sleep stage, REM latency, arousal index, and index of periodic limb movements.

Sleep spindles were automatically detected during NREM sleep using a recently developed algorithm (Lacourse, Delfrate, Beaudry, Peppard, & Warby, 2019) implemented by Wonambi 6.06 (https://wonambi-python.github.io/). In brief, this

method (named “A7”) detects spindles using a combination of 4 parameters related to sigma power (absolute and relative sigma power, sigma covariance and correlation, see Lacourse et al., 2019 for details about the algorithm). Based on the peak frequency we divided sleep spindles based into slow and fast spindles based (10–13 Hz and 13–16 Hz, respectively, see Merikanto et al., 2017). We computed the number, density (number of spindles per 60 second epoch), duration (s), amplitude (root-mean square of the signal, µV) of the frontal (Fz) and parietal (Pz) spindles. We also derived spindles intensity as duration (s) multiplied by amplitude (µV).

Procedure

In order to assess the inclusion criteria, we conducted a non-structured interview with the caregivers of the children collecting sociodemographic data and carried out the cognitive assessment. In the second phase, we performed the PSG recordings. Children were not allowed to consume caffeine during that day. Specific medication for ADHD was withdrawn 36 hours before the PSG, and children consumption was as follows: Methylphenidate (41), atomoxetine (5), lisdexamphetamine (3), guanfacine (1), and unmedicated (27). No information is available on the medication of one medicated child.

Statistical analysis

Analysis of variance (ANOVA) and chi-square test were performed for age, sleep characteristics, sex and medication use group comparisons. We then focused on spindles characteristics in two steps.

First, to investigate the spindles characteristics (number, density, duration, amplitude, and intensity) in the ADHD groups, we ran a mixed factorial design (3×2×2×2) with the three presentations of ADHD (ADHD-I, ADHD-H/I, ADHD-

C) as between-subjects factor and Derivation (Fz, Pz), sleep Stage (N2, N3), and Type of spindles (fast, slow) as within-subjects factors.

The Huynh-Feldt correction was applied when the Sphericity was violated (Huynh & Feldt, 1976). In this case, we report the ε value. Whenever statistically significant differences were observed in any analysis, other comparisons were made with Tukey HSD test. All statistical analyses were performed using JASP 0.10.2 (JASP Team, 2019).

Results

Table 1 presents the participant characteristics for the three groups and the sleep architecture. A higher proportion of males were noted in all groups ($\chi^2(2)=21.01$, $p<.001$), but there were no statistical differences in age or IQ. Comparing the percentage of medication between ADHD presentations we observed a higher percentage of medication use in children with ADHD-C than the ADHD-I ($\chi^2(1)=6.53$, $p=.011$) and ADHD-I/HI ($\chi^2(1)=4.72$, $p=.030$). Regarding sleep architecture, no differences between groups were observed in any variable (all p values > .05) (Table 1).

Table 1

Participants Characteristics and Sleep Architecture

	ADHD-I (n = 28)	ADHD-H/I (n = 27)	ADHD-C (n = 23)	*F*
Male/Female	16/12	24/3	22/1	8.4**
Age(M, SD)	9.3(1.3)	9 (1.5)	9.5(1.3)	0.94
IQ(M, SD)	96.04(18)[a]	98.9(18.2)	96.1(15.1)[b]	0.23
Clinical diagnosis	85.7 %	77.8 %	100%	2.88
ADHD medication use	53.6 %	59.3%	87%	3.64*
Time in bed (min)	548.36 (57.88)	557.09 (59.84)	550.22 (50.89)	0.18
Sleep period time (min)	529.22 (60.02)	533.17 (57.28)	532.10 (48.36)	0.03
Total sleep time (min)	506.49 (54.55)	506.09 (58.29)	503.29 (46.38)	0.03
Sleep onset latency (min)	12.95 (8.52)	14.59 (9.08)	15.42 (11.53)	0.44
Sleep efficiency (%)	92.28 (3.31)	91.30 (4.20)	91.59 (5.22)	0.37
Wake time (%)	2.93 (2.82)	3.47 (3.07)	3.70 (5.29)	0.27
N1 (%)	2.25 (2.11)	1.49 (0.96)	2.50 (4.58)	0.87
N2 (%)	36.34 (5.77)	36.23 (8.76)	34.34 (7.98)	0.54
N3 (%)	36.19 (7.91)	36.33 (9.84)	37.68 (8.64	0.33
REM (%)	25.05 (6.52)	25.90 (4.18)	24.82 (4.35)	0.31
REM latency (min)	143.49 (64.91)	126.59 (57.74)	150.50 (59.10)	1.04
Arousal (index)	0.70 (0.69)[c]	0.83 (1.21)[d]	1.74 (2.99)[e]	1.77
Periodic limb movements (index)	0.82 (1.26)[f]	1.04 (1.37)[c]	0.71 (0.98)	0.43

Note. ADHD-I = Attention Deficit Hyperactivity Disorder inattentive presentation; ADHD-H/I = ADHD hyperactive/impulsive presentation; ADHD-C = ADHD combined presentation; IQ = Intelligence quotient measured by Wechsler Scale for Children IV (Wechsler, 2010); M = mean; SD = standard deviation. *p<.05; **p<.001, REM = rapid eye movement. Data on sleep architecture are presented as mean and (standard deviation), and all p values were > .05. [a] Sample for this variable was 27; b sample for this variable was 22.; [c] sample for this variable was 23; [d] sample for this variable was 15; [e] sample for this variable was 21; [f] sample for this variable was 25.

Number of spindles

Table 2 summarizes the spindles number for all groups in each derivation. The analysis on the three presentations of ADHD revealed a significant Type main effect ($F_{1,71}$=288.043, p<.001, $\acute{\eta}^2_p$=.80), showing a higher number of slow compared to fast spindles, a Derivation main effects ($F_{1,71}$=75.74, p<.001, $\acute{\eta}^2_p$=.52), with a higher number of spindles detected in Fz compared to Pz, and a Stage main effect ($F_{1,71}$=111.13, p<.001, $\acute{\eta}^2_p$=.61), with more spindles in N2 than N3. We also observed a Stage × Type

($F_{1,71}$ =61.13 p<.001, $\acute{\eta}^2_p$=.46), showing a reduction of spindles for both slow (p<.001) and fast (p=.008) spindles in N3 compared to N2 , and Type × Derivation interaction ($F_{1,71}$ =74.74, p<.001, $\acute{\eta}^2_p$=.51), which showed that slow spindles were more frequent in frontal site than lower in parietal site, but no difference was observed for fast spindles (p=.769). No differences between ADHD presentations ($F_{2,71}$ =1.14, p=.325, $\acute{\eta}^2_p$=.03) or interactions were observed (all p's>.275)

Table 2

Number of Spindles in Children with Attention Deficit/Hyperactivity Disorder

Derivation	Stage	Type of Spindle	ADHD-I M(SD) n = 27	ADHD-H/I M(SD) n = 25	ADHD-C M(SD) n = 22
Fz	N2	Fast	102.48(148.94)	124.88(153.46)	69.36(57.70)
		Slow	590.30(241.66)	668.36(268.28)	582.36(229.67)
	N3	Fast	41.48(61.02)	46.84(59.92)	29(48.43)
		Slow	278.37(138.40)	345.20(195.64)	333.27(170.03)
Pz	N2	Fast	127.89(179.43)	145.32(158.67)	91.95(106.94)
		Slow	464.67(154.18)	477.00(242.81)	460.50(170.75)
	N3	Fast	37.74(51.33)	45.88(61.98)	31.45(51.23)
		Slow	173.63(128.94)	176.80(127.58)	207.41(179.01)

Note. ADHD-I = attention deficit hyperactivity disorder, inattentive presentation; ADHD-H/I = ADHD hyperactive/impulsive presentation; ADHD-C = ADHD combined presentation. M = mean; SD = standard deviation.

Density of spindles

Since the total number of spindles depends on the duration of N2 and N3 sleep, we also analysed the sleep density, i.e. the number of spindles per minute of N2 and N3 (Table 3).

Table 3

Density of Spindles in Children with Attention Deficit/Hyperactivity Disorder

Derivation	Stage	Type of Spindle	ADHD-I M(SD) n = 27	ADHD-H/I M(SD) n = 25	ADHD-C M(SD) n = 22
Fz	N2	Fast	0.52(0.63)	0.62(0.63)	0.43(0.39)
		Slow	3.17(0.95)	3.50(0.93)	3.25(0.94)
	N3	Fast	0.24(0.40)	0.27(0.27)	0.15(0.20)
		Slow	1.53(0.70)	2.13(1.64)	1.75(0.83)
Pz	N2	Fast	0.65(0.77)	0.72(0.69)	0.52(0.56)
		Slow	2.55(0.69)	2.53(1.05)	2.61(0.73)
	N3	Fast	0.21(0.31)	0.26(0.28)	0.16(0.22)
		Slow	0.90(0.55)	1.08(0.96)	1.03(0.65)

Note. ADHD-I = attention deficit hyperactivity disorder, inattentive presentation; ADHD-H/I = ADHD hyperactive/impulsive presentation; ADHD-C = ADHD combined presentation. M = mean; SD = standard deviation.

The analysis confirmed the observation on the number of spindles, revealing a significant Stage ($F_{1,71}$=197.22, p<.001, $\acute{\eta}^2_p$=.73), Type ($F_{1,71}$=328.64, p<.001, $\acute{\eta}^2_p$=.82), Derivation main effects ($F_{1,71}$=76.02, p<.001, $\acute{\eta}^2_p$=.51), as well as a Type × Derivation ($F_{1,71}$ =72.428, p<.001, $\acute{\eta}^2_p$=.71) and Stage × Type interactions ($F_{1,71}$ =76.18, p<.001, $\acute{\eta}^2_p$=.52). As depicted in Figure 1b, we observed i) a higher spindle density in N2, ii) a general higher density for slow spindles, iii) a higher density of slow spindles in the frontal compared to the parietal derivation (all *p's*<.001). No differences between ADHD presentations were observed ($F_{2,71}$ =2.02, p=.141, $\acute{\eta}^2_p$=.05), although ADHD-H/I showed a nominally higher density compared to ADHD-I and ADHD-C (p=.161 and p=.257 respectively).

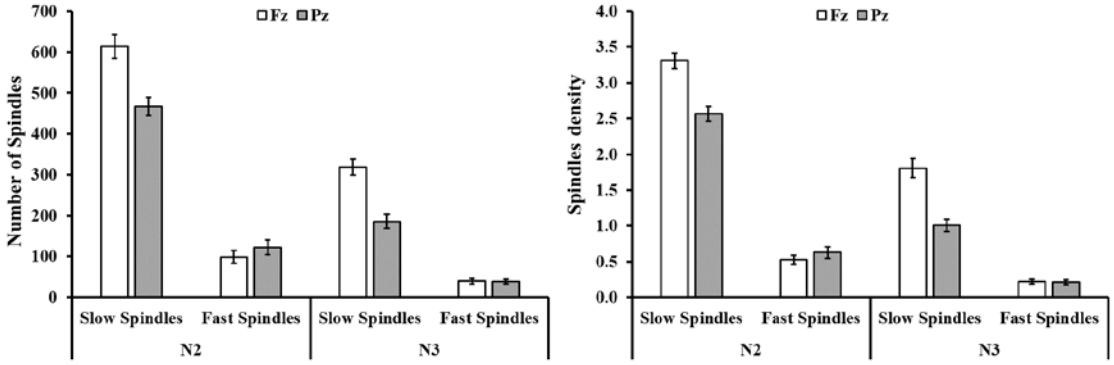

Figure 1. Fast and slow spindles number (a) and density (b) in N2 and N3 in children with ADHD.

Duration of Spindles

Table 4 summarizes spindles duration in the three ADHD presentations. The analysis revealed a significant Stage ($F_{1,71}$=22.91, p<.001, $\acute{\eta}^2_p$=.24), Type ($F_{1,71}$=111.58, p<.001, $\acute{\eta}^2_p$=.61), and Derivation ($F_{1,71}$=22.15, p<.001, $\acute{\eta}^2_p$=.24) main effects, as well as a Stage × Type interaction ($F_{1,71}$=10.15, p<.001, $\acute{\eta}^2_p$=.13), with longer duration for slow spindles compared to fast during both N2 and N3, and longer duration during N2 compared to N3 (all *p's*<.001). Again, no differences between ADHD presentations were observed ($F_{2,71}$ =0.12, p=.886, $\acute{\eta}^2_p$=.01).

Amplitude of spindles

Analysis of spindles amplitude showed only a significant Stage ($F_{1,71}$=107.98, p<.001, $\acute{\eta}^2_p$=.60) and Derivation ($F_{1,71}$=791.25, p<.001, $\acute{\eta}^2_p$=.53) main effects, with higher amplitude during N3 and in Fz. Again, ADHD presentation was not significant ($F_{2,71}$ =0.79, p=.460, $\acute{\eta}^2_p$=.02), with no differences for fast spindles between ADHD-C and the other presentations (all *p's* >.498).

Table 4

Spindles Duration (s) in Children with Attention Deficit/Hyperactivity Disorder

Derivation	Stage	Type of Spindle	ADHD-I M(SD) n = 27	ADHD-H/I M(SD) n = 25	ADHD-C M(SD) n = 23
Fz	N2	Fast	0.83(0.22)	0.85(0.17)	0.80(0.21)
		Slow	1.07(0.11)	1.11(0.10)	1.12(0.08)
	N3	Fast	0.82(0.18)	0.81(0.22)	0.77(0.19)
		Slow	0.99(0.13)	1.03(0.10)	1.06(0.10)
Pz	N2	Fast	0.90(0.22)	0.91(0.26)	0.86(0.28)
		Slow	1.18(0.13)	1.18(0.15)	1.21(0.14)
	N3	Fast	0.88(0.21)	0.88(0.24)	0.82(0.24)
		Slow	1.08(0.14)	1.09(0.15)	1.12(0.15)

Note. ADHD-I = attention deficit hyperactivity disorder, inattentive presentation; ADHD-H/I = ADHD hyperactive/impulsive presentation; ADHD-C = ADHD combined presentation. M = mean; SD = standard deviation.

Table 5

Amplitude of Spindles in Children with Attention Deficit/Hyperactivity Disorder

Derivation	Stage	Type of Spindle	ADHD-I M(SD) n = 27	ADHD-H/I M(SD) n = 25	ADHD-C M(SD) n = 22
Fz	N2	Fast	33.91(10.83)	37.29(12.06)	31.88(9.98)
		Slow	33.52(9.87)	34.99(6.08)	32.28(5.17)
	N3	Fast	41.31(11.05)	43.00(10.92)	39.72(11.91)
		Slow	40.82(11.44)	44.35(8.30)	40.29(6.57)
Pz	N2	Fast	27.68(10.00)	28.68(6.40)	27.06(5.28)
		Slow	27.80(9.61)	28.29(3.85)	28.00(3.55)
	N3	Fast	32.25(11.40)	35.87(15.43)	34.23(17.51)
		Slow	32.65(9.95)	33.59(5.92)	33.84(4.24)

Note. ADHD-I = attention deficit hyperactivity disorder, inattentive presentation; ADHD-H/I = ADHD hyperactive/impulsive presentation; ADHD-C = ADHD combined presentation. M = mean; SD = standard deviation.

Intensity of Spindles

Analysis of spindles intensity showed only a significant Stage ($F_{1,71}$=37.96, p<.001, $\acute{\eta}^2_p$=.35), with, Type ($F_{1,71}$=58.63, p<.001, $\acute{\eta}^2_p$=.45), and Derivation ($F_{1,71}$=22.89, p<.001, $\acute{\eta}^2_p$=.24), main effects, showing: a) higher intensity for a) spindles

in N2 compared to N3 b) for slow compared to fast spindles, c) a significant decrease in intensity for spindles in Pz compared to Fz (p<.001). Again, no significant differences were observed between ADHD presentations ($F_{2,71}$ =1.29, p=.283, $\acute{\eta}^2_p$=.01), with no significant differences for fast spindles between ADHD-C and the other presentations (all *p's* >.45).

Table 6

Intensity of Spindles in Children with Attention Deficit/Hyperactivity Disorder

Derivation	Stage	Type of Spindle	ADHD-I M(SD) n = 27	ADHD-H/I M(SD) n = 25	ADHD-C M(SD) n = 22
Fz	N2	Fast	27.89(8.90)	32.18(12.16)	25.32(8.43)
		Slow	36.44(12.22)	39.13(8.39)	36.26(6.62)
	N3	Fast	34.02(12.59)	36.53(16.57)	30.64(11.30)
		Slow	41.44(14.25)	45.99(11.93)	42.68(8.50)
Pz	N2	Fast	41.44(14.25)	45.99(11.92)	42.68(8.50)
		Slow	32.59(10.34)	33.32(6.74)	34.04(6.47)
	N3	Fast	24.40(7.28)	26.54(10.00)	24.08(9.98)
		Slow	35.16(10.81)	36.73(9.98)	37.99(7.59)

Note. ADHD-I = attention deficit hyperactivity disorder, inattentive presentation; ADHD-H/I = ADHD hyperactive/impulsive presentation; ADHD-C = ADHD combined presentation. M = mean; SD = standard deviation.

Exploratory correlations

Using a single spindles measure (the average of all the spindles in all the channels), we observed a trend for a positive association between spindle frequency and age as hypothesized (r=.23, p=.054, Figure 2a) and a negative association, although not significant, between spindle frequency and IQ (r=-.15, p=.206, Figure 2b), in the whole sample. Interestingly, these associations were mainly driven by ADHD-C (r=.42, p=.050 and r=-.47, p=.031 for age and IQ respectively).

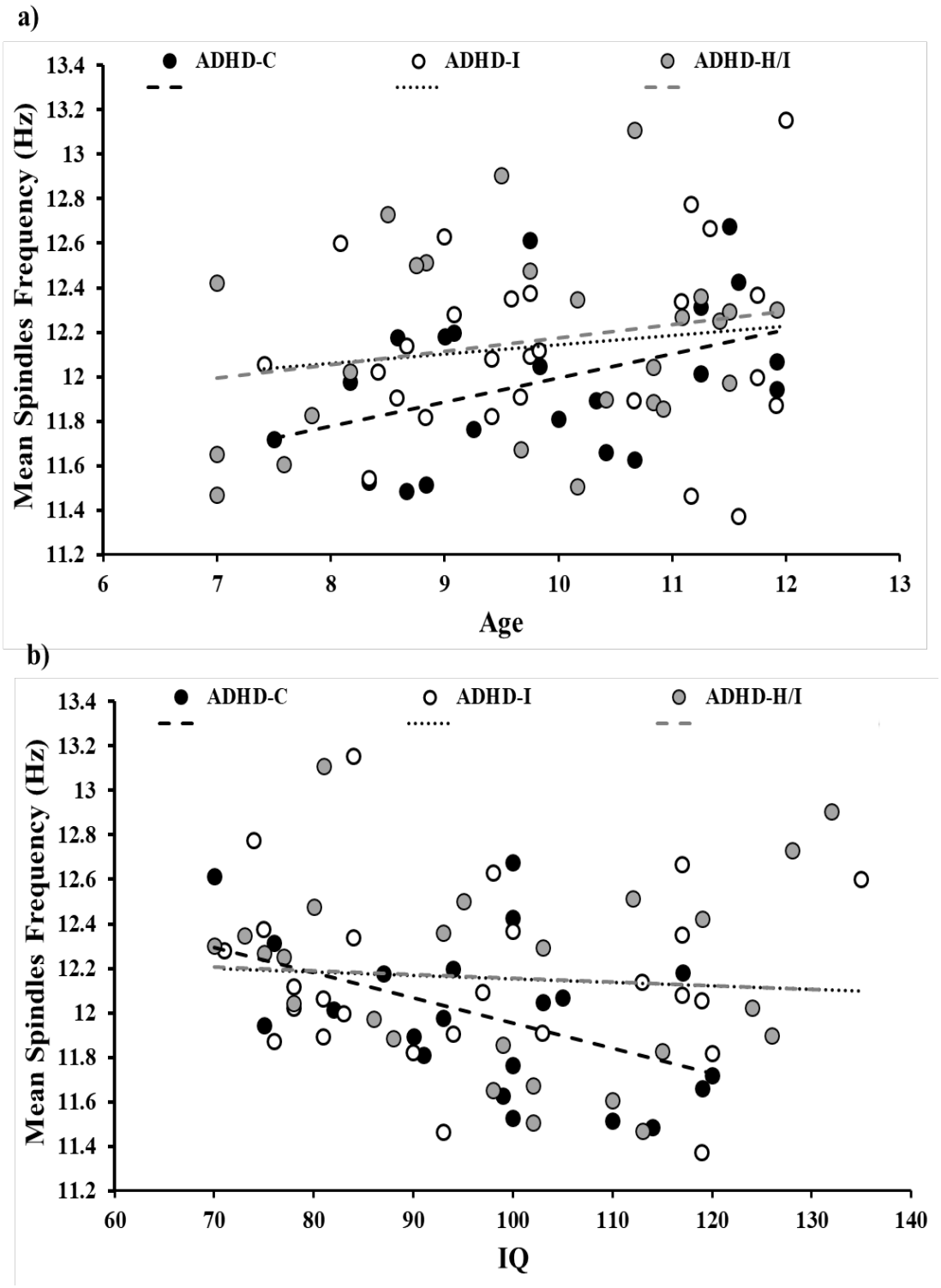

Figure 2. Correlations between mean spindles frequency and a) age, and b) IQ in the three ADHD presentations.

Moreover, we observed a positive association between fast spindles density and age (r=.28, p=.017), Figure 3a. Again, the stronger effect was observed for ADHD-C (r=.52, p=.014). Lastly, spindles intensity was negatively associated with age only in ADHD-C (r=-.43, p=.044), mainly due to the shortening of spindles duration with aging (r=-.45, p=.038, Figure 3b). Of note, these correlations were not controlled for multiple comparisons; therefore, they need to be taken with caution.

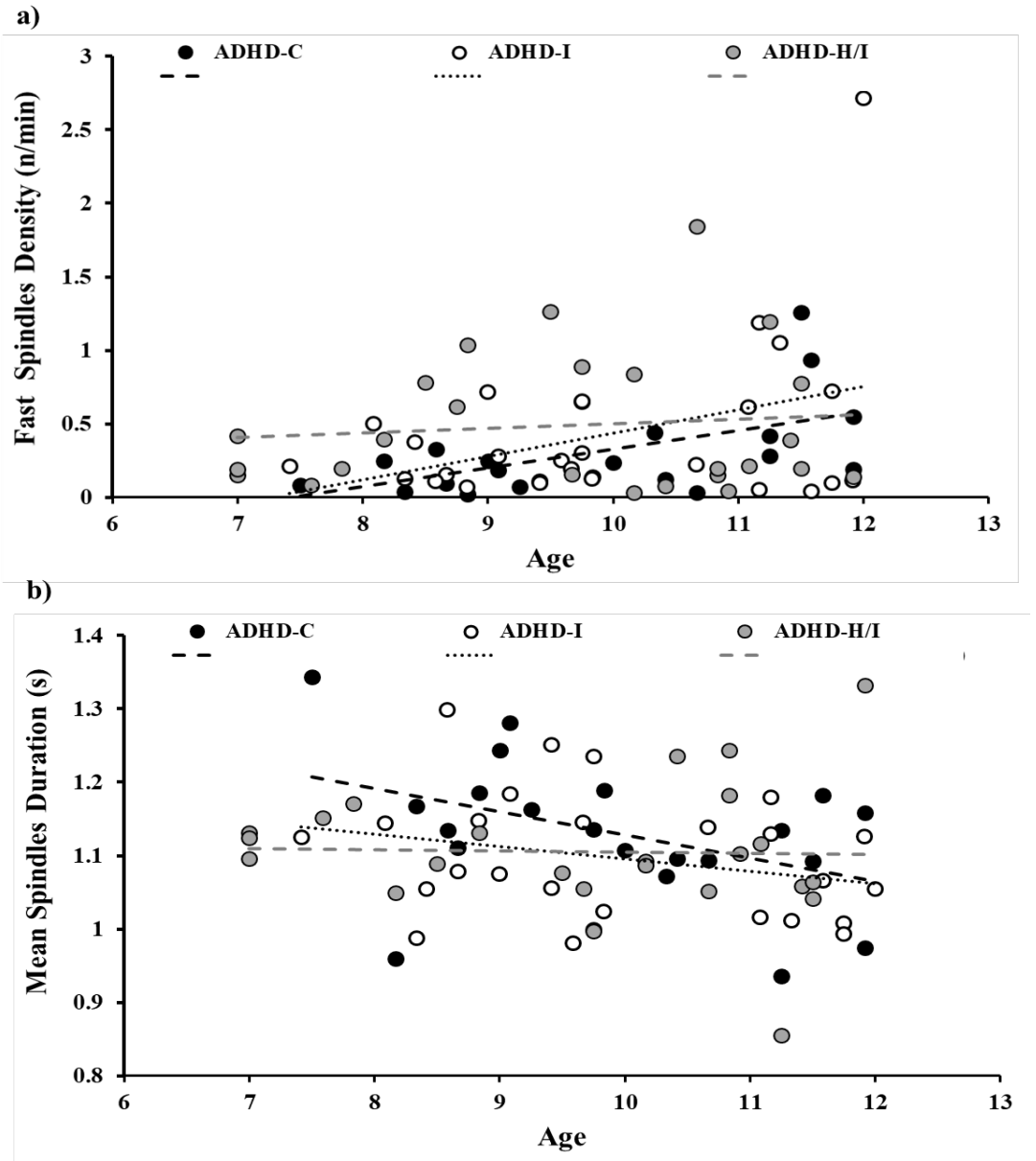

Figure 3. Correlations between a) fast spindles density and age, and b) spindles duration and age in the three ADHD presentations.

Discussion

Here we analysed spindles characteristics in children with ADHD to explore potential differences among presentations. A differential pattern in the spindles characteristics between the three ADHD presentations was hypothesized, with greater spindle intensity in the ADHD-C presentation with respect to the other groups. Although, no differences were observed between groups in any of the evaluated variables (number, density, duration, amplitude, and intensity of spindles), we reported significant correlations between the age of the participants and spindles frequency, intensity, and fast spindles density, indicating a maturation

Our sample was characterized by a similar number and density of spindles, with increased density in N2 with respect to N3. These results are congruent to previous scientific literature indicating a higher number and density of spindles in N2 in healthy population (see De Gennaro & Ferrara, 2003, for a review; Purcell et al., 2017). With respect to the assumption that spindles play essential roles in regulating sleep architecture (Kim et al., 2012), our data are not in line with this assumption, since there was not an increase of duration of N2 driven by a greater density of spindles in N2. Moreover, these results are not in accordance with studies in adults that indicated a higher presence of slow spindles during slow wave sleep (N3) (Mölle, Bergmann, Marshall, & Born, 2011) as slow spindles were more pronounced during N2.

With respect to the topography, children with ADHD showed the typical spindles distribution observed in TD, i.e. spindles smoothly change along the caudo-rostral axis with higher number and density of fast spindles in the parietal derivation and a prevalence of slow spindles in the frontal derivation (see Clawson et al., 2016; De Gennaro & Ferrara, 2003, Gorgoni, et al., 2020; Gruber & Wise, 2016, for reviews;

Martin et al., 2013). Similar results were yielded in terms of duration and amplitude. A greater duration and amplitude of slow than fast spindles were observed. At this respect, the results reported by Merikanto et al., (2019) could be comparable to ours as they (although in adolescence) observed that a higher ADHD symptomatology is associated with weaker fast sleep spindle activity. Taking those results together, we could suggest that ADHD is associated with an increase in slow (and a reduction of fast) spindles in both childhood and adolescence.

Regarding associations between spindles characteristics and age, some significant results were found in this sample. We can thus confirm the assumption of the evolvement of spindles with age (see Clawson et al., 2016, for a review; Scholle et al., 2007), also in children with ADHD. Positive associations were found in terms of frequency and fast spindles density, and, contrary to what expected, negative associations were observed in spindles intensity. Although the results should be taken with caution, a different pattern of development was observed in ADHD-C, since changes with age were mainly driven by this group and, in terms of intensity, occurred only in this group. Regarding spindles frequency and density, our results followed the previous reported normal maturation pattern, with previous reports indicating that frequency increases across childhood and adolescence (see Clawson et al., 2016, for a review), and that mature centroparietal fast spindles emerge in adolescence (Goldstone et al., 2019; Hahn et al., 2017; Hoedlmoser et al., 2014; Shinomiya et al., 1999). Interestingly, Hahn et al. (2017) showed that slow spindles density in children (8-11 years old) was dominant in both frontal and central sites, whereas fast spindle density was extremely few (in both derivations), and matured drastically in adolescence (14-18 years old), primarily in the central derivation. Thus, our data are comparable to those of

TD children, as the topographical pattern of fast spindles increase in adolescence are similar. With respect to spindles intensity, our results do not support the literature that claims that shorter and lower-amplitude spindles are characteristic of more efficient brain networks (Goldstone et al, 2019), since intensity of spindles was reduced in the ADHD-C (the most affected by the symptomatology). However, our results could be again in line with those obtained by Merikanto et al., (2019), since their results in adolescence indicated that elevated symptoms of ADHD were associated with lower amplitude and shorter duration of fast spindles. In our sample, although there were no differences in terms of duration and amplitude between groups, as ADHD-C approached adolescence, the intensity of the spindles decreased. These results could suggest that a greater symptomatology of ADHD could be associated with a pre-maturation of the spindles.

No significant associations between spindle activity and IQ were found in this sample, which is contrary to other findings in healthy adults (Bódizs et al., 2005; Schabus et al., 2006) and children (Geiger et al., 2011; Hoedlmoser et al., 2014). Nevertheless, our results (although not methodologically comparable), could be in line with previous studies on cognitive performance in children with ADHD (Prehn-Kristensen et al., 2011; Prehn-Kristensen et al., 2013), in which no correlations were found between spindles activity and memory performance (Prehn-Kristensen et al., 2011; Prehn-Kristensen et al., 2013). The association between spindles frequency and IQ (although not significant) was negative and mainly driven by the ADHD-C group, These results could be in agreement with the results of Bestmann et al.,(2019), who found negative correlations between IQ and sigma power in children with ADHD over parietal positions. Since other areas of cognitive performance were not analysed in this

sample, we have no evidence to help disentangle the previous inconsistencies in the scientific literature in this respect.

The main limitation to this study is that we present data from a cross-sectional study of children, which may have resulted in an oversimplification of the relationship between age and spindle characteristics. Longitudinal studies may help provide more evidence for the characterization of spindles and the maturational changes that emerge in ADHD throughout the lifespan. Moreover, we did not manipulate spindles activity by administering a pre-sleep cognitive task, which may have induced a change in spindles characteristics as a response to the task. Also, the lack of a control group (i.e., a TD group) does not allow us to make a direct comparison of spindles characteristics of ADHD and TD children. Lastly, we used an automated, although validated, spindle detection algorithms. As most of these algorithms, they have been trained and tested with adult populations. Therefore, we cannot exclude that the algorithm may have a certain degree of error in the detection of spindles (and their characteristics). Further studies should be aimed to test these algorithms in population of different ages.

In conclusion, although the existence of different neurobiological characteristics between ADHD presentations has been previously reported, we did not observed such differences in terms of spindles characteristics. However, the topography of spindles in children with ADHD follows the same organization as that of TD children. Significant associations were observed between spindles characteristics and age, being the ADHD-C group who showed the most prominent effects.

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ESTUDIO 4

Sleep, academic achievement, and cognitive performance in children with attention-deficit/hyperactivity disorder: A polysomnographic study

Abstract

Objective: To examine the influence of parent-reported and polysomnography (PSG)-measured sleep patterns on academic and cognitive performance of children with attention-deficit/hyperactivity disorder (ADHD). **Method:** We assessed 91 children (18 girls) diagnosed with ADHD aged 7—11 years (29 ADHD-I, 32 ADHD-H/I and 31 ADHD-C). The *Pediatric Sleep Questionnaire* and *Pediatric Daytime Sleepiness Scale* were used to assess subjective sleep quality, as perceived by parents, and objective sleep variables were assessed by PSG. Cognitive performance was evaluated using the fourth edition of the Wechsler Intelligence Scale for Children, and the final average grade of the last school year was used as a measure of academic performance. **Results:** Subjective daytime sleepiness predicted academic and, in a lesser extent, cognitive performance. Sleep-disordered breathing and behavioural variables did not predict any academic or cognitive outcome. Academic and cognitive performance were predicted by the following objective sleep variables: Time in bed, sleep onset latency, sleep/wake time, sleep efficiency, percentage of stages 1, 2, 4, and REM sleep, arousal index, periodic limb movement index, and sleep continuity and organization. The main predictor of academic outcomes was the arousal index, and of cognitive performance were the sleep time and the percentage of stage 1 sleep. **Conclusions:** Sleep parameters are closely associated with the academic and cognitive functioning of children with ADHD. As these children are likely to suffer from sleep problems, they are at higher risk of experiencing cognitive impairments which may lead to their academic failure.

Keywords: Attention-deficit/hyperactivity disorder, sleep, academic achievement, cognitive performance, children.

Introduction

Approximately 3.4% of the world's population is dealing with attention-deficit/ hyperactivity disorder (ADHD) (Polanczyk, Salum, Sugaya, Caye, & Rohde, 2015). This is characterized by inattention, hyperactivity, and impulsivity symptoms, and it can be classified into three clinical presentations: Inattentive (ADHD-I), hyperactive/impulsive (ADHD-H/I), and combined (ADHD-C) (American Psychiatric Association, 2013). Cognitive impairments are remarkable in ADHD-affected children (Fried et al., 2017; Simone, Marks, Bédard, & Halperin, 2018; Sjöwall & Thorell, 2014; Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005), and these impact their school achievement and their performance in cognitive tasks (Baweja, Mattison, & Waxmonsky, 2015; Fleming et al., 2017; Kubo et al., 2018; Roberts, Martel, & Nigg, 2017; Taddei & Contena, 2017). This situation contributes to an increased risk for educational problems, thus conferring a substantial burden on healthcare and educational systems worldwide, affecting also the child's quality of life (Beecham, 2014; Fleming et al., 2017).

Sleep problems have been widely associated with ADHD in children (see reviews of Cortese, Faraone, Konofal, & Lecendreux, 2009; Díaz-Román, Hita-Yáñez, & Buela-Casal, 2016; Hvolby, 2015), and given the abundance of evidence describing the importance of sleep for cognitive health, this factor is of increasing scientific and clinical interest in early intervention. For instance, sleep problems were suggested to be a main cause of the daytime deficits associated with ADHD, including low academic and cognitive functioning, with prior research in clinical and non-clinical samples (see Kirov and Brand, 2014 for a review; Lee et al., 2014; Schneider, Lam, & Mahone,

2016; Um, Hong, & Jeong, 2017; Um et al., 2016; Virring, Lambek, Jennum, Ruge, & Thomsen, 2017).

Despite the relationship between sleep and academic achievement (see Chaput et al., 2016 for a review), few studies have focused on determining how this relationship affects children with ADHD symptoms (Cusick, Isaacson, Langberg, & Becker, 2018; Langberg, Dvorsky, Becker, & Molitor 2014; Langberg, Dvorsky, Marshall, & Evans, 2013; Mayes et al., 2008; Reynolds, Patriquin, Alfano, Loveland, & Pearson, 2017), and these have provided contradictory results, partially due to the use of different study methods. In this respect, apart from the heterogeneity found between participants' age ranges, while some studies have used objective measures to assess sleep (e.g. Mayes et al., 2008), others have used subjective ones (e.g. Cusick et al., 2018). For instance, Mayes et al. (2008) did not observe any relationship between sleep and academic performance in children with ADHD symptoms using polysomnographic recordings. In contrast, other studies have noted an association between school maladjustment and academic performance in some important school subjects and several self-reported sleep variables, such as daytime sleepiness and night awakenings (Cusick et al., 2018; Langberg et al., 2013, 2014).

With respect to the relationship between sleep and the cognitive processes involved in academic performance, previous research has also yielded contradictory results. For instance, studies using objective sleep measures in children with ADHD have revealed that shorter sleep duration and lower sleep efficiency are associated with executive function (Moreau, Rouleau, & Morin, 2013), attention (Waldon, Vriend, Davidson, & Corkum, 2018), and memory deficits (Prehn-Kristensen et al., 2013) in children with ADHD. Moreover, slow wave sleep (SWS), stage 2 sleep, rapid eye

movement sleep (REM sleep), and periodic limb movements (PLMs), as well as sleep fragmentation, have also shown to predict cognitive performance in these children (Kirov, Brand, Banaschewski, & Rothenberger, 2017; Lee et al., 2014; O'Brien et al., 2003; Um et al., 2016). However, some studies using subjective measures like parental-reported questionnaires have suggested that inattention and executive dysfunctions are not attributable to sleep (Schneider et al., 2016).

Therefore, prior attempts to determine the influence of sleep on academic and cognitive performance in children with ADHD have failed to reach a conclusion. Indeed, few studies have used both subjective and objective sleep measures to assess this influence in a large sample of children diagnosed with ADHD. Therefore, the objective of our study was to analyse the influence of sleep—assessed through parents' reports and polysomnography (PSG) recordings—on academic and cognitive performance in children with ADHD. Regarding variables assessed by PSG, we hypothesized that sleep duration, efficiency, and fragmentation, as well as sleep stages would predict the school and cognitive performance of children with ADHD, according to the results of previous studies (e.g. Lee et al., 2014; Prehn-Kristensen et al., 2013; Um et al., 2016; Waldon et al., 2018). In relation to subjective measures, we expected both daytime sleepiness and breathing-related sleep problems to account for academic and cognitive performance (Cusick et al., 2018; Langberg et al., 2013, 2014; Reynolds et al., 2017).

Method

Participants

Participants were 91 children with ADHD from the province of Granada, Spain (29 ADHD-I, 32 ADHD-H/I and 30 ADHD-C), aged 7—11 (Table 1), recruited through educational and clinical institutions. The project was approved by the ethics committee of the University of Granada and the Andalusian Biomedical Research Ethics, Coordinating Committee. The anonymity of the participants and the confidentiality of the data were guaranteed. More information about collaborating entities can be found in Ruiz-Herrera, Guillén-Riquelme, Díaz-Román, Cellini, & Buela-Casal (in press).

Eighty-eight percent of children had a clinical diagnosis of ADHD as a primary disorder, according to the criteria of the International Classification of Diseases, 10th revision (ICD-10-CM; World Health Organization, 1992). The remaining 12% of the children had ADHD symptomatology as informed by the educational psychologist of the child's school. Psycho-educational reports based on specific questionnaires and cognitive tests (e.g EDAH [Farré & Narbona, 2013]; attention test d2 [Brickenkamp, 2002]) were considered equivalent to the clinical diagnosis when children had been registered as children with ADHD ('specific educational support needs' with no significant curricular adaptation) into the SENECA platform of the Spanish Ministry of Education and Science (Spanish Organic Law 8/2013, 9th December, for the improvement of the educational quality [Ley Orgánica 8/2013, de 9 de diciembre, para la mejora de la calidad educativa]). Children with a diagnosis of severe organic disorders associated with sleep impairments (e.g., severe respiratory-related diseases, sensory deficits, and/or generalized developmental disorders), or a body mass index > 30 were not included. Furthermore, we excluded three children whose scores were

lower than 70 on the Wechsler Intelligence Scale for Children–Fourth Edition (WISC-IV; Wechsler, 2010).

Sleep measures

Subjective sleep data were obtained through two questionnaires filled out by children's parents: The Pediatric Sleep Questionnaire (PSQ) (PSQ; Tomás, Miralles, & Beseler, 2007) and the Pediatric Daytime Sleepiness Scale (PDSS) (PDSS; Drake et al., 2003). The PSQ allows detecting sleep-disordered breathing (α = .81), sleepiness (α = .63), and behavioural problems (α = .86). A higher PSQ score reflects a lower sleep quality and it has been clinically validated (cutoff score ≥ .33 reflects clinical problems; Chervin, Hedger, Dillon, & Pituch, 2000). The PDSS (α = .80) assesses the child's level of daytime sleepiness and related school outcomes. A higher PDSS scores imply higher levels of daytime sleepiness, and a score of > 20 indicates clinical levels of excessive daytime sleepiness (Drake et al., 2003).

Objective sleep data were obtained through a home polysomnography recording to promote a more ecological assessment environment, and thus preventing sleep disturbances derived from changes in children's habitual sleep environment. The following components were calculated: Time in bed (TIB: Time elapsed from going to bed to final arising), sleep period time (SPT: Time spent from sleep onset to the last epoch of sleep), total sleep time (TST: Time spent in each sleep stage during SPT), sleep onset latency (SOL: Time interval between wakefulness and the beginning of stage 1 sleep), sleep efficiency (TST/SPT), the proportion of TST spent in each sleep stage, REM latency (time interval between sleep onset and the first occurrence of an epoch of REM sleep), arousal index (number of arousals per hour; changes in electroencephalography frequency of at least 3 seconds and preceded by a minimum of

10 continuous seconds of sleep), and PLM index (frequency of periodic limb movements per hour). A number of short (< 2 min), long (>2 min), and total awakenings, as well as the mean of awakenings duration were used as the measure of sleep continuity. A number of state transitions were used as a measure of sleep stability, and the number of sleep cycles and their duration were used as a measure of sleep organization. More information about questionnaires and PSG assessment can be found in Ruiz-Herrera et al., (in press).

Cognitive measures

The Spanish version of the WISC-IV (Wechsler, 2010) was used to measure cognitive performance. We applied the ten core subtests to obtain the following indexes: Verbal comprehension (VC, composed of similarities, vocabulary, and comprehension subtests, $\alpha = .94$), perceptual reasoning (PR, obtained through block design, concepts, and matrix subtests, $\alpha = .92$), working memory (WM, composed of digits and letter-number sequencing subtests, $\alpha = .92$), and processing speed (PS, obtained from coding and symbol search subtests, $\alpha = .88$). We obtained the full-scale intelligent quotient (FSIQ) as a measure of general cognitive performance ($\alpha = .97$).

School performance

We collected the final average grade of the last school year as a measure of academic performance. This included all the school subjects studied during the academic year: Spanish, Mathematics, Natural Sciences, Social Sciences, Physical Education, Art, and English as a second language.

Procedure

Written informed consents were obtained from the children's parents before the beginning of the research. In order to assess the inclusion criteria, an interview on

sociodemographic and clinical data, as well as the administration of the subjective sleep measures to the parents were conducted during the first study session. The WISC-IV was administered between one week before and one week after sleep assessment (depending on the availability of the child's family) to children who did not have previous reports of their cognitive assessment. Data on their last academic outcomes were collected from their teachers.

The second phase of the study comprised the PSG recordings at the children's home. Consumption of stimulant beverages (e.g. caffeinated) during that day was not allowed, and specific medication for ADHD (atomoxetine, guanfacine, methylphenidate, and lisdexamphetamine) was withdrawn 36 hours before the PSG assessment. Children were required to maintain, to the extent possible, their usual nighttime schedule.

Statistical analysis

ANOVA analyses were conducted for age group comparisons and to explore differences between ADHD presentations on cognitive and academic variables. As no statistically significant differences were observed between presentations in these variables (all *p*-values > .10; Table 2), or in sleep variables (Ruiz-Herrera et al., in press), regression analyses were performed for the total sample. Similarly, the Student *t* tests comparing treated vs. not treated children in cognitive and academic (all *p*-values > .09), and sleep variables (Ruiz-Herrera et al., in press) did not reveal significant results supporting an effect of treatment on data that justifies separated analyses. Once we confirmed that the assumptions of regression (e.g. normality of residuals, multicollinearity of predictors) were not violated, we conducted backward multiple regression analyses for each academic and cognitive variable to test whether sleep

variables predicted academic and cognitive performance. Multicollinearity diagnostics were performed to exclude possible confounding influences between the independent variables. The significance level specified for all statistical analyses was $p < .05$. All analyses were performed using SPSS/PASW Statistics 21.0 for Windows.

Table 1

Sociodemographic Data of the Total Sample (N = 91)

ADHD presentation (girls)	ADHD-I n = 29(12)	ADHD-H/I n = 32(3)	ADHD-C n = 30(3)	*F*	*P*
Age	9.24(1.33)	9.19(1.49)	9.00(1.44)	0.31	.734
Medication (% yes)	55.17	56.25	90	5.86	.004
FSIQ	95.43(17.92)[a]	98.25(18.27)	96.00(16.51)	0.22	.803

Note. ADHD-I = attention deficit hyperactivity disorder, inattentive presentation; ADHD-H/I = ADHD hyperactive/impulsive presentation; ADHD-C = ADHD combined presentation. FSIQ = full scale intelligence quotient.
[a] ADHD-I sample for this variable was 28.

Results

Table 1 summarizes the sociodemographic data of the sample. No significant differences in age or IQ were observed in the three ADHD presentations, but significant differences were observed in the medication use between the groups ($p < .05$), with a higher medication use among children with the ADHD-C presentation.

Data on academic and cognitive achievement can be found in Table 2. No differences were found in any academic or cognitive variable when distinguishing the three ADHD presentations.

Data on objective and subjective sleep variables are reported elsewhere (Ruiz-Herrera et al., in press).

Table 2.

Academic and Cognitive Achievement of the Total Sample (N = 91)

Academic and cognitive performance (mean, SD)	ADHD-I n = 29	ADHD-H/I n = 32	ADHD-C n = 30	*F*	*p*
Language Arts [a]	5.96 (1.45)	6.18 (1.70)	5.60 (1.90)	0.69	.502
Mathematics [a]	5.73 (1.59)	5.82 (1.72)	5.75 (1.80)	0.02	.979
Natural Sciences [a]	6.27 (1.31)	6.21 (1.68)	5.85 (1.75)	0.45	.638
Social Sciences [a]	5.88 (1.50)	6.07 (1.86)	5.60 (1.98)	0.41	.666
Physical Education [a]	8.00 (1.46)	7.96 (1.40)	7.40 (1.31)	1.26	.291
Art [a]	7.15 (1.51)	6.64 (1.33)	6.45 (1.60)	1.45	.241
English (2nd language) [a]	5.96 (1.43)	5.93 (1.70)	5.55 (1.27)	0.51	.604
Block Design	9.18 (3.26)[b]	8.53 (3.60)	9.79 (3.23)[e]	1.06	.351
Similarities	11.64 (3.70)[b]	12.46 (3.79)	11.52 (3.49)[e]	0.61	.545
Digit Span	8.25 (2.82)[b]	8.28 (2.21)	8.55 (2.94)[e]	0.11	.893
Picture Concepts	9.59 (3.86)[C]	10.90 (3.22)[d]	10.55 (3.49)[e]	0.05	.354
Coding	8.60 (2.50)[b]	8.59 (3.69)	8.52 (5.60)[e]	0.00	.996
Vocabulary	10.46 (4.04)[b]	11.87 (3.76)	11.27 (4.85)[e]	0.83	.439
Letter-Number Sequencing	8.40 (3.44)[c]	8.87 (3.22)[d]	9.93 (3.56)[e]	1.49	.232
Matrix Reasoning	7.81 (3.00)[c]	9.71 (3.93)[d]	9.38 (3.63)[e]	2.27	.110
Comprehension	8.93 (2.85)[c]	10.00 (3.72)	10.34 (3.73)[e]	1.26	.290
Symbol Search	9.59 (3.17)[c]	8.87 (2.65)[d]	9.03 (2.86)[e]	0.49	.618
Verbal Comprehension	102.37 (16.37)[c]	106.28 (21.68)	105.00 (16.32)	0.34	.715
Perceptual Reasoning	92.48 (14.94)[c]	95.23 (20.84)[d]	97.90 (17.46)	0.64	.529
Working Memory	89.89 (14.63)[c]	87.96 (18.11)[d]	93.00 (17.05)	0.70	.500
Processing Speed	96.11 (13.29)[c]	92.03 (19.99)[d]	90.50 (12.61)	0.95	.392
Full Scale IQ	96.43 (17.92)[b]	98.25 (18.27)	96.00 (16.51)	0.22	.803

Note. ADHD-I = attention deficit hyperactivity disorder, inattentive presentation; ADHD-H/I = ADHD hyperactive/impulsive presentation; ADHD-C = ADHD combined presentation.

[a] Score out of ten; data on academic performance was obtained for 26 children with ADHD-I, 28 children with ADHD-H/I, and 20 children with ADHD-C.

[b] ADHD-I sample for these variables was 28

[c] ADHD-I sample for these variables was 27

[d] ADHD-H/I sample for these variables was 31

[e] ADHD-C sample for these variables was 29

Objective sleep variables and academic achievement

The relationships found between the objective sleep variables and academic performance measures are summarized in Table 3. TIB accounted for 8.2% of the variance in Spanish. The arousal index had a 5.9% of predictive power of the children's scores in Mathematics. TST, REM sleep, and the arousal index predicted 18.6% of the children's qualifications in Natural Sciences. In relation to Social Sciences, stages 2, 4, and REM sleep, as well as the arousal index were the most relevant predictors, accounting for 17.3% of the children's scores. Bedtime, SPT, and stage 1 sleep, predicted 14.4% of Physical Education outcomes. TIB, SPT, sleep efficiency, wake time, stage 1 sleep, REM onset latency, and duration of sleep cycles accounted for 28.2% of the variance in Arts. Finally, 7.7% of the average qualifications obtained in English were explained by the arousal index; the most important predictive variable in academic achievement.

Subjective sleep variables and academic achievement

The PDSS scores explained a large part of the variance of academic achievement: 16.5% in Spanish, 25% in Mathematics, 7.1% in Natural Sciences, 11.8% in Social Sciences, 5.2% in Art, and 6.4% in English. In contrast, children's scores in the PSQ did not predict their academic achievement. These results are shown in Table 4.

Objective sleep variables and cognitive achievement

Objective sleep variables explained the variability in children's scores in almost all subtests, except for block design and symbol search, and all global indexes. Specifically, TST, stage 1 sleep, and the arousal index accounted for 15.6% of the variance in the similarities subtest. Concepts subtest was explained in 19.6% by TST, stage 1 sleep, and REM sleep. Regarding the coding subtest, TST, SOL and sleep

cyclyes duration explained 15.6% of the variance. Variability across scores of the vocabulary subtest was predicted by the arousal index and the number of short awakenings in 12.3%. TST, stage 1 sleep, and PLM index accounted for 15.5% of the variance in the letter-number sequencing subtest. Matrix reasoning was predicted by the REM onset latency and the number of sleep cycles in 7.8%. Finally, results in global indexes were statistically significant in WM (stage 1 sleep accounting for 4.6% of their variance) and FSIQ (stage 1 sleep, and number of awakenings predicting 16% of their variance). These results are provided in Table 5.

Subjective sleep variables and cognitive achievement

PSQ Sleepiness scores only predicted outcomes in similarities and coding subtests (respectively, $F[1,73] = 7.39$, $R^2 = .09$, $p < .01$, $\beta = -0.31$, $t = -2.72$ and $F[1,73] = 5.60$, $R^2 = .07$, $p < .01$, $\beta = 0.27$, $t = 2.37$). Both PSQ Snoring and PDSS scores did not explain any cognitive performance outcome.

Table 3

Regression Analyses of Objective Sleep Measures and Academic Achievement

	Spanish			Mathematics			Natural Sciences			Social Sciences		
	β	t	sig	β	t	sig	β	t	sig	β	t	sig
Time in bed	0.29	2.48	.015									
Total sleep time							0.33	2.85	.006			
Stage 2 sleep										-0.34	-2.27	.026
Stage 4 sleep										-0.28	-1.74	.087
REM sleep							-0.29	-2.48	.016	-0.27	-2.00	.049
Arousal (index)				-0.24	-2.08	.041	-0.20	-1.77	.081	-0.28	-2.43	.018
Total												
R^2	.082			.059			.186			.173		
F (gl)	6.17(1,70)			4.32(1,70)			5.11(3,70)			3.46 (4,70)		
p	**.015**			**.041**			**.003**			**.013**		

	Physical Education			Art			English (2nd language)		
	β	t	sig	β	t	sig	B	t	sig
Time in bed	1.01	3.11	.003	1.28	3.76	.000			
Sleep period time	-0.89	-2.69	.009	-1.30	-3.63	.001			
Sleep efficiency				0.803	3.06	.003			
Wake time				0.81	2.99	.004			
Stage 1 sleep	-0.35	-2.53	.014	-0.59	-4.05	.000			
REM latency				0.23	2.01	.048			
Arousal (index)							-2.77	-2.39	.019
Mean sleep cycle duration (min)				-2.61	-2.13	.037			
Total									
R^2	.144			.282			.077		
F (gl)	3.76(3,70)			3.54(7,70)			5.72(1,70)		
P	**.015**			**.003**			**.019**		

Note. REM = rapid eye movement.

Table 4

Regression Analyses of Subjective Sleep Measures and Academic Achievement

	Spanish			Mathematics			Natural Sciences			Social Sciences			Art			English		
	β	t	sig	β	t	sig	β	t	sig	β	t	sig	β	t	Sig	β	t	sig
PDSS Total	-0.41	-3.61	<.000	-0.50	-4.69	.000	-0.27	-2.26	.028	-0.34	-2.97	<.005	-0.23	-1.90	.062	-0.25	-2.13	.037
R^2	.165			.250			.071			.118			.052			.064		
F (gl)	13.01 (1,67)			21.97 (1,67)			5.07 (1,67)			8.85 (1,67)			3.61 (1,67)			4.53 (1,67)		
p	**<.000**			**.000**			**.028**			**<.000**			**.062**			**.037**		

Note. PDSS = pediatric daytime sleepiness scale.
*PSQ data were not included because no significant results were obtained for any model.
* no variable significantly predicted Physical Education scores ($p > .05$).

Table 5

Regression Analyses of Objective Sleep Measures and Cognitive Achievement (1st Part; Subtests)

	Similarities			Digit Span			Concepts			Coding		
	β	t	sig	β	t	sig	β	t	sig	β	t	sig
Total sleep time	0.22	2.15	.034				0.19	1.85	.067	0.23	2.16	.033
Sleep onset latency										0.30	2.92	.004
Stage 1 sleep	-0.25	-2.42	.018				-0.40	-3.89	.000			
REM							-0.20	-1.92	.059			
Arousal (index)	-0.24	-2.35	-.021									
Total awakenings (n)				-0.18	-1.72	.088						
Sleep cycle (dur)										-0.22	-2.08	.041
Total												
R^2	.156			.034			.196			.156		
F	5.04 (3,85)			2.97(1,85)			6.51 (3,83)			5.05 (3,85)		
p	**.003**			.088			**.001**			**.003**		

	Vocabulary			Letter-Number Sequencing			Matrix Reasoning			Comprehension		
	β	t	sig	β	t	sig	β	T	sig	β	t	sig
Total sleep time				0.19	1.88	.063						
Sleep efficiency										0.29	1.95	.054
Stage 1 sleep				-0.19	-1.84	.070						
REM latency							-0.28	-2.37	.020			
PLM index				-0.27	-2.61	.011						
Arousal (index)	-0.27	-2.64	.010									
Awakenings (mean durat)										0.31	2.06	.043
Short awakenings (n)	-0.25	-2.46	.016									
Sleep cycle (n)							-0.25	-2.06	.043			
Total												
R^2	.123			.155			.078			.055		
F	5.82(2,85)			4.90(3,83)			3.42(2, 83)			2.38(2,84)		
P	**.004**			**.004**			**.038**			.099		

Note. REM = rapid eye movement; PLM = periodic limb movements.

Table 5.

Regression Analyses of Objective Sleep Measures and Cognitive Achievement (2nd Part; Global Indexes)

	Perceptual Reasoning			Working Memory			Processing Speed			Verbal Comprehension			Full Scale IQ		
	β	t	sig	β	t	sig	β	t	sig	β	t	sig	β	t	sig
Stage 1 sleep				-0.21	-2.00	.049				0.18	-1.66	.100	-0.26	-2.47	.016
REM latency	-0.23	-1.92	.058												
Total awakenings (n)							-2.54	-2.15	.035				-2.67	-2.40	.019
Short awakenings (n)							2.22	2.11	.038				2.21	2.23	.028
Long awakenings (n)							0.65	1.91	.060				0.70	2.18	.032
Sleep cycle (n)	-0.25	-2.15	.034												
Total															
R^2	.066			.046			.056			.032			.160		
F	2.88(2,84)			4.00(1,84)			1.61(3,84)			2.77(1,85)			3.89(4,86)		
p	.062			**.049**			.193			.100			**.006**		

Note. REM = rapid eye movement.

Discussion

This study is, to the best of our knowledge, the first to analyse the influence of sleep parameters on academic achievement and cognitive performance in a large sample of children diagnosed with ADHD by using PSG and subjective sleep measures. The key findings are that objective and subjective sleep variables are predictors of academic achievement and cognitive performance in children with ADHD, balanced across disorder presentations.

Sleep and academic performance

Objective sleep variables. Previous research suggest a positive relationship between sleep efficiency and duration with cognitive and academic functioning in both children with ADHD, and in non-clinical samples of children (Gruber et al., 2011; Gruber et al., 2014; Moreau et al., 2013; see Wolfson & Carskadon, for a review, 2003). However, we could only partially validate this because we found that sleep time predicted performance in only three subjects and sleep efficiency in only one. Furthermore, SPT was negatively associated with academic achievement in two subjects and wake time was positively associated in one. Further research is needed in order to clarify this association between sleep/wake time and academic achievement in children with ADHD. With respect to REM sleep results and academic achievement, our findings could be in accordance with previous research that suggest an adverse impact of REM sleep in neurobehavioral functions in children with ADHD (Kirov et al., 2017; Prehn-Kristensen et al., 2013). However, they are at odds with findings from other studies that show that REM sleep could positively correlate, and REM latency negatively correlate, with cognitive performance in children with ADHD (O'Brien et al., 2003).

Other objective sleep markers involved in children's academic performance in our study were sleep fragmentation and arousal index; the latter sleep variable predicting the greatest number of school subjects. All of these sleep variables were negatively related to academic performance, which is consistent with the evidence available in this regard. Specifically, arousals are known to promote sleep fragmentation (see Halász, Terzano, Parrino, & Bódizs, 2004, for a review), and sleep disruption is associated with a wide range of cognitive and academic impairments (Lee et al., 2014; O'Brien et al., 2003, 2004). In conclusion, objective sleep variables predicted children's academic performance in all school subjects in our sample of children with ADHD, although the arousal index was the most important predictor variable.

Subjective sleep variables and academic achievement. Daytime sleepiness significantly predicted outcomes in almost all the school subjects. These results support those obtained in previous studies on ADHD (Langberg et al., 2013, 2014; Sadeh, Raviv, & Gruber, 2000). Interestingly, the only score that was not related to daytime sleepiness as reported by parents was Physical Education. According to the model of Baweja et al. (2015), cognitive abilities are not the only variables involved in school performance measured as grade point average. Our results tentatively indicate that the resources required to master particular school subjects are not the same, and that daytime sleepiness does not equally affect all components of school achievement in children with ADHD.

Sleep and cognitive performance

Objective sleep variables and cognitive performance. Cognitive performance in children with ADHD was predicted by several objective sleep variables. Indeed, the FSIQ score was predicted by the greatest number of objective sleep variables, which is

consistent with previous scientific literature (Um et al., 2016), revealing again the close association between sleep and cognitive characteristics in children with ADHD.

Time spent in stage 1 sleep and overall sleep time were two of the most relevant predictive variables. As it has been previously reported, children with ADHD spend more time in stage 1 sleep than control children (Díaz-Román et al., 2016) and in our sample it was observed that an increase in stage 1 sleep implied a reduction in cognitive performance. This sleep characteristic could thus lead to several cognitive problems in children with ADHD. Regarding sleep time, it has been previously reported that sleep restriction may lead to a deterioration of neurobehavioral functioning (Gruber et al., 2011; Um et al., 2017). In this respect, our results are more or less consistent with those reported by previous studies, in which a positive association between sleep time or sleep efficiency, and cognitive performance was revealed (Gruber et al., 2007; Moreau et al., 2013). Moreover, concerning sleep disruption, the arousals and other measures of sleep continuity and organization were also predictors of cognitive performance in our study, thus supporting the above-mentioned negative relationship between sleep fragmentation and cognitive abilities (Lee et al., 2014; O'Brien et al., 2003).

Nevertheless, despite the fact that the influence of sleep on cognitive performance is verified by research on this topic, some related aspects are still unclear. For example, we could not confirm either the relationship between SWS and memory function or provide new insights into the influence of stage 2 sleep on cognitive performance in children with ADHD, as our results were neither sufficient nor similar to be compared with previous studies (Um et al., 2016). Furthermore, the actual relationship between sleep arousals, sleep disruption, and cognitive function remains unclear. On the one hand, contrary to what was found in relation to academic

performance, the arousal index negatively predicted performance scores in only two cognitive subtests and lost its predictive value in the global indices and in FSIQ. On the other hand, there are findings suggesting that arousals could be a preservative mechanism of sleep, which could lead to an improvement of cognitive functions (Miano et al., 2011). Therefore, further research is needed to clarify the actual function of arousals and other sleep fragmentation variables, and their involvement in academic and cognitive performance among children with ADHD.

Subjective sleep variables and cognitive performance. Daytime sleepiness predicted cognitive performance scores in only two cognitive subtests, which supports previous results (Schneider et al., 2016). It is contrary to what Mayes (2008) observed among their participants, rejecting the conception that cognitive performance is not necessarily attributable to daytime sleepiness in children with ADHD. Based on our findings, it might be suggested that daytime sleepiness does affect academic and cognitive performance, though the latter to a lesser extent.

Limitations and strengths

The major strengths of our study were that every child was medication-free, to exclude the effects of medication in PSG assessment (see Konofal, Lecendreux, & Cortese, 2010, for a review), and underwent polysomnography at home. In addition, the ADHD presentations were balanced among participants, which is rarely presented in scientific literature because of the lower diagnosis rate of the ADHD-H/I presentation (see Willcut et al., 2012, for a review). However, this study also presents limitations to be noted and addressed in future works. First, the objective sleep assessment was carried out during a single night, so a first night of adaptation to polysomnography did not take place. Second, it would be appropriate to assess the children in a more

ecological environment (Areces, Dockrell, García, González-Castro, & Rodríguez, 2018), as a way of obtaining useful information about other components also involved in cognitive and academic achievement. Finally, the greatest predictive value of the arousal index and daytime sleepiness in terms of academic achievement than in terms of cognitive performance generates a line of research on whether sleep disruption and sleepiness differently affect academic and cognitive performance.

Conclusion

The findings of this study indicate that objective sleep patterns are predictive of academic achievement and cognitive performance in children with ADHD with IQ scores within the average range. Daytime sleepiness levels, as reported by parents, predicts academic achievement and, to a lesser extent, cognitive performance, whereas sleep-disordered breathing problems do not predict any academic or cognitive variable. Sleep time, stage 1 sleep, arousals, sleep continuity, and sleep organization could be important objective sleep markers for understanding academic and cognitive performance in children with ADHD. Overall, the current evidence suggests that the relationship between sleep, academic achievement, and cognitive performance in school-aged children with ADHD is complex and requires further attention in research.

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DISCUSIÓN GENERAL

La presente Tesis Doctoral tuvo como objetivo principal evaluar la relación entre el sueño y el rendimiento cognitivo y escolar de los niños con TDAH, teniendo en cuenta las diferentes presentaciones del trastorno (TDAH-I, TDAH-H/I, TDAH-C). Para ello, se realizaron cuatro estudios que perseguían objetivos específicos a través de los que se obtuvieron nuevas evidencias en el área. Todos los protocolos de estudio se diseñaron manteniendo el principio tradicional y categórico de psicopatología (basado en los manuales diagnósticos vigentes), entendiendo el TDAH como un trastorno y, por tanto, como un problema de salud pública.

En el Estudio 1 se incluyó una revisión exhaustiva de la literatura sobre el rendimiento cognitivo en los niños con TDAH en edad de escolarización. Posteriormente, los Estudios 2 y 3 estuvieron centrados en el análisis de las características del sueño de estos niños y, por último, el Estudio 4 se focalizó en el análisis de la relación existente entre las diferentes variables de sueño (calidad y estructura) y el rendimiento cognitivo y escolar de estos niños (ver Figura 3).

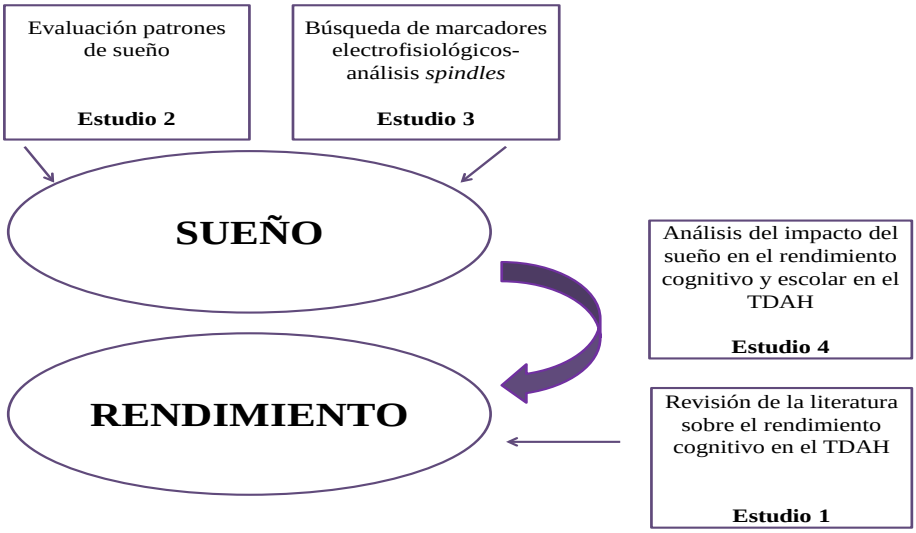

Figura 3. Resumen de los objetivos principales de la Tesis Doctoral y Estudios relacionados.

En el Estudio 1, se realizó un meta-análisis en el que se revisaron estudios observacionales, cuasi-experimentales y experimentales que cumplieran con unos criterios específicos. De este modo, se pretendía actualizar la literatura científica existente sobre el rendimiento cognitivo de estos niños en comparación con los niños sin el trastorno y, siempre que fuera posible, se realizó la diferenciación entre las presentaciones. Se evaluó el mayor número de áreas cognitivas hasta la fecha en esta población.

Si bien aún no se cuenta con un único modelo que pueda explicar la complejidad de las funciones cognitivas debido a su propia naturaleza dinámica (esto es, por su sometimiento a las demandas cambiantes del entorno), se tuvieron en cuenta algunas de las teorías cognitivas más relevantes en el estudio del TDAH: la teoría de las funciones ejecutivas de Barkley (1997), la teoría de las redes atencionales de Posner y Petersen (1990) y el modelo multicomponente de memoria de trabajo de Baddeley (1983). Teniendo en cuenta el concepto de diversidad funcional de la corteza frontal (afectada en el TDAH e implicada en muchas de las funciones evaluadas en el meta-análisis, véase Figura 1), se asumió la existencia de un procesamiento multimodal con componentes independientes, pero interconectados. Esto es, se entendió que existe una superposición entre áreas cognitivas evaluadas (v.gr. las FE y las funciones atencionales, ya que ambas implican procesos de control atencional que son dependientes de las regiones prefrontales), aunque estas se evaluaron por separado.

Según los resultados obtenidos, se confirmó un peor rendimiento en la mayoría de áreas evaluadas en estos niños en comparación con los niños sin el trastorno. Las áreas cognitivas que se constituían de mayor número de estudios fueron el índice general de inteligencia (dato habitualmente reportado en los estudios por su carácter

inclusivo/exclusivo de los participantes), la inhibición de respuesta y la memoria de trabajo, áreas consideradas 'centrales' en la cognición del TDAH desde el surgimiento de las teorías de Pennington y Ozonoff (1996) y Barkley (1997). Áreas como la categorización y la toma de decisiones contaron con un número reducido de estudios, por lo que los resultados fueron escasos y, por tanto, poco concluyentes.

Con respecto a la diferenciación de las presentaciones, la mayoría de estudios del meta-análisis incluían lo que se puede denominar como presentación combinada o no especificada. Como quedó expuesto en la introducción (véase sección *TDAH: diagnóstico y bases neurobiológicas*), la diferenciación diagnóstica entre las presentaciones de TDAH es relativamente reciente. Este término se comenzó a utilizar con la publicación del DSM 5 en 2013, como evolución del término 'subtipo' del DSM-IV (APA, 1994) y su versión revisada DSM-IV-TR (APA, 2002). Sin embargo, desde la publicación del DSM-III (APA, 1980), ya se reconocía que el TDAH ocurría en dos tipos: 'con y sin hiperactividad'. Es por esto que, a pesar de haber sido denominados como 'no especificados o mixtos', y en ausencia otras indicaciones concretas en el estudio (v.gr. Chee, Logan, Schachar, Lindsay y Wachsmuth, en 1989 especificaban que los niños eran hiperactivos), se sugiere que muchos de los estudios incluidos podrían referirse a 'presentación combinada' por el año de publicación y el manual de diagnóstico vigente.

Los resultados reflejaron un perfil cognitivo diferenciado entre TDAH-C y TDAH-I en algunas áreas cognitivas, aunque deberían interpretarse con precaución, ya que el porcentaje de estudios que incluyó la diferenciación entre presentaciones de TDAH fue muy bajo. De hecho, no se pudo confirmar ningún perfil específico del TDAH-H/I debido a la escasez de estudios que aportaran esta separación. Solo ocho

estudios de los 116 incluidos en el meta-análisis reportaron de manera explícita esta presentación (de los cuales cuatro utilizaban como referencia diagnóstica el DSM-IV, tres el DSM-IV-TR y uno el DSM-II). Esta escasez de estudios que reporten la presentación TDAH-H/I ya había sido destacada en el meta-análisis previo (Willcutt et al., 2005), en el que solo se incluyeron tres que cumplieran esta característica (Bedard et al., 2003; Chhabildas, Pennington y Willcutt, 2001; Schmitz et al., 2002). Por otro lado, el rango de edad seleccionado fue el criterio que excluyó el mayor número de estudios del meta-análisis. Con una ampliación del rango de edad de los niños, se habrían incluido más estudios que aportaran no solo diferenciación entre presentaciones, sino información relevante sobre rendimiento cognitivo.

La revisión de la literatura realizada sugiere la necesidad de analizar la cognición de los niños con TDAH y de los factores que influyen sobre la misma diferenciando las presentaciones de manera separada. Además, esto podría representar un punto de partida para una mejor comprensión de las características diferenciales entre perfiles.

A este respecto, los Estudios 2 y 3 de esta Tesis Doctoral se orientaron al análisis del sueño desde diferentes perspectivas de análisis (v.gr. medidas subjetivas y medidas objetivas) y en diferentes niveles (v.gr. conductual y fisiológico). Como ya se ha mencionado, uno de los pilares de esta disertación fue el interés por conocer indicadores fisiológicos del TDAH innovadores y fiables (véase la Figura 3).

Para ello, el Estudio 2 se centró en la descripción de los patrones de sueño de 92 niños con TDAH en edad de escolarización. Este incluyó medidas objetivas y medidas subjetivas de evaluación, a través de las cuales se analizó la cantidad, calidad y fragmentación del mismo. En los resultados (no afectados por la medicación), se

observó que el tiempo de sueño de los niños fue adecuado según las recomendaciones de la Fundación Nacional de Sueño (Hirshkowitz et al., 2015). Además, los niños tuvieron buena eficiencia, ya que en todos los casos esta fue superior al 90%. Si bien el sueño sufre cambios en cantidad y calidad a lo largo de la vida en población general (Ohayon, Carskadon, Guilleminault y Vitiello, 2004), también lo hace en los niños con TDAH. Así lo indicaron los resultados obtenidos mediante las correlaciones; habiendo una reducción en el SOL y un aumento de la fragmentación de sueño con la edad, lo que apoya resultados previos (Moraes et al., 2014; Redline et al., 2004). Por el contrario, aunque o se pudo confirmar la consistencia entre padres y madres a la hora de evaluar subjetivamente el sueño de sus hijos (Becker, Isaacson, Servera, Sáez y Burns, 2017), se observaron problemas de sueño en casi el 13% de la muestra.

Aunque recientemente se ha indicado una cierta consistencia entre padres y madres a la hora de evaluar el sueño de sus la discrepancia existente entre medidas objetivas y subjetivas de sueño ya se había reportado previamente (Corkum, Tannock y Moldofsky, 1998; Hvolby, Jørgensen y Bilenberg 2008; ver revisión de Owens, 2005a), habiendo varias teorías especulativas que han tratado de explicarla (ver Owens, 2009, para una revisión). Por ejemplo, se ha sugerido que las familias de estos niños puedan ser más propensas a percibir y reportar mayores niveles de conductas problemáticas (tanto diurnas como relacionadas con el sueño). Además, tanto las familias como los médicos podrían estar más atentos de cara a la obtención de evidencia de problemas de sueño, basándose en la percepción de que éstos están comúnmente presentes y asociados con el tratamiento farmacológico. Por tanto, las cuestiones metodológicas podrían estar a la base de algunas de las discrepancias entre los hallazgos subjetivos y objetivos del sueño.

Con respecto a la diferenciación entre las presentaciones de TDAH, no hubo resultados significativos en las variables objetivas y subjetivas de sueño, lo que concuerda con lo observado en los estudios previos (Virring et al., 2016; Wiggs et al., 2005). A este respecto, en algunos estudios se ha indicado una relación entre la gravedad de la sintomatología del TDAH y los trastornos de sueño (Hysing, Lundervold, Posserud y Sivertsen, 2016; Vélez-Galarraga, Guillén-Grima, Crespo-Eguílaz y Sánchez-Carpintero, 2016). De hecho, los datos sobre la fragmentación, no siendo estadísticamente significativos, sugirieron una peor continuidad para el grupo de TDAH-H/I, lo que coincide con literatura científica a este respecto (Chiang et al., 2010; Mayes et al., 2009; Wagner y Schlarb, 2012). Sin embargo, las puntuaciones sobre la severidad de los síntomas de TDAH no revelaron diferencias entre las presentaciones. De este modo, podría especularse que esta falta de diferencias en las variables de sueño pudiera deberse a un equilibrio en la severidad sintomática o incluso solapamiento de síntomas entre los grupos (i.e. siendo posible tener hasta cinco síntomas hiperactivos-impulsivos y aun así mostrar una presentación TDAH-I y tener más de seis síntomas de inatención tanto en las presentaciones TDAH-I como TDAH-C).

Una vez que se observó una falta de diferencias en la arquitectura y calidad de sueño entre los grupos, realizó el Estudio 3 para llevar a cabo la exploración de *biomarcadores*. Así, se analizó una huella electrofisiológica específica del sueño: los *spindles*. Este análisis supuso un abordaje general en la investigación fenotípica del TDAH desde el sueño, siendo la primera caracterización de estos eventos en términos de número, densidad, duración, amplitud e intensidad (duración multiplicada por amplitud) diferenciando entre presentaciones. Se filtraron las señales de EEG de 74 de los registros de sueño y se detectaron los *spindles* para la derivación frontal (Fz) y

central (Cz) del cerebro (aquellas que aportan información relevante sobre el desarrollo madurativo del cerebro en la infancia).

A la luz de los resultados obtenidos, los *spindles* de los niños con TDAH siguieron una topografía similar a la de los niños sin TDAH (ver revisiones de Clawson et al., 2016, De Gennaro y Ferrara, 2003, Gorgoni, Scarpelli, Reda y De Gennaro, 2020; Gruber y Wise, 2016). Fueron predominantes en N2 y hubo un incremento de *spindles* lentos en Fz. Además, se observó una mayor duración y amplitud de los *spindles* lentos en comparación a los rápidos. A este respecto, los resultados podrían ser comparables a los reportados por Merikanto et al., (2019), ya que en su estudio con adolescentes indicaron que una mayor sintomatología del TDAH se asocia con una actividad más débil de los *spindles* rápidos. De este modo, se podría sugerir que el TDAH está relacionado con un incremento en *spindles* lentos (y una reducción de los rápidos) tanto en la infancia como en la adolescencia. Sin embargo, la ausencia de un grupo control de referencia limita la inferencia de conclusiones a este respecto.

De manera similar a lo ocurrido en el Estudio 2, no se observaron diferencias entre las presentaciones de TDAH en ninguno de los parámetros evaluados. Estos resultados difieren de estudios previos que, evaluando la señal diurna, han propuesto un patrón EEG diferente entre las presentaciones de TDAH (Aldemir et al., 2018; González-Castro, Rodríguez, López, Cueli y Álvarez, 2013). Además, estos resultados (y aquellos obtenidos en el Estudio 2) no permiten apoyar las conclusiones de aquellos estudios que sugieren la existencia de diferencias cerebrales en las presentaciones de TDAH (v.gr. Qian et al., 2019). No obstante, los resultados obtenidos al respecto de la edad arrojaron datos susceptibles de debate.

En el desarrollo típico, la sinaptogénesis, la apoptosis y la mielinización (cruciales en la formación de circuitos neurales funcionales), continúan desde la infancia hasta la adolescencia (Cao et al., 2014; Tau y Peterson, 2010). Los *spindles*, que al igual que la arquitectura de sueño, cambian de forma y función a lo largo la vida, alcanzarían en la adolescencia su frecuencia y densidad máxima, mostrando también una menor duración y amplitud (por los procesos de poda sináptica y mielinización), representando redes cerebrales más eficientes (Clawson et al., 2016; Goldstone et al., 2019; Hoedlmoser et al., 2014; Shinomiya et al., 1999). A este respecto, diversas observaciones indican que la aparición del TDAH y su persistencia en la edad adulta, son el resultado de una mielinización no regulada y un déficit de sinaptogénesis que se refleja en menores volúmenes cerebrales (Demontis et al., 2019; Lesch, 2019; Valera et al., 2007). En base a esta literatura científica y a los resultados obtenidos en el Estudio 2 (donde se confirmaron cambios en la arquitectura de sueño con la edad) se esperaban observar resultados similares en los *spindles* de los niños con TDAH. Además, en este caso, se especuló que fuera el grupo TDAH-C aquel que mostrara un desarrollo más lento traducido en una mayor intensidad de los *spindles*.

Según los resultados obtenidos se observó que, ciertamente, los *spindles* cambian con la edad también en los niños con TDAH. Hubo incrementos en la frecuencia y en la densidad de los *spindles* rápidos (principalmente impulsados por el grupo TDAH-C). Además, se observó una reducción de la intensidad de los *spindles* en el grupo TDAH-C con la edad. El aumento en la frecuencia de los de los *spindles*, así como la densidad de los *spindles* rápidos fue similar a los datos reportados por Hahn et al., (2017) en niños y adolescentes con desarrollo típico. En su estudio longitudinal, mostraron que, en la infancia (8-11 años), los *spindles* lentos predominan tanto en la

zona frontal como central (similar a lo observado en el presente Estudio), mientras que la densidad de los *spindles* rápidos aumenta drásticamente (desde niveles muy bajos) en la adolescencia (14-18 años) sobre todo en la zona central (con la consecuente reducción de los *spindles* lentos). Al respecto de la intensidad, los resultados confirmaron también las propuestas previas sobre la reducción de la duración y amplitud de los *spindles* desde la infancia hasta la adolescencia en población sin TDAH (Clawson et al., 2016; Goldstone et al., 2019; Hoedlmoser et al., 2014; Shinomiya et al., 1999). Además, es interesante volver a apelar a la investigación realizada por Merikanto et al., (2019), ya que sus resultados reflejaron que una mayor sintomatología de TDAH se asocia con una menor amplitud y duración de los *spindles* rápidos. En el presente Estudio, a medida que el grupo TDAH-C aumentaba en edad, la intensidad de los *spindles* disminuía. Sin embargo, asumiendo que la reducción de la duración y amplitud de los *spindles* en el desarrollo refleja la maduración de circuitos, los datos del presente Estudio y del de Merikanto et al., (2019), podrían resultar contradictorios. Esta discrepancia partiría de la hipótesis del retraso en la maduración del TDAH; esto es, entendiendo que el TDAH implica un retraso en el desarrollo cerebral (ver revisión de Castellanos y Aoki, 2016). En este caso, por tanto, lo esperable era que el grupo TDAH-C (i.e. el grupo más afectado por la sintomatología), mostrara un desarrollo más lento. Este grupo sería aquel que mostraría los efectos menos prominentes en las asociaciones con la edad (habiendo una mayor frecuencia y densidad de los *spindles*, así como una reducción de la duración y amplitud en los grupos TDAH-I y TDAH-H/I). Según los resultados se podría especular que el grupo TDAH-C mostrara spindles *prematuros*. Además, se podría sugerir que las diferentes presentaciones de TDAH, aun no mostrando diferencias en la arquitectura de sueño o en las características de los *spindles*,

pudieran mostrar diferentes procesos de maduración cerebral (i.e. de aquellas estructuras implicadas en la generación de los *spindles*).

Por un lado se podría concluir que los *spindles* sirven como marcador biológico para el desarrollo del TDAH, aunque aún quedan por dilucidar los patrones de maduración cerebral diferenciales entre las presentaciones. Por el contrario, es posible que también, como parafrasea Pérez-Álvarez (2018), «la heterogeneidad clínica, etiológica y neuropsicológica del trastorno probablemente desvanece la fiabilidad de posibles biomarcadores (Lenartowicz et al., 2018, pág. 25)». Estudios longitudinales podrían clarificar este asunto, abarcando mayores rangos de edad y comparando los resultados con un grupo control con desarrollo típico.

Por último, el Estudio 4 se realizó para responder al principal objetivo de esta disertación: la influencia de los parámetros de sueño en el rendimiento cognitivo y escolar en los niños con TDAH. Debido a la falta de diferencias entre los grupos en las variables de sueño y rendimiento cognitivo y escolar, los análisis se llevaron a cabo fusionando los datos (de arquitectura y calidad de sueño) de los tres grupos. Los resultados indicaron que los parámetros de sueño evaluados mediante PSG y la somnolencia diurna reportada por los padres, predicen el rendimiento académico y cognitivo de los niños con TDAH.

En cuanto a los parámetros objetivos de sueño, los resultados sobre el tiempo y eficiencia, reflejaron ciertas contradicciones. Se esperaba observar una predicción positiva de estas las variables, ya que se partió de la literatura científica que ha indicado asociaciones positivas entre la cantidad y calidad de sueño, y el rendimiento académico y neurocomportamental (Gruber et al., 2011; Gruber et al., 2014; Moreau et al., 2013; Um, Hong y Jeong, 2017). Sin embargo, en este caso, el tiempo de sueño se relacionó

con el rendimiento solo en tres asignaturas (de manera positiva con Naturales y negativa con Educación Física y Artes Plásticas) y la eficiencia de sueño solo con una (Artes Plásticas). En el rendimiento cognitivo, en cambio, el tiempo y la eficiencia de sueño no explicaron los índices globales, aunque en los subíndices sobre los que predijeron un efecto, este fue en todo caso positivo. De este modo, solo se pueden apoyar de manera parcial las conclusiones de estos estudios y aún queda por desentrañar el papel específico que el tiempo y la eficiencia de sueño ejercen en el rendimiento académico y cognitivo de estos niños.

Con respecto al sueño MOR, los resultados obtenidos podrían apoyar los estudios en los que se sugiere que este ejerce un impacto negativo en las funciones neuroconductuales de los niños con TDAH (Kirov et al., 2017; Prehn-Kristensen et al., 2013). De manera similar a lo que ocurre con los *spindles*, el sueño MOR cumple un papel importante en permitir la plasticidad neuronal y el aumento de la conectividad sináptica (Grosmark, Mizuseki, Pastalkova, Diba y Buzsaki, 2012; Ribeiro et al., 2002). De hecho, se ha propuesto que el decremento del sueño MOR desde la infancia hasta la adolescencia ayuda a la maduración cerebral a través de la reorganización sináptica y/o la poda (Jouvet, 1998; Marks, Shaffery, Oksenberg, Speciale y Roffwarg, 1995). A este respecto, una reducción insuficiente o desviaciones en la reducción normal durante el desarrollo, podría sustentar un amplio espectro de trastornos en niños y adolescentes, entre ellos el TDAH (Kirov, Kinkelbur, Banaschewski y Rothenberger, 2007). Efectivamente, se ha indicado que los niños con TDAH pasan más tiempo en esta fase de sueño que los niños sin el trastorno (Prehn-Kirstensen et al., 2011), y, además, la proporción de sueño MOR se ha correlacionado positivamente con la falta de atención y negativamente con el CI (Kirov, Uebel, Albrecht, Banaschewski y Rothenberger, 2011).

Por tantolo esperable habría sido observar (en el Estudio 2) no solo cambios en el sueño MOR con la edad de los niños con TDAH, sino también diferentes patrones de maduración según la presentación. En este caso, es posible que incluso esa falta de cambios observada con la edad, pudiera estar a la base del impacto negativo que ejerció en el rendimiento académico (y un subíndice de rendimiento cognitivo). No obstante, se necesitará más investigación que permita desentrañar no solo el desarrollo del sueño MOR en la infancia de los niños con TDAH, sino el impacto que ejerce sobre diferentes áreas del rendimiento y en las diferentes presentaciones.

Por su parte, el papel de los *arousals* del sueño (cambios rápidos en la frecuencia EEG de 3 o más segundos y precedidos por un mínimo de 10 segundos continuos de sueño) es de gran interés tanto entre los investigadores básicos como entre los profesionales clínicos. En las dos últimas décadas, se han obtenido pruebas que demuestran que están implicados en la fisiopatología de los trastornos del sueño, aunque su naturaleza es todavía un tema de debate. Por un lado, de acuerdo con el marco conceptual de los criterios de la Asociación Americana de Trastornos del Sueño (American Sleep Disorders Association, 1992), los *arousals* son un marcador de la alteración de sueño. Por el contrario, más recientemente se ha indicado que los *arousals* desempeñan un papel protector del sueño y participan en la regulación de este (ver revisión de Halász, Terzano, Parrino y Bódizs, 2004). En relación al rendimiento académico y cognitivo de este estudio, los *arousals* predijeron un peor rendimiento en más de la mitad de las asignaturas, aunque solo lo hicieron con un subíndice cognitivo. Es decir, los *arousals* predijeron más el rendimiento académico que el cognitivo. A este respecto, los resultados, aunque inconsistentes en su relación a las diferentes áreas del rendimiento, apoyan la asunción de que los *arousals* promueven la fragmentación del

sueño y también que esto se asocia con una amplia gama de deficiencias cognitivas y académicas (Lee et al., 2014; O'Brien et al., 2003, 2004). Al respecto de la variable específica de fragmentación de sueño, solo predijo (de manera negativa) las puntuaciones en Artes Plásticas, aunque también lo hizo con las puntuaciones de varios subíndices de rendimiento cognitivo y las puntuaciones del CI total. Es decir, la fragmentación de sueño predijo más el rendimiento cognitivo que el académico. En conclusión, la fragmentación del sueño (incluidos los arousals), se asocian con un peor rendimiento académico y cognitivo en los niños con TDAH. Sin embargo, aún queda por aclarar cuál es el papel específico que desempeñan los *arousals* y cómo estos afectan a la fragmentación de sueño, ya que resulta contradictorio que, si se asume que ambas variables promueven la fragmentación, lo hicieran en modo diverso para las diferentes áreas de rendimiento.

Por su parte, la fase 1 del sueño predijo una peor puntuación en dos asignaturas y varios subíndices de rendimiento cognitivo. Aun así, lo que resulta más interesante es que predijo un peor rendimiento en la memoria de trabajo (una de las áreas más afectadas en el TDAH; Barkley, 1997, Castellanos y Tannock, 2002) y en el CI total. A este respecto, recientemente se ha publicado un meta-análisis en el que se ha indicado que los niños con TDAH se caracterizan por tener una mayor cantidad de fase 1 (lo que implica que estos niños tienen un sueño más ligero en comparación con los niños sin TDAH). Además, esta fue señalada como la única diferencia entre ellos y los niños no diagnosticados con TDAH (Díaz-Román et al., 2016). Estos resultados podrían sugerir que, ciertamente, uno de los indicadores del peor desempeño diurno de los niños con TDAH fuera el sueño más ligero.

Al respecto del SOL, ocurre de nuevo como con los *spindles* y el sueño MOR; cambia durante el desarrollo, disminuyendo desde la infancia a la edad adulta (Ohayon et al., 2004). Además, este cumple una función importante en la consolidación de la memoria (ver revisión de Gais y Born, 2004) y se ha propuesto que los niños se benefician más del sueño que los adultos con respecto a la memoria dependiente del hipocampo debido al aumento SOL (Wilhelm, Prehn-Kristensen y Born, 2012). En los niños con TDAH, se ha reportado una asociación positiva entre el SOL y la memoria (Um et al., 2016), aunque un estudio sugirió que los niños y adolescentes con TDAH (10-16 años) no se benefician del SOL en la misma medida que lo hacen los niños sin TDAH (i.e. que el SOL tiene una funcionalidad menor en las funciones de memoria dependiente del sueño, Prehn-Kristensen et al., 2011). En el Estudio 2 se reportó que, efectivamente, hay reducciones en el SOL con la edad de los niños, aunque en el Estudio 4 no se pudo confirmar ninguna asociación con el rendimiento cognitivo de estos niños.

Del mismo modo, tampoco se pudo aportar información sobre la influencia de N2 en el rendimiento en los niños con TDAH. A este respecto, en las correlaciones del Estudio 3 entre los *spindles* y el CI, tampoco se observaron asociaciones significativas en ninguna variable, lo que apoya los resultados obtenidos en los estudios previos sobre la actividad sigma/spindles y el rendimiento cognitivo (Prehn-Kristensen et al., 2011, 2013). Sin embargo, será necesario realizar análisis que contemplen la influencia de los *spindles* en todas las áreas del rendimiento cognitivo y académico de los niños con TDAH para conocer el rol específico que desempeñan.

Por último, en cuanto a las medidas subjetivas de sueño, la somnolencia diurna (que ya se había asociado al TDAH; ver revisiones de Cortese et al., 2009; Díaz-Román

et al., 2016) predijo el rendimiento académico y, en menor medida, el rendimiento cognitivo. Debido a los resultados obtenidos en el Estudio 2, no se pudo confirmar que la somnolencia diurna se asocie más con el grupo TDAH-I (Chiang et al., 2010; LeBourgeois et al., 2004; Lecendreux et al., 2000; Mayes et al., 2009), aunque en el Estudio 4 sí se pudo apoyar la asunción de que esta ejerce un rol en el desempeño del TDAH en la infancia, lo que (en muestras de adolescentes y estudiantes universitarios), ya había sido reportado (Langberg et al., 2013, 2014). Estos resultados habrá que interpretarlos con cautela, puesto que la medida de somnolencia diurna extraída del cuestionario evalúa la presencia (pero no la gravedad) de la variable.

Como conclusión, una mayor cantidad de sueño MOR y de sueño ligero, así como la fragmentación de sueño indicaron un peor rendimiento diurno en los niños con TDAH. Todavía queda por dilucidar el papel que juegan otras variables como el tiempo y la eficiencia de sueño, así como el SOL y N2 en el desempeño cognitivo y académico de estos niños. Parece que esta relación podría depender de la manera en que se mida el funcionamiento académico y cognitivo, ya que las pruebas de rendimiento cognitivo (teniendo en cuenta los índices generales) posiblemente sean sensibles a la influencia de menos variables de sueño.

Aportaciones de la presente tesis doctoral

A lo largo de la disertación se han abordado diversas cuestiones con implicación para la práctica clínica y la investigación en estos niños. Se ha realizado una actualización de la literatura sobre el rendimiento cognitivo en los niños con TDAH diferenciando (siempre que fuera posible) entre las presentaciones. Además, se ha

aportado el mayor estudio comparativo hasta la fecha de la arquitectura y calidad de sueño en estos niños, teniendo en cuenta tanto medidas objetivas como subjetivas de evaluación y diferenciando entre las presentaciones. Por vez primera, se han analizado las características de unos eventos específicos del sueño en la señal eléctrica del cerebro de estos niños (los *spindles*). En cuanto al rendimiento cognitivo y escolar, se han aportado datos comparativos entre los grupos y se ha analizado la influencia que tienen las características del sueño en dicho rendimiento.

En cuanto al primer Estudio, la interpretación del meta-análisis fue complicada debido a dos aspectos principales. Por un lado, la distribución de las presentaciones entre los participantes fue desigual, por lo que no se pueden generalizar los resultados ni obtener conclusiones convincentes. Por otro, el hecho de que muchas tareas cognitivas implican múltiples procesos neurocognitivos. De este modo, es difícil estar seguro de que el peor rendimiento en una tarea se deba realmente a una debilidad en el constructo para el cual la tarea es nombrada. En futuros estudios se deberían delimitar las tres presentaciones de TDAH a la hora de aportar datos sobre el rendimiento de los niños. Además, para la evaluación cognitiva sería importante desarrollar tareas que puedan aislar mejor los parámetros de interés. Esto puede lograrse a través de un cuidadoso análisis de tareas o mediante el desarrollo de controles apropiados dentro de la tarea y entre tareas.

Con respecto al Estudio 2, se aportaron indicadores fisiológicos del TDAH en la infancia y se pudo comprobar no solo que estos cumplen con la cantidad y calidad objetiva de sueño adecuada, sino que no existen diferencias en la arquitectura y calidad de sueño entre las tres presentaciones. Cabe destacar el uso de medidas tanto objetivas como subjetivas de sueño y la diferenciación entre presentaciones. Sin embargo, la

principal limitación reside en la evaluación objetiva del sueño en una sola noche. Es posible que algunas diferencias entre las presentaciones del TDAH puedieran no haber sido capturadas por una sola grabación.

En relación al Estudio 3, se realizó el primer análisis sobre las características de los *spindles* en niños con TDAH diferenciando entre las presentaciones. Gracias a este estudio se pudo confirmar que no existen diferencias entre presentaciones de TDAH tampoco en las características de los *spindles*, aunque los resultados referentes a las correlaciones con edad y CI arrojaron ciertas inconsistencias que deberán ser resueltas en estudios longitudinales. Estos estudios podrían abarcar mayores rangos de edad, evaluar más áreas del rendimiento cognitivo y comparar los resultados con un grupo control con desarrollo típico.

Por último, a través de los resultados obtenidos en el Estudio 4, se pudo confirmar que los *arousals* promueven la fragmentación del sueño, que el sueño MOR ejerce un impacto negativo en las funciones neuroconductuales de los niños con TDAH y que la fase 1 del sueño influye de manera negativa en la memoria de trabajo y el CI total de estos niños. Sin embargo, aún queda por dilucidar el papel que juegan otras variables como el tiempo y la eficiencia de sueño, así como el SOL y N2 en el desempeño cognitivo y académico de estos niños. Como propuestas futuras, de nuevo se propone evaluar el sueño de manera longitudinal y tener en cuenta las diferentes maneras de evaluación del rendimiento cognitivo y escolar.

La presente Tesis Doctoral se encuentra limitada a la hora de aportar conclusiones relevantes al debate actual sobre la existencia o no del TDAH, ya que no hubo ninguna comparación con un grupo control. Sin embargo, los datos objetivos que han mostrado una falta de diferencias entre presentaciones en las variables de sueño, así

como en los datos sobre rendimiento cognitivo y escolar, promueven la idea del posible diagnóstico erróneo o el solapamiento de sintomatología entre presentaciones. Esto es, no se pudo confirmar un perfil cognitivo, académico y fisiológico diferente según la sintomatología de TDAH.

En resumen, a la luz de los resultados obtenidos en los Estudios que componen la presente Tesis Doctoral, se puede destacar que se trata de un trabajo novedoso en tanto que ha contribuido a la literatura científica aportando información relevante sobre el rendimiento cognitivo en el TDAH. Además, se han proporcionado datos sobre el sueño en las diferentes presentaciones y se ha aportado el primer estudio sobre la influencia del sueño en el rendimiento cognitivo y escolar de estos niños. Se ha demostrado que el sueño es un mediador importante en el rendimiento cognitivo y debe tenerse en cuenta a la hora de comprender las deficiencias cognitivas en uno de los trastornos más diagnosticados en la infancia y la adolescencia.

CONCLUSIONES

Conclusiones

1. Los niños con TDAH muestran un peor rendimiento cognitivo que los niños sin TDAH.
2. Los niños con TDAH-C muestran déficits cognitivos en un mayor número de áreas que los niños de las otras dos presentaciones.
3. La literatura científica sobre rendimiento cognitivo en niños con TDAH que reporta la diferenciación entre presentaciones es escasa.
4. No existen diferencias en arquitectura y calidad de de sueño entre las presentaciones de TDAH.
5. No existen diferencias en cómo las familias de los niños con TDAH perciben el sueño de estos niños según la presentación.
6. Los niños con TDAH pueden experimentar problemas respiratorios durante el sueño y somnolencia diurna según lo informado por sus padres, aunque estos resultados no concuerdan con los datos objetivos.
7. La arquitectura de sueño en los niños con TDAH evoluciona con la edad, habiendo una relación inversa con el SOL y un aumento de despertares.
8. La topografía de los *spindles* en los niños con TDAH sigue la misma organización que la de los niños sin TDAH.
9. No existen diferencias en las características de los *spindles* de sueño entre las presentaciones de TDAH.
10. Los *spindles* evolucionan con la edad en los niños con TDAH y esta asociación es impulsada principalmente por el grupo TDAH-C.
11. No hay asociaciones entre las características de los *spindles* y la puntuación total del CI en los niños con TDAH.

12. No existen diferencias en rendimiento cognitivo y escolar entre las presentaciones de TDAH.
13. Los parámetros del sueño están estrechamente asociados con el funcionamiento académico y cognitivo de los niños con TDAH.
14. Las medidas objetivas y subjetivas de sueño aportan información inconsistente sobre el impacto que este ejerce sobre el rendimiento cognitivo y escolar.

CONCLUSIONS

Conclusions

1. Children with ADHD show worse cognitive performance than children without ADHD.
2. Children with ADHD-C show cognitive deficits in a greater number of areas than children in the other two presentations.
3. The scientific literature on cognitive performance in children with ADHD that reports the differentiation between presentations is scarce.
4. There are no differences in architecture and quality of sleep among ADHD presentations.
5. There are no differences in the way families of children with ADHD perceive the sleep of these children according to the presentation.
6. Children with ADHD may experience sleep breathing problems and daytime sleepiness, as reported by their parents, although these results are not consistent with objective data.
7. The sleep architecture evolves with age in children with ADHD, with an inverse relationship with the SWS and an increase in awakenings.
8. The topography of spindles in children with ADHD follows the same organization as that of children without ADHD.
9. There are no differences in the characteristics of sleep spindles among ADHD presentations.
10. Spindles evolve with age in children with ADHD and this association is mainly driven by the ADHD-C presentation.
11. There are no associations between the spindle’s characteristics and the total IQ score in children with ADHD.

12. There are no differences in cognitive and school performance between ADHD presentations.
13. Sleep parameters are closely associated with academic and cognitive functioning in children with ADHD.
14. Objective and subjective measures of sleep provide inconsistent information about the impact of sleep on cognitive and school performance.

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APÉNDICE

Apéndice 1.

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ORIGINAL ARTICLE

Sleep among presentations of Attention-Deficit/Hyperactivity Disorder: Analysis of objective and subjective measures

Noelia Ruiz-Herrera[a,*], Alejandro Guillén-Riquelme[b], Amparo Díaz-Román[a], Nicola Cellini[c], Gualberto Buela-Casal[a]

[a] *Laboratorio del Sueño y Promoción de la Salud; Centro de Investigación, Mente, Cerebro y Comportamiento (CIMCYC), Universidad de Granada, España*
[b] *Cátedra de Investigación del Sueño Universidad de Granada y Grupo LaMonaco, España*
[c] *Departamento de Psicología General, Universidad de Padua, Italia*

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Abstract
Background/ Objective: To examine subjective and objective sleep patterns in children with different Attention-Deficit/Hyperactivity Disorder (ADHD) presentations. Method: We assessed 92 children diagnosed with ADHD (29 ADHD-Inattentive [ADHD-I], 31 ADHD-Hyperactive/Impulsive [ADHD-H/I], and 32 ADHD-Combined [ADHD-C]) aged 7–11 years. The Pediatric Sleep Questionnaire (PSQ), Pediatric Daytime Sleepiness Scale (PDSS), and a sleep diary were used as subjective sleep measures, and polysomnography was used to objectively assess sleep quantity, quality, and fragmentation. Results: Subjective data showed impaired sleep in 12.7% of the sample. No significant differences were found between ADHD presentations in any objective and subjective sleep variable. Nevertheless, data on sleep fragmentation suggested a worse sleep continuity for the ADHD-H/I group, and correlation analyses confirmed that sleep is affected by age. Conclusions: Children with ADHD may suffer from sleep breathing problems and daytime sleepiness, as reported by their parents, even when their total sleep time and sleep efficiency are not affected. It seems that sleep in this population does not largely vary as a function of the ADHD presentation. Sleep in children with ADHD evolves with age.

* Corresponding author at: Sleep and Health Promotion Laboratory, Mind, Brain, and Behavior Research Center (CIMCYC), University of Granada, 18011 Granada, Spain.
E-mail address: noeliarh@ugr.es (N. Ruiz-Herrera).

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