UNIVERSITAT DE BARCELONA

Brain functional correlates of theory of mind in neurodevelopmental disorders

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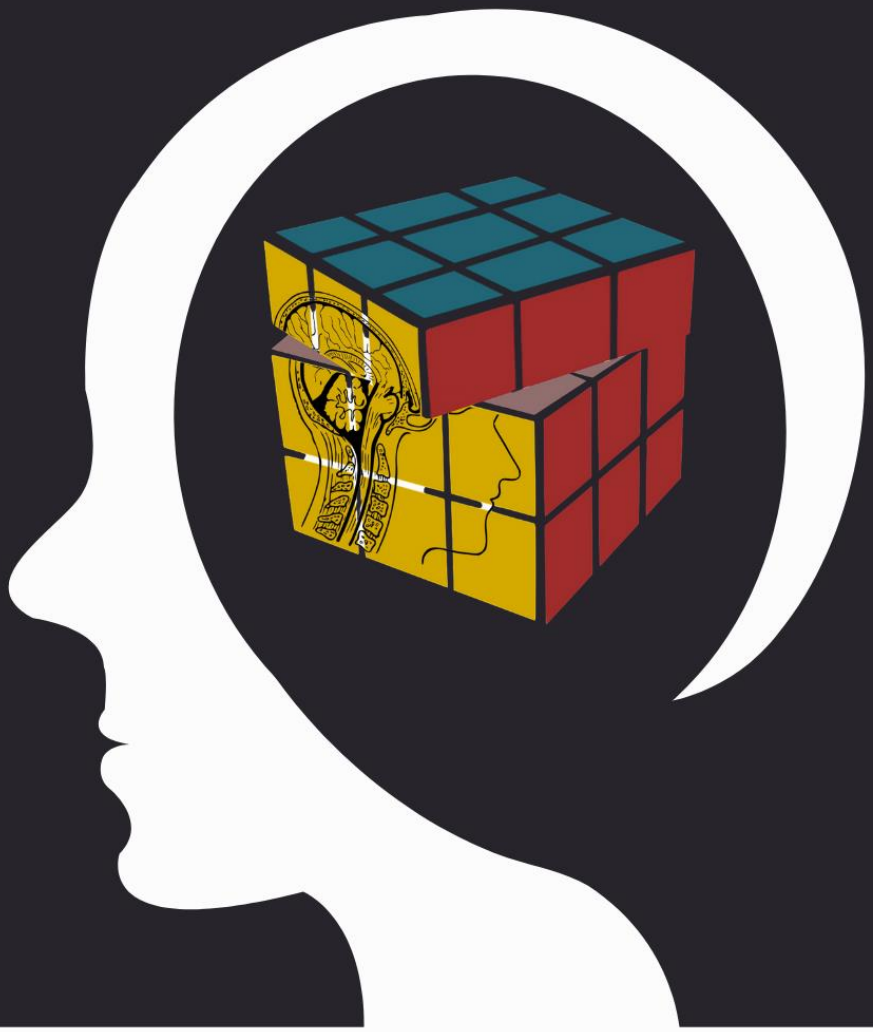

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UNIVERSITAT DE BARCELONA

Programa de Doctorat Medicina i Recerca Translacional

Facultat de Medicina i Ciències de la Salut - Universitat de Barcelona

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Thesis # Brain functional correlates of theory of mind in neurodevelopmental disorders

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"Man is by nature a social animal"

Aristotle (384 BC – 322 BC)

Barcelona, 23rd of May of 2021

Dr. Gisela Sugranyes Ernest and Prof. Josefina Castro-Fornieles certify that they have guided and supervised the doctoral thesis entitled "*Brain functional correlates of theory of mind in neurodevelopmental disorders*", presented by Daniel Ilzarbe Simorte. They hereby assert that this thesis fulfills the requirements to be defended in order to be awarded the title of Doctor.

Dr. Gisela Sugranyes Ernest

Prof. Josefina Castro-Fornieles

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INDEX

1. LIST OF ABBREVIATIONS

ADHD Attention Deficit and Hyperactivity Disorder

ASD Autism Spectrum Disorder

BOLD Blood-Oxygen-Level-Dependent

DMN Default Mode Network

EOP Early-Onset Psychosis

fMRI Functional Magnetic Resonance Imaging

mPFC Medial PreFrontal Cortex

ToM Theory Of Mind

TPJ Temporo-Parietal Junction

2. ARTICLE-BASED THESIS DISSERTATION

This thesis, submitted to obtain the degree of Doctor by the Universitat de Barcelona, includes results from three independent studies. All studies have been accepted for publication in international peer-reviewed journals with a global impact factor (IF) of 12.79 and are listed below:

- Study I: **Ilzarbe D**, Lukito S, Moessnang C, O'Daly OG, Lythgoe DJ, Murphy CM, Ashwood K, Stoencheva V, Rubia K, Simonoff E. Neural Correlates of Theory of Mind in Autism Spectrum Disorder, Attention-Deficit/Hyperactivity Disorder, and the Comorbid Condition. Front Psychiatry 2020 Nov 6;11:544482. doi: 10.3389/fpsyt.2020.544482. (IF: 2.85; Q2 in psychiatry)
- Study II: **Ilzarbe D**, de la Serna E, Baeza I, Rosa M, Puig O, Calvo A, Masias M, Borras R, Pariente JC, Castro-Fornieles J, Sugranyes G. The relationship between performance in a theory of mind task and intrinsic functional connectivity in youth with early onset psychosis. Dev Cogn Neurosci. 2019 Dec;40:100726. doi: 10.1016/j.dcn.2019.100726 (IF: 4.97; Q1 in neurosciences and Q1 in developmental psychology – first decile)
- Study III: **Ilzarbe D**, Baeza I, De la Serna E, Fortea A, Valli I, Puig O, Masias M, Borras R, Pariente JC, Dolz M, Castro-Fornieles J, Sugranyes G. Theory of mind performance and prefrontal connectivity in adolescents at clinical high risk for psychosis. Dev Cogn Neurosci. 2021 Apr (48):100940. doi: 10.1016/j.dcn.2021.100940 (IF: 4.97; Q1 in neurosciences and Q1 in developmental psychology – first decile)

These manuscripts have been approved for publication and represent the culmination of the research training I have received at the Department of Child and Adolescent Psychiatry and Psychology, Institute of Neuroscience, Hospital Clínic de Barcelona and University of Barcelona (Spain), and the Department of Child and Adolescent Psychiatry, Institute of Psychiatry, Psychology and Neuroscience, King's College London (United Kingdom).

Upon completion of medical school (2004-2010), I started my training as a psychiatrist at the Hospital Clinic of Barcelona (2011-2015) and I enrolled in post-graduate studies of "Research Methodology: Design and Statistics in Health Sciences" of the Universitat Autonoma de Barcelona (2013-2015). The combination of my clinical training and studies in research methodology raised my interest in translational medicine; catalysed by joining the research team focused on Psychosis and High Risk at the Department of Child and Adolescent Psychiatry and Psychology of Hospital Clínic de Barcelona. After finishing my training as a psychiatrist in May 2015, I was awarded a 2-year Advanced Training Fellowship by the Alicia Koplowitz Foundation (2015-2017) to work at the Department of Child and Adolescent Psychiatry of King's College London (United Kingdom); where I had the opportunity to expand my clinical experience in children and adolescent psychiatry and conduct neuroimaging research in neurodevelopmental disorders under the supervision of Prof. Emily Simonoff and Prof Katya Rubia. During my period in London, I enrolled in the PhD programme at University of Barcelona (2016): and have since elaborated the project which has culminated in this thesis. Following my time in London, so as to continue with the research for my thesis, I received funding from the Spanish Ministry of Science, Innovation and Universities, Instituto de Salud Carlos III

through a 'Rio Hortega' contract (CM17/00019), with the support of the European Social Fund, to work in Dr. Josefina Castro-Fornieles' research group of Child and Adolescent Psychiatry and Psychology, at Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS) during two years (2018-2020). During this period, I spent 6 months at the Universitair Medisch Centrum Utrecht (Netherlands; Jun - Nov 2019) thanks to a mobility aid from the Spanish Ministry of Science, Innovation and Universities, Instituto de Salud Carlos III. Thus, in total, I have been able to carry out a 4-year part-time research placement at King's College London, Hospital Clínic de Barcelona and Universitair Medisch Centrum Utrecht. During my time in these institutions, I have worked in Prof. Katya Rubia's, Dr. Gisela Sugranyes', Dr. Dienke Bos' and Dr.Marieke Begemann's research teams, which has given me the opportunity to work on the studies that have led to the scientific publications included in the present thesis, among others.

The PhD experience has stimulated my interest in research and prepared me for the demands and responsibilities of this field. I am pleased to report my continued professional involvement with the teams that have made this dissertation possible. Together, we are currently focusing on longitudinal studies to elucidate the impact of disrupted neurodevelopment in neural networks and their cognitive and behavioural correlates.

List of other publications, not included in the thesis, co-authored by the PhD candidate:

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3. SUMMARY IN SPANISH/RESUMEN EN CASTELLANO

3.1. Introducción

La *teoría de la mente* o *mentalización* es un dominio cognitivo de la cognición social que se utiliza para designar la capacidad de atribuir emociones, pensamientos e intenciones a otras personas, y que son diferentes a los propios. La teoría de la mente es una habilidad que se adquiere progresivamente durante el neurodesarrollo hasta la edad adulta. Durante tareas que implican la teoría de la mente aumenta la actividad cerebral del córtex prefrontal medial, las uniones temporo-parietales bilaterales y córtex cingulado posterior/precuneus. La conectividad funcional entre estas áreas también incrementa durante las tareas de teoría de la mente. Esta red funcional de mentalización se superpone anatómicamente con la red de activación por defecto, que se activa durante los estados de reposo, en los que no se realiza ninguna actividad concreta. Con frecuencia, durante la divagación mental que caracteriza el estado de reposo, tienen lugar cogniciones de tipo social. Por ello, se han utilizado estudios de neuroimagen con tarea y de reposo para estudiar las bases neuronales de la teoría de la mente.

Los déficits en teoría de la mente, tradicionalmente asociados con el trastorno del espectro autista, se han identificado también en otros trastornos del neurodesarrollo, como el trastorno por déficit de atención e hiperactividad y en la esquizofrenia. El trastorno por déficit de atención e hiperactividad es un diagnóstico frecuentemente comórbido a los trastornos del espectro del autismo, aunque las dificultades en teoría de la mente parecen ser menos marcadas en el primero. La esquizofrenia ha sido conceptualizada en las últimas décadas como un trastorno del neurodesarrollo, y algunos estudios apoyan que las dificultades en teoría de la mente son más marcadas cuando el primer episodio de psicosis se produce a edades más tempranas. Además, estos déficits en teoría de la mente podrían iniciarse antes de desarrollarse el primer episodio psicótico. Pese a esto, la literatura que evalúa el rendimiento en teoría de la mente en la presentación comórbida de trastorno del espectro autista con un trastorno por déficit de atención e hiperactividad, en la psicosis de inicio temprano (cuando el primer episodio psicótico tiene lugar durante la infancia o la adolescencia) o en los síndromes de alto riesgo de psicosis es más escasa. En este

sentido, el efecto de la edad sobre la adquisición de habilidades de teoría de la mente en adolescentes dentro del espectro de la psicosis ha sido escasamente reportado y con resultados inconcluyentes.

Aunque existe evidencia sobre los déficits neuronales que subyacen a los déficits en teoría de la mente de los sujetos con trastorno del espectro autista y los adultos con esquizofrenia, no hay estudios de resonancia magnética funcional que los evalúen en sujetos con trastorno por déficit de atención e hiperactividad, con o sin comorbilidad con el trastorno del espectro autista, en adolescentes con psicosis de inicio temprano o en adolescentes con alto riesgo clínico de psicosis. Dentro del espectro de la psicosis, tampoco se ha estudiado el efecto de la edad sobre los correlatos neuronales de teoría de la mente. Por lo tanto, se desconoce el impacto que ejercen sobre la conectividad cerebral algunos de los principales trastornos del neurodesarrollo, y si los déficits en teoría de la mente subyacen a vías neuronales similares o diferenciales entre diferentes trastornos del neurodesarrollo. El objetivo de esta tesis es evaluar los correlatos neuronales subyacentes a la teoría de la mente en adultos jóvenes con trastorno por déficit de atención e hiperactividad, con o sin comorbilidad con trastorno del espectro de autismo, y adolescentes con psicosis de inicio temprano y con alto riesgo clínico de psicosis.

3.2.Hipótesis

3.2.1. Principales

- Los adultos jóvenes con trastorno por déficit de atención e hiperactividad mostrarán un peor desempeño en tareas de teoría de la mente que los controles sanos, pero mejor que los adultos jóvenes con trastorno del espectro autista, con o sin trastorno por déficit de atención e hiperactividad comórbido.
- Los adultos jóvenes con trastorno del espectro autista y trastorno por déficit de atención e hiperactividad comórbido mostrarán un peor desempeño en

tareas de teoría de la mente que aquellos con un trastorno del espectro autista o un trastorno por déficit de atención e hiperactividad por separado, o que controles sanos.

- Los jóvenes con psicosis de inicio temprano y adolescentes con alto riesgo clínico de psicosis que posteriormente desarrollan un trastorno psicótico mostrarán un peor desempeño en una tarea de teoría de la mente que los controles sanos y que los adolescentes con alto riesgo de psicosis que desarrollan la enfermedad.
- Los adultos jóvenes con trastorno por déficit de atención e hiperactividad presentarán una activación en el córtex prefrontal y temporo-parietal, así como una conectividad entre las áreas cerebrales de mentalización, reducidas en relación a los controles sanos, pero incrementadas en comparación con adultos jóvenes con trastornos del espectro autista, con o sin comorbilidad con trastorno por déficit de atención e hiperactividad.
- Los adultos jóvenes con trastorno por déficit de atención e hiperactividad con un trastorno del espectro autista comórbido presentaran una actividad cerebral en el córtex prefrontal y temporo-parietal, así como una conectividad entre las áreas cerebrales de mentalización reducidas en relación a los controles sanos y a adultos jóvenes con trastorno por déficit de atención e hiperactividad o con trastorno del espectro autista por separado.
- Los jóvenes con psicosis de inicio temprano y adolescentes con alto riesgo clínico de psicosis que posteriormente desarrollan un trastorno psicótico, presentarán una conectividad funcional cerebral menor en el córtex prefrontal dentro de la red de activación por defecto, en comparación con los controles sanos y adolescentes con alto riesgo clínico de psicosis que no desarrollan la enfermedad.

- En todos los participantes, el rendimiento en tareas de teoría de la mente se correlacionará positivamente con la conectividad funcional cerebral; por lo que, un peor desempeño en la tarea de teoría de la mente se correlacionará con una menor conectividad funcional cerebral.

3.2.2. Secundarias

- Los jóvenes con psicosis de inicio temprano y adolescentes con alto riesgo clínico que transitan a psicosis no mostrarán las mejoras relacionadas con la edad en el rendimiento de teoría de la mente y los aumentos en la conectividad funcional cerebral exhibidos por controles sanos o adolescentes con alto riesgo clínico de psicosis que no desarrollan un primer episodio psicótico.
- Los adolescentes con trastornos psicóticos del espectro de la esquizofrenia presentarán déficits en teoría de la mente más marcados y menor conectividad funcional cerebral que adolescentes con trastornos afectivos con síntomas psicóticos.
- Un rendimiento deficiente de teoría de la mente o una menor conectividad funcional cerebral se asociarán con tasas más altas de transición a trastorno psicótico en adolescentes con alto riesgo clínico de psicosis.

3.3. Objetivos

3.3.1. Principales

- Evaluar teoría de la mente en adultos jóvenes con trastorno por déficit de atención e hiperactividad, con y sin trastorno del espectro autista comórbido, y compararlos con controles sanos.

- Evaluar la conectividad funcional en adultos jóvenes con trastorno por déficit de atención e hiperactividad, con y sin trastorno del espectro autista comórbido, y compararlos con controles sanos.
- Evaluar teoría de la mente en adolescentes con psicosis de inicio temprano o con alto riesgo clínico de psicosis, y en función de si desarrollan un trastorno psicótico al seguimiento, y compararlos con controles sanos.
- Evaluar la conectividad funcional cerebral en adolescentes con psicosis de inicio temprano o con alto riesgo clínico de psicosis, y en función de si desarrollan un trastorno psicótico al seguimiento, y compararlos con controles sanos.
- Evaluar la correlación entre el rendimiento de teoría de la mente y los patrones de conectividad funcional cerebral en todos los participantes con trastornos del neurodesarrollo y controles sanos.

3.3.2. Secundarios

- Evaluar la influencia de la edad en el desempeño de tareas de teoría de la mente y la conectividad funcional cerebral en adolescentes con psicosis de inicio temprano o con alto riesgo clínico de psicosis.
- Evaluar la teoría de la mente y la conectividad funcional cerebral entre adolescentes con trastornos psicóticos del espectro de la esquizofrenia y trastornos afectivos con síntomas psicóticos.
- Evaluar la asociación entre el rendimiento en una tarea de teoría de la mente y la conectividad funcional cerebral, con la transición a la psicosis en adolescentes con alto riesgo de psicosis.

3.4.Métodos

3.4.1. Estudio I

El artículo I (*correlatos neurales de teoría de la mente en el trastorno del espectro autista, el trastorno por déficit de atención e hiperactividad y su comorbilidad*) presenta un estudio transversal de casos y controles en el que participaron adultos jóvenes de entre 20 y 27 años con trastorno del espectro autista (n=19), trastorno por déficit de atención e hiperactividad (n=21), la comorbilidad de ambos trastornos (n=18) y controles sanos (n=25). Para evaluar la teoría de la mente se utilizó la tarea de triángulos animados de Frith-Happé. Es una tarea en bloques que muestra 12 vídeos con unos triángulos dibujados que reflejan diferentes tipos de movimiento: 1) teoría de la mente (p.ej. persuasión), 2) dirigido a un objetivo o de interacción física (p.ej. siguiendo) o 3) aleatorio o sin sentido (p.ej. flotando). Se adquirió una secuencia de resonancia magnética funcional mientras el participante realizaba esta tarea de teoría de la mente. Las diferencias de activación entre grupos se evaluaron a nivel cerebral global, reportando sólo los resultados que sobreviven a la corrección de tasa de error por familia. Posteriormente se realizó un análisis por región de interés utilizando 8 esferas de 10 milímetros de diámetro ubicadas en las siguientes zonas: giro frontal inferior bilateral, córtex prefrontal medial, córtex cingulado posterior, giro angular bilateral y unión temporo-parietal o surco temporal superior bilateral. Se llevó a cabo un análisis de conectividad cerebral entre las regiones de interés. Se aplicaron modelos mixtos multinivel de regresión lineal donde grupo, condición del vídeo (teoría de la mente, interacción física o aleatorio) y la interacción grupo x condición se incluyeron como efectos fijos, y el factor individual como efecto aleatorio; se aplicó la corrección de Bonferroni para comparaciones múltiples en los análisis post-hoc.

3.4.2. Estudio II

El artículo II (*relación entre el desempeño en una tarea de teoría de la mente y la conectividad funcional intrínseca en jóvenes con psicosis de inicio temprano*) presenta un estudio transversal de casos y controles en el que participaron adolescentes y jóvenes de entre 15 y 20 años con psicosis de inicio temprano (n=27), dos años después del primer episodio, y controles sanos (n=41). Para evaluar la teoría de la mente se utilizó la versión para niños y adolescentes del Test de la Mirada. Es una tarea que presenta 28 imágenes con los ojos de diferentes sujetos mostrando múltiples expresiones. Incluye una condición control, donde se les pide a los participantes que identifiquen el sexo del modelo y una condición experimental con el objetivo de identificar las emociones, en una pregunta de opción múltiple (se dan 4 opciones). En estos pacientes, además se adquirió una secuencia de resonancia magnética funcional en reposo. Se identificó la red de activación por defecto entre los componentes obtenidos en un Análisis de Componentes Independiente. Se compararon los mapas espaciales de la red de activación por defecto entre grupos, y se evaluó la interacción grupo x edad. Para los análisis grupales se utilizó una máscara de la red de activación por defecto creada a partir de la muestra, y sólo se reportan los resultados que sobreviven a la corrección de tasa de error por familia. Se realizó un análisis de mediación para evaluar qué proporción del efecto total en el desempeño de la tarea de teoría de la mente estaba mediado por la conectividad funcional de aquellas regiones cerebrales que mostraron resultados significativos. En un segundo paso se repitieron los análisis por grupos diagnóstico: psicosis del espectro de la esquizofrenia y psicosis afectivas de inicio temprano en comparación a los controles sanos.

3.4.3. Estudio III

El artículo III (*teoría de la mente y conectividad prefrontal en adolescentes con alto riesgo clínico de psicosis*) presenta un estudio de casos y controles en el que participaron adolescentes de entre 12 y 17

años con alto riesgo clínico de psicosis (n=50), y controles sanos (n=36); y que se siguieron longitudinalmente durante 18 meses. El análisis de los datos es transversal (de la evaluación basal) pero se utilizó la información clínica longitudinal sobre transición a psicosis para clasificar a los sujetos en tres grupos: adolescentes en alto riesgo que transitaron a psicosis (n=15), que no transitaron (n=24) y los controles sanos que completaron el seguimiento (n=27). Para evaluar la teoría de la mente se utilizó nuevamente la versión para niños y adolescentes del Test de la Mirada. Como se ha descrito en el estudio anterior, es una tarea que presenta 28 imágenes con los ojos de diferentes sujetos mostrando múltiples expresiones. Incluye una condición control, para identificar el sexo del modelo, y una condición experimental para la identificación de emociones en una pregunta de opción múltiple (se dan 4 opciones). Se realizó asimismo una adquisición de resonancia magnética funcional en reposo. Se identificó la red de activación por defecto entre los componentes obtenidos en un Análisis de Componentes Independiente. Se compararon los mapas espaciales de la red de activación por defecto entre grupos, y la interacción grupo x edad, utilizando una máscara de la red creada a partir de la propia muestra; y reportando sólo los resultados que sobreviven a la corrección de tasa de error por familia. En un segundo paso, se realizó un análisis de supervivencia para evaluar cuál era el riesgo de desarrollar psicosis en el grupo de adolescentes con alto riesgo clínico asociado al rendimiento en la tarea de teoría de la mente y/o a la conectividad funcional de aquellas regiones cerebrales que mostraron resultados significativos.

3.5.Resultados

3.5.1. Estudio I

El estudio I (*correlatos neurales de teoría de la mente en el trastorno del espectro autista, el trastorno por déficit de atención e hiperactividad y su comorbilidad*) no mostró diferencias significativas en las variables principales sobre el rendimiento en la tarea de teoría de la mente entre los grupos. Los resultados del análisis cerebral global y por regiones de interés mostró una hiperactivación significativa

en regiones temporo-parietales derechas en el grupo de pacientes con trastornos del espectro del autismo, con o sin comorbilidad con trastorno por déficit de atención e hiperactividad respecto al grupo con trastorno por déficit de atención e hiperactividad (que mostró hipoactivación); e hiperactivación en el grupo de pacientes con trastorno del espectro del autismo a nivel de tendencia con respecto al grupo de controles sanos. El análisis de conectividad funcional reveló que los tres grupos clínicos carecían del aumento en conectividad global asociado a los vídeos de teoría de la mente respecto a los vídeos control que mostraba el grupo de controles sanos. Por regiones, este hallazgo se replicaba en la conectividad entre el giro angular derecho y las regiones temporo-parietales de ambos hemisferios. Asimismo, los grupos con trastorno del espectro autista (con y sin comorbilidad con el trastorno por déficit de atención e hiperactividad) tampoco mostraban el incremento de conectividad entre giro frontal inferior derecho y el córtex cingulado posterior durante los vídeos de teoría de la mente que, por el contrario, sí exhibían el grupo de controles sanos y el grupo con trastorno por déficit de atención e hiperactividad. Por último, los grupos con trastorno por déficit de atención e hiperactividad (con y sin trastorno del espectro autista comórbido) mostraban un descenso de la conectividad entre el córtex prefrontal medial y la unión temporo-parietal izquierda durante los vídeos de teoría de la mente, al contrario que el grupo de controles sanos.

3.5.2. Estudio II

El estudio II (*relación entre el desempeño en una tarea de teoría de la mente y la conectividad funcional intrínseca en jóvenes con psicosis de inicio temprano*) mostró que los adolescentes y jóvenes con psicosis de inicio temprano desempeñaban significativamente peor la tarea de teoría de la mente que los controles sanos. Asimismo, los adolescentes y jóvenes con psicosis de inicio temprano no mostraban la correlación positiva entre edad y rendimiento en la tarea de teoría de la mente que exhibían los controles sanos. En neuroimagen, los adolescentes y jóvenes con psicosis de inicio temprano presentaban un área en el córtex prefrontal dorsomedial con reducción de la conectividad dentro de la red de activación por

defecto, y un área en el córtex prefrontal ventromedial con una correlación negativa con la edad, al contrario que los controles sanos, que mostraban una correlación positiva. El análisis de mediación demostró que la conectividad en el córtex prefrontal medial explicaba un 16.7% del bajo rendimiento en la tarea de teoría de la mente de los adolescentes y jóvenes con psicosis de inicio temprano respecto a los controles sanos. El análisis secundario mostró que sólo el grupo con psicosis del espectro de la esquizofrenia de inicio temprano presentaba un bajo rendimiento en la tarea de teoría de la mente en comparación con los controles sanos y el grupo con psicosis afectivas de inicio temprano. Los hallazgos de neuroimagen se replicaron en ambos grupos con trastornos psicóticos de inicio temprano, tanto aquellos del espectro de la esquizofrenia como los trastornos afectivos, respecto a los controles sanos.

3.5.3. Estudio III

El estudio III (*teoría de la mente y conectividad prefrontal en adolescentes con alto riesgo clínico de psicosis*) no mostró diferencias en el rendimiento en la tarea de teoría de la mente entre los grupos. Sin embargo, los controles sanos exhibían una correlación positiva entre edad y teoría de la mente que, por el contrario, el grupo de adolescentes con alto riesgo clínico que transitaron a psicosis no mostraba. En neuroimagen, el grupo de adolescentes con alto riesgo clínico que transitaron a psicosis presentaba un área en el córtex prefrontal dorsomedial con reducción de la conectividad dentro de la red de activación por defecto respecto a los controles sanos y el grupo de adolescentes con alto riesgo clínico que no transitaron. Además, ambos grupos de adolescentes con alto riesgo clínico (que transitaron y que no transitaron a psicosis) presentaban un área en el córtex prefrontal ventromedial con una correlación negativa con la edad, al contrario que los controles sanos, que mostraban una correlación positiva. El análisis de supervivencia demostró una asociación significativa entre la transición a psicosis y la conectividad funcional reducida en el córtex prefrontal dorsomedial de la red de activación por defecto en el grupo de adolescentes con alto riesgo de psicosis.

3.6. Conclusiones

- Los adultos jóvenes con trastorno por déficit de atención e hiperactividad, trastorno del espectro autista y la comorbilidad presentaron un rendimiento similar a los controles sanos en tareas de teoría de la mente.
- Los adultos jóvenes con trastorno por déficit de atención e hiperactividad mostraron una reducción de activación en las regiones parieto-temporales derechas en relación con las personas con trastorno del espectro autista, con o sin trastorno por déficit de atención e hiperactividad comórbido, lo que apunta a un mecanismo cerebral diferencial entre los dos trastornos.
- Los adultos jóvenes con trastorno por déficit de atención e hiperactividad, con trastorno del espectro autista o ambas comorbilidades no presentaron el patrón de conectividad funcional entre regiones fronto-parietales y parieto-temporales exhibido por controles sanos durante tareas de teoría de la mente, y mostraron patrones con características comunes y propias de cada trastorno.
- Los jóvenes con psicosis de inicio temprano presentaron dificultades en el desempeño de la tarea de teoría de la mente; y no presentaban el patrón de maduración normativo en teoría de la mente relacionado con la edad que exhibieron los controles sanos. Dentro de la psicosis de inicio temprano, los jóvenes con trastornos del espectro de la esquizofrenia presentaban déficits en teoría de la mente que no presentaban los controles sanos o los jóvenes con trastornos afectivos con síntomas psicóticos. Estos últimos presentaban un rendimiento similar a los controles sanos en teoría de la mente.
- Los jóvenes con psicosis de inicio temprano mostraron una menor conectividad en el córtex prefrontal medial dentro de la red de activación por defecto en

comparación con los controles sanos. También presentaron una asociación negativa entre la conectividad en el córtex prefrontal medial y la edad, al contrario de lo observado en controles sanos, que presentaron una asociación positiva. Tanto los jóvenes con trastorno del espectro de la esquizofrenia como con trastornos afectivos con síntomas psicóticos mostraron una menor conectividad en el córtex prefrontal medial dentro de la red de activación por defecto en comparación con los controles sanos, sin diferencias entre ellos.

- La conectividad funcional en el córtex prefrontal medial dentro de la red de activación por defecto estaba parcialmente asociada con el desempeño de teoría de la mente en jóvenes con psicosis de inicio temprano.
- Los adolescentes con alto riesgo clínico que transitaron a psicosis no mostraron la maduración normativa en teoría de la mente relacionada con la edad que exhibían los controles sanos o adolescentes con alto riesgo clínico de psicosis que no transitaron a psicosis.
- Los adolescentes con alto riesgo clínico que transitaron a psicosis mostraron una menor conectividad en el córtex prefrontal dorsomedial dentro de la red de activación por defecto en comparación con los controles sanos y con el grupo con alto riesgo clínico de psicosis que no desarrolló la enfermedad. Ambos grupos de alto riesgo clínico presentaron una asociación negativa entre la conectividad en el córtex prefrontal ventromedial y la edad, al contrario de lo observado en controles sanos.
- Los adolescentes con alto riesgo clínico de psicosis y menor conectividad en el córtex prefrontal medial presentaron tasas más altas de transición a psicosis en comparación con aquellos con mayor conectividad en el córtex prefrontal medial.

- El estudio trans-diagnóstico de los correlatos neurales de los déficits en teoría de la mente en adolescentes y jóvenes con trastornos del neurodesarrollo aumenta la comprensión de los mecanismos cerebrales subyacentes en cada trastorno.
- La conectividad del córtex prefrontal medial podría ser un biomarcador para la predicción de transición a psicosis en adolescentes con alto riesgo clínico de psicosis.
- Este nuevo conocimiento puede ayudar a adaptar las intervenciones específicas de los trastornos dirigidas a la teoría de la mente en edades tempranas durante el neurodesarrollo y proporcionar posibles marcadores de neuroimagen para monitorizar la eficacia de dichas intervenciones.

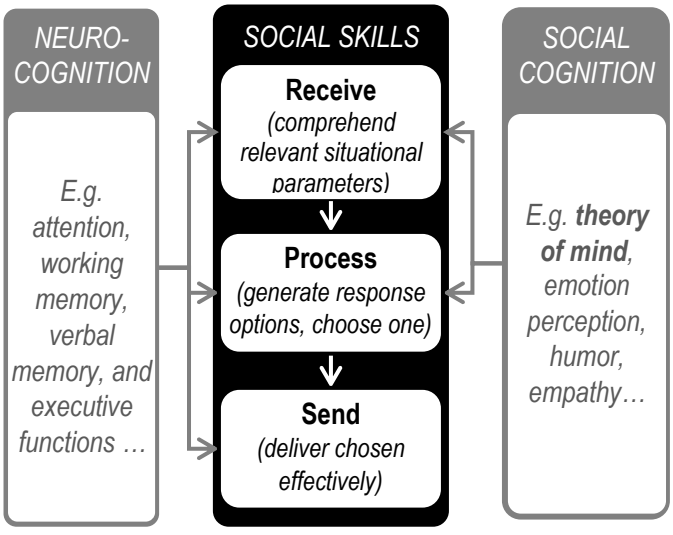
4. INTRODUCTION

Impairment in social functioning is a common diagnostic criteria for most psychiatric disorders (1,2). Multiples causes may be involved in the loss, or the lack of acquisition, of social skills in psychopathological conditions (3). Social cognition is progressively acquired during childhood and adolescence (4), coinciding with the age of onset of most psychiatric disorders (5) and especially neurodevelopmental disorders, which frequently exhibit impairment in theory of mind performance (6). Along the Introduction, the concept of theory of mind (ToM) (section 4.1) is presented, in addition to the role of functional neuroimaging (section 4.2) for studying the neural correlates underlying ToM (section 4.3). This is contextualized in neurodevelopment (subsections 4.1.1, 4.2.1 and 4.3.1). Secondly, the current knowledge about the impairments in ToM and its associated functional brain correlates is reviewed within three neurodevelopmental disorders (section 4.4): autism spectrum disorders (4.4.1), attention-deficit and hyperactivity disorder (4.4.2) and early-onset psychosis (4.4.3).

4.1. Theory of Mind

The abilities of human beings to interact with others encompass *receiving* and *processing* social messages, as well as *sending* a social message to the interlocutor (7). These three processes require adequate neurocognitive abilities such as attention, executive functions or working memory, although this is not sufficient to achieve successful social interactions (8,9). In addition to neurocognition, *receiving* and *processing* social messages also require recognizing other's emotions and thoughts through a set of different psychological processes, which has been denominated social cognition (8). Social cognition encompasses emotion perception and recognition and understanding others' minds, empathy or humour (10) (see figure 1).

Figure 1. Cognitive processes implicated in social functioning.



Within social cognition, **ToM** (11) or *mentalization* (12) is the capacity of understanding that others present independent beliefs, intentions, desires, etcetera from one's own and of attributing mental states to others in order to predict their reactions and behaviours. ToM is highly correlated with everyday functioning in severe mental disorders, stronger than any other neurocognitive domain (13–15). ToM can be subdivided into different categories according to different criteria (16):

- According to stimulus modality (16):
    - **Verbal ToM** (for instance ToM stories)
    - **Visual ToM** (for instance ToM cartoons, silent videos, and photographs)

- According to type of instructional cues (17):
    - **Implicit ToM** (also labelled lower-level, spontaneous or automatic): it is usually fast and reflexive, responsible for monitoring emotion and "belief-like" states and independent of executive functions; emerges early on in neurodevelopment.
    - **Explicit ToM** (also labelled higher-level, intentional or controlled): it is usually slow and reflective, language-based declarative reasoning, dependant on executive functions; arises during a later stage of neurodevelopment.

- According to the kind of inference (18):
    - **Affective ToM** (also labelled "*hot*" ToM): focused on understanding others' emotions or feelings.
    - **Cognitive ToM** (also labelled "*cold*" ToM): focused on understanding others' beliefs, thoughts or intentions.

Different social contexts demand different combinations of these ToM categories, which has led to the use of a range of tests for assessing ToM in research studies, according to each criteria [see table 1] and also adapted to neurodevelopmental stage, as discussed in the next section.

Table 1. Main theory of mind task types with descriptions (adapted from Jáni et Kašpárek. 2018, Schurz et al. 2014 and Henry et al. 2012) (19–21).

Theory of mind task	Examples	Description (Experimental task)	Control task/condition
False belief task (first- and second-order belief tasks)	**Sally-Anne test** (22); **Hinting task** (23); **Deception task** (24)	The task exists in various versions, from reading a vignette to a scene with dolls. Participants are asked to read a short story describing a character holding a false belief and are required to predict the behaviour of that person based on their belief. For example: '*Julia sees the ice cream van go to the lake. She doesn't see the van turn off to the town hall. Therefore, Julia will look for the ice cream van at the…'*	Participants are asked to read a short vignette involving a sign where the contents become false throughout the story, and to answer a question about that sign. Or they are asked to look at a false photograph where something is changed in the scene and to identify the changed object. For example: *'The ice cream vendor's sign points to the lake. The ice cream van goes to the town hall without changing the sign. According to the sign post the ice cream van is at the…'*
Stories	**Stories of Everyday Life** (25); **Strange Stories** (26)	Participants are asked to demonstrate their understanding of a written story in which a character's behaviour can be best understood by positing an underlying mental state.	Participants are asked to demonstrate their understanding of a written story in which a character's behaviour can be best understood by reasoning about a physical event.
Faux Pas	**Faux Pas Test** (27)	Participants are asked to recognize social gaffes (a social embarrassing mistake)	Participants are asked to recognize socially appropriate behaviour or answer questions related to the behaviour of a protagonist that does not require an inference about their mental state
Trait judgement task (28,29)		Participants are presented with photographs of people and must judge if the individuals are approachable or trustworthy. Or read written statements conveying trait diagnostic information about people (describing behaviour): and then read a single trait-adjective and indicate whether it is consistent with the behaviour of that person.	Participants must judge the age or gender of the person in a photograph or in a sentence. Or read written statement about a person doing something: this behaviour is neutral and does not convey trait diagnostic information about the person.

Strategic games	**Prisoner's Dilemma Game** (30); **"stone, paper, scissors"** (31); **Ultimatum game** (32)	Prisoner's dilemma game: participants play against another human player for game points. Participants are required to decide about cooperating or defecting with their partner. If both players (participant and partner) choose defective, they gain almost no game points at all. If both choose cooperative, both gain some game points. If players choose differently, the defective player gains more points.	Participants play an adapted version of the prisoner's dilemma game against a computer for game points. Strategy choices (cooperate or defect) are randomized.
Social animations	**Frith-Happé Animated Triangles Task** (33); (34)	Participants watch moving geometric shapes that appear to be interacting and are asked to describe it and about the intentionality of the shapes.	Same as experimental task, but the movement pattern appears to be random/casual.
Mind-in-the-Eyes	**"Read-the-Mind-in-the-Eyes" Test** (35)	Participants are presented eyes or faces and are asked to guess the intentions or thoughts of that person. Generally, it is surrounded by four possible options describing a mental state such as, for example: *frustrated*, *excited*, *annoyed*, and *bored*.	Participants are asked to guess the gender/sex of the person in the photograph.
Videos	**MASC: Movie for the Assessment of Social Cognition** (36)	Video clips that portray characters interacting. Participants are instructed to choose the word that best describes the thoughts or feelings of the person in the video. As in the previous one, each clip is surrounded by four possible options describing mental states.	The same video clips are presented, but participants are required to answer a question regarding physical details in the film clip. For example, *'Was the door to the room open when Michael arrived?*
Rational action	**Character intention task** (37); **Cartoon jokes** (38)	Participants are presented with cartoon sequences and required to choose between two frames that appropriately fit what the character would do next based on their mental states.	Participants must predict what will happen next based on the comprehension of physical causality.
Irony comprehension	**The metaphor and sarcasm scenario test** (39)	Participants read sentences and indicate whether irony is present.	Participants read sentences with literal meanings.
Perspective taking	**Director's task** (40)	Participants are asked to move objects between shelves according to the instructions given by a director on the other side of the shelves, thus taking the director's perspective.	Participants are asked to move objects between shelves from their own perspective.

4.1.1. Theory of Mind and Neurodevelopment

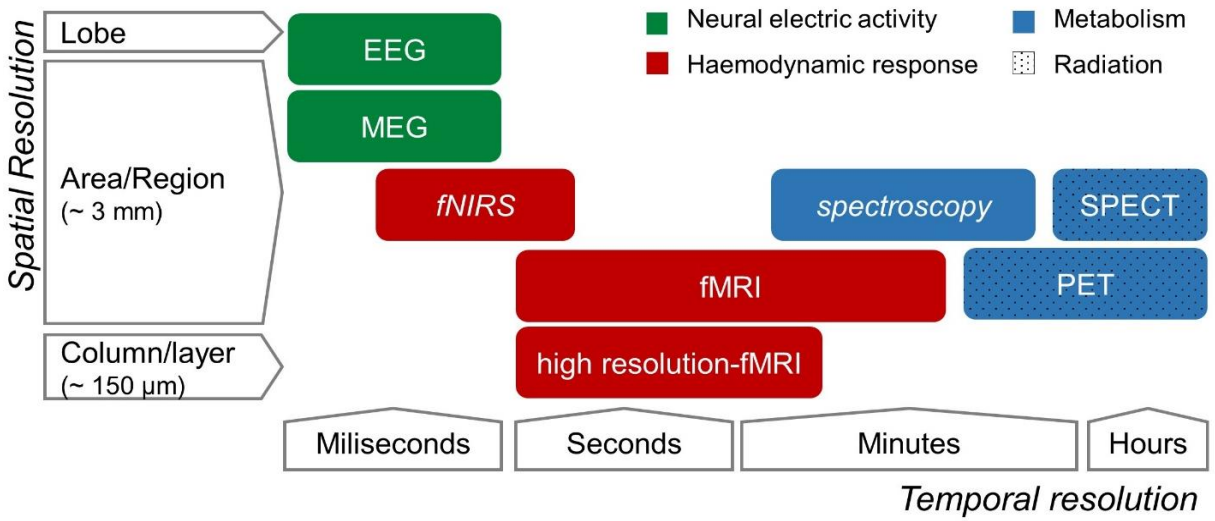
ToM is progressively acquired during neurodevelopment (4), as illustrated in longitudinal studies demonstrating improvement of task performance with age in typically developing children and adolescents (41,42). Cross-sectional studies have also showed a positive correlation between ToM performance and age in healthy controls (43–45). Earliest signs of ToM have been described in 15-month-old children (46), although more evident ToM abilities start to arise around 4 years of age (41,47). Studies report that "cognitive" ToM develops earlier than "affective" ToM, which continues to develop during late adolescence and into early adulthood (48,49). Typical improvement in ToM skills during childhood impacts on better social functioning, as proved by studies showing a positive correlation between ToM performance and peer-oriented social behaviours (50).

Various models have been proposed to explain how ToM abilities are acquired during neurodevelopment in the field of Developmental Psychology: 1) ToM underlies innate neural mechanisms [*modularity theories*]; 2) ToM is based on the access to one's own psychological states in order to make mental state attributions of others [*simulation theories*]; 3) ToM requires a developed executive function in order to inhibit one's own perspective in order to generate a different one [*executive accounts*]; 4) ToM is developed by abstraction based on child's social experiences [*theory theory*] (51). Neuroimaging has been used to further study some of these models (51) and to assess the acquisition and improvement of ToM abilities during neurodevelopment, which has been associated with functional brain maturation (52), as described in the following sections.

4.2.Functional Neuroimaging

Functional neuroimaging studies brain activity by measuring changes in the neural activation signal over time depending on the stimuli and/or task-performance. Neural activity is associated with the passage of electrical activity between cells, which leads to an increase in metabolic demand, and generates greater blood flow, oxygen and glucose consumption. All these changes have been conceptualized as the haemodynamic response (53). The measurement of the electrical activity and/or the haemodynamic response have been used as a non-invasive approach to study neuronal activity through different techniques, such as electroencephalogram or functional magnetic resonance imaging (fMRI), among others (see figure 2).

Figure 2. Classified functional neuroimaging techniques based on spatial and temporal resolution.



Note: EEG: electroencephalogram; fMRI: functional magnetic resonance imaging; fNIRS: Functional near-infrared spectroscopy; MEG: magnetoencephalography; PET: Positron emission tomography; SPECT: Single-photon emission computed tomography

Specifically, fMRI measures the haemodynamic response through cerebral oxygen consumption, because oxy- and deoxyhaemoglobin have differential magnetic properties between them and magnetic signal changes accordingly to the proportion or concentration of each one. This signal is called the blood-

oxygen-level-dependent (BOLD) response (53). Although fMRI has medium temporal resolution and is sensitive to head movement, it has been widely used in studies with children and adolescents because it is safe, non-invasive and has the highest spatial resolution in comparison to other functional neuroimaging techniques.

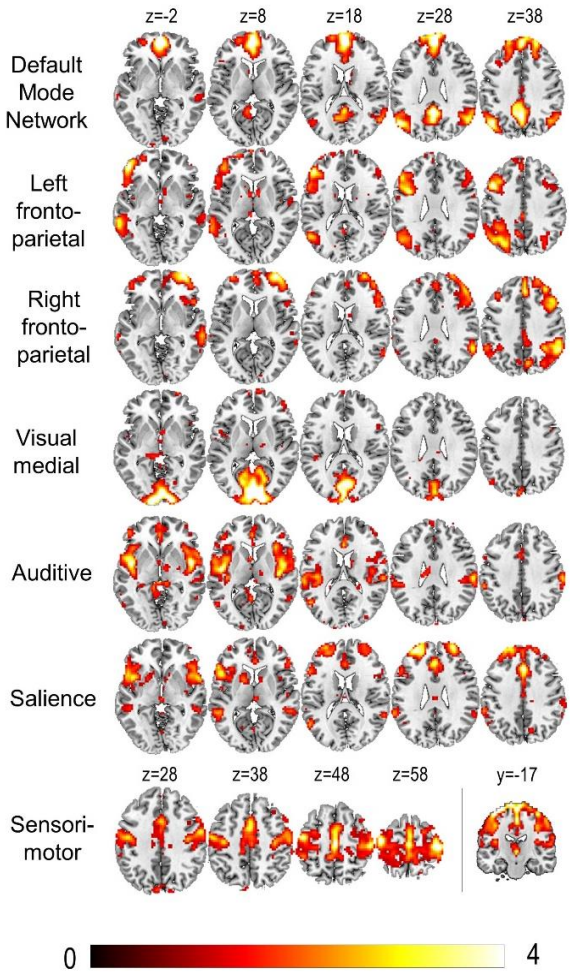
Neural activity over time depends on the task carried out during the neuroimaging acquisition. Based on this activity, functional neuroimaging distinguishes several types of research studies:

- In **task-based fMRI** studies, the subject is exposed to an external stimulus so as to evaluate their neural response simultaneously to their behavioural performance. The origin and presentation of the stimulus can vary:
    - According to sensory modality: The stimulus can be visual (for example, faces are shown to assess facial and emotional recognition), auditory (for example, alternating sounds are reproduced in the left and right ear to assess laterality), tactile, etcetera.
    - According to presentation: the stimulus can be intermittent or continuous, and therefore it can be an event-task design (single and brief exposure to multiple stimuli), a block-design (sustained exposure to the stimulus) or mixed (combining events and blocks).
- In **resting-state fMRI** the subject does not perform any particular task: they are instructed to remain awake (with their eyes closed or open, or looking at a cross reflected on a screen).

Task-based fMRI studies usually measure the variation of the BOLD signal between experimental conditions or relative to a control condition (comparison stimulus), which allow to quantify hyperactivation or hypoactivation with respect to the control condition. Resting-state fMRI studies, as well as task-based fMRI studies, allow to estimate functional connectivity between different brain areas by measuring the correlation of the BOLD signal between them. Areas functionally connected are more likely to activate

together and simultaneously, therefore presenting synchronous activation (higher positive correlation). On the other hand, an asynchronous activation would indicate that those regions are activated independently of each other, meaning they are less likely to be functionally connected.

Figure 3. Main neural networks detected during resting-state fMRI in healthy individuals.



Brain areas which are functionally connected form neural network patterns, which have been consistently found during the resting-state, and have been associated with cognitive functions, such as the salience network, the visual network, or the sensorimotor network (see figure 3). Regions that are jointly engaged during task performance also tend to show synchronous activity during rest (54).

The most frequently studied network during the resting-state is the default mode network (DMN). The DMN, first described in a Positron Emission Tomography (PET) study (55), involves the medial prefrontal cortex (mPFC), bilateral temporo-parietal junctions (TPJ), precuneus and posterior cingulate (56). In contrast with other cognitive networks, the DMN usually deactivates during goal-directed tasks (56,57) and typically activates during the resting-state, when the subject is not engaged in any cognitive activity (57,58). The DMN shows a negative temporal correlation with the central executive network. It has been hypothesized that a switch takes place between the central executive network (which would activate when involved in a task) and the DMN (which would

activate during rest) depending on the main focus of attention. The salience network would mediate this switch between both networks, shifting between external (central executive network and task-focused) and internal (DMN and mind-wandering) attention (59–61). Given that resting-state fMRI is a task-free scanning, where the subject is asked to remain awake (closed eyes, open eyes or fixed looking to a cross) without thinking anything in particular, it has been widely used to study the DMN.

All these functional networks, consistently found in healthy subjects during both resting-state and task-based fMRI, have been proved to undergo variations during development (62,63); as described in the next section. Both, within-network (intrinsic) or between-network (extrinsic) functional connectivity can be assessed in fMRI studies. Altered functional connectivity has been related with psychopathological dimensions (64), and may present common and differential characteristics between subjects with different neurodevelopmental disorders (65).

4.2.1. Development of Typical Brain Connectivity

During development, brain connectivity tends to segregate between areas which are close to each other and to integrate between selected areas which are distant, conforming the mentioned functional networks (66). Therefore, over time, each network improves its intrinsic functional connectivity and progressively differentiates from others (62), gaining specificity (63) and optimizing functionality (66). The architecture of some networks is built intra-uterus, such as the sensory-motor, visual or auditive networks (67). Others, such as language and salience networks, become organized during the first two years after birth (68); or later, in the case of the executive control network, which develops around the age of 4-5 years (69). The increase in functional connectivity and global efficiency within-networks over development achieves its maximum around the age of 22 years (70,71). The development of functional connectivity coincides with a period of active myelination leading to the maturation of white matter tracts (72–74), which conform the substrate of brain structural connectivity.

In particular, DMN develops during the first year of life (75), and increases its connectivity up until adulthood (76). Within the DMN, mPFC connectivity is the region with the greatest number of connections correlating with age (77). Twin-studies have demonstrated an additive effect of genetics and environment in the development of intrinsic functional connectivity of the DMN and its connectivity with other networks during adolescence (78).

4.3.Neural Correlates of Theory of Mind

The mPFC and bilateral TPJ are the structures which are most frequently activated during ToM tasks in healthy controls, and consistently across different ToM tasks, as reported by two meta-analyses (16,20). In addition, the precuneus, bilateral inferior frontal gyrus, posterior superior temporal sulcus, amygdala and anterior cingulate cortex are also frequently involved, depending on the type of ToM paradigm (16,52). In healthy subjects, during task performance, these brain regions are activated, and functional connectivity between them is also increased, conforming the mentalizing network (79,80).

This mentalizing network, active and connected during ToM tasks, anatomically overlaps with the DMN (81,82), given that the DMN also involves the mPFC, bilateral TPJ, precuneus and posterior cingulate (56) (see figure 3). As mentioned before, the DMN activates during rest (57,58), when the subject is not involved in any activity and is mind-wandering. In fact, ToM is one of the main cognitive dimensions which is engaged during the mind-wandering which takes place during the resting-state (83). Due to this, the role of the DMN and its intrinsic functional connectivity has been widely related with social cognition in healthy subjects (84). Further, age-related changes in DMN connectivity in adults are found to mediate ToM performance (85). ToM and intrinsic functional connectivity of the DMN both develop during childhood and adolescence, and are inter-related, as discussed in the next section.

4.3.1. Neural Correlates of Theory of Mind during Typical Neurodevelopment

It has been suggested that some areas of the social brain, especially the mPFC and posterior superior temporal sulcus, within the TPJ, undergo critical functional and structural changes during childhood and adolescence (52,86). Few studies have focused on describing differences in ToM tasks comparing children or adolescents with adults. Studies comparing children vs. adults usually report greater selectivity in the activation of mentalizing network areas (especially TPJ) during ToM in adults; and that activation correlates with age in children (87,88). Studies comparing adolescents vs. adults, with similar ToM task performance between groups, show increased activation in mentalizing network areas (especially the mPFC) (49,89,90), and increased functional connectivity between the mPFC and TPJ, in adolescents (91).

All these findings point to childhood and adolescence as key periods in brain development for the acquisition of ToM abilities; therefore, suggesting that any disruption taking place during neurodevelopment may potentially lead to ToM deficits in adulthood. In fact, it has been reported that earlier damage in social cognition areas could lead to more severe impairment later on; while the same damage during adulthood could be compensated by other areas, sparing ToM abilities (52). This is supported by lesion studies which have revealed discrepant clinical syndromes following prefrontal damage depending on the age of onset (92,93).

Deficits in ToM have been historically associated with autism spectrum disorders (ASD) (22,94). However, in the last decades it has been suggested that impairments in ToM also underlie social difficulties observed in other mental health conditions (6,95), especially for disorders affecting neurodevelopment (6), as presented in the next section.

4.4.Neurodevelopmental Disorders

Neurodevelopmental disorders are complex conditions involving disruption of brain development and characterized by neurocognitive deficits since childhood. Neurodevelopmental disorders have been studied frequently together due to their overlap in symptomatology (96) and frequent comorbid presentation (see table 2). Neurodevelopmental disorders encompass: ASD, attention deficit and hyperactivity disorder (ADHD), intellectual disability, communication disorders, specific learning disorders and some motor disorders (for instance, persistent motor tic disorder or Tourette's disorder) (2). Schizophrenia has been also conceptualized as a neurodevelopmental disorder (97,98), given evidence that brain changes associated with the disease begin to take place during childhood and adolescence, in many cases years before the first episode of psychosis (99,100). The presence of brain abnormalities seems to be more severe in those with early-onset psychosis (EOP), defined as onset of a first psychotic episode under the age of 18 (101). Specific epidemiological findings and diagnostic criteria of ASD, ADHD and schizophrenia are detailed in table 2.

The onset of ASD and ADHD takes place during childhood, and the onset of EOP takes place during childhood or adolescence, which is a critical period for brain development (70), and coincides with the time in which the acquisition and consolidation of ToM abilities also takes place (48). Therefore, the onset of a disorder at this age may have an impact on the development of social cognition and the neural mechanisms underlying ToM. Some of the disrupted patterns in the maturation of brain connectivity during childhood and adolescence may be shared by the different neurodevelopmental disorders (102), and could explain common clinical and cognitive phenotypes. At present, it remains unclear whether the neural correlates of ToM are common between these neurodevelopmental disorders or whether they are disorder-specific, as discussed in the following sections for each disorder.

Table 2. Comparison of epidemiological findings and diagnostic criteria of neurodevelopmental disorders: Autism Spectrum Disorder, Attention Deficit and Hyperactivity Disorder and Schizophrenia.

	Autism Spectrum Disorder (ASD)	Attention Deficit and Hyperactivity Disorder (ADHD)	Schizophrenia ->> Psychosis
Incidence	4.3-8.3/10,000/year in younger than 5 years (103,104)	11.7/10,000/year in younger than 19 years (105)	15.2/100,000/year (106) ->> 31.7/100,000/year for all psychosis (107), where schizophrenia and non-affective psychotic disorders are the most incident (108)
Prevalence	.8% (109)	7.2% (110)	.7% (106) ->> 1 % for all psychotic disorders (111)
Age of onset	Symptoms typically recognized at 12-24 months (2)	Symptoms present prior to age 12 years (2)	Psychotic symptoms present usually between 18-30 years (112,113) ->> Peak rates of incidence of psychosis ~45/100,000/year at 16-17 y/o in women and ~80/10,000/year at 18-19 y/o in men (108)
Male:female ratio	3.3:1 (114)	2:1 (115)	1.4:1 (106)
Hereditability	64-91% (116)	72% (117)	80% (100,118)
Environmental Risk Factors (Class I – Convincing evidence from Umbrella Reviews)	Maternal age ≥ 35 y/o; maternal hypertension or pre-eclampsia, maternal overweight, maternal exposure to antidepressants (pre-pregnancy or gestational) (119)	Pre-pregnancy maternal obesity; gestational maternal hypertension or pre-eclampsia, maternal exposure to acetaminophen, childhood eczema (120)	->> Clinical-High Risk state for psychosis, and black-Caribbean ethnicity in England (121)
Diagnostic Criteria (2)	Symptoms must be present in the early developmental period: A. Persistent deficits in social communication and social interaction across multiple contexts: 1) deficits in social-emotional reciprocity; 2) deficits in nonverbal communicative behaviours used for social interaction; 3) deficits in developing, maintaining, and understanding relationships.	Persistent pattern of inattention and/or hyperactivity-impulsivity: A. Inattention (minimum 6 symptoms for 6 months): 1) often fails to give close attention to details or makes careless mistakes in schoolwork, at work, or during other activities; 2) often has difficulty sustaining attention in tasks or play activities; 3) often does not seem to listen when spoken to directly; 4) often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace; 5) often has difficulty organizing tasks and activities; 6) often avoids, dislikes, or is reluctant to	A. Psychotic symptoms (minimum 2 symptoms for one month, or less if treated): 1) delusions; 2) hallucinations; 3) disorganized speech; 4) grossly disorganized or catatonic behaviour; 5) negative symptoms. B. Social and/or occupational dysfunction (minimum 6 months)

	B. Restricted, repetitive patterns of behaviour, interests, or activities (minimum 2): 1) stereotyped or repetitive motor movements, use of objects, or speech; 2) insistence on sameness, inflexible adherence to routines, or ritualized patterns of verbal or nonverbal behaviour; 3) highly restricted, fixated interests that are abnormal in intensity or focus; 4) hyper- or hypo-reactivity to sensory input or unusual interest in sensory aspects of the environment.	engage in tasks that require sustained mental effort; 7) often loses things necessary for tasks or activities; 8) is often easily distracted by extraneous stimuli; 9) is often forgetful in daily activities. B. Hyperactivity and impulsivity (minimum 6 symptoms for 6 months): 1) often fidgets with or taps hands or feet or squirms in seat; 2) often leaves seat in situations when remaining seated is expected; 3) often runs about or climbs in situations where it is inappropriate; 4) often unable to play or engage in leisure activities quietly; 5) is often "on the go," acting as if "driven by a motor"; 6) often talks excessively; 7) often blurts out an answer before a question has been completed; 8) often has difficulty waiting his or her turn; 9) often interrupts or intrudes on others.	->> The presence of delusions, hallucinations, disorganized speech or behaviour is common to all psychotic disorders, including schizophrenia, schizoaffective disorder, bipolar I disorder with psychotic features, major depressive disorder with psychotic features or other specified schizophrenia spectrum and other psychotic disorder
Comorbid ASD	-	12.5% individuals with ADHD are diagnosed with ASD (122)	3-52% of individuals with schizophrenia present diagnostic criteria for ASD (123)
Comorbid ADHD	30-60% of individuals with ASD are diagnosed with ADHD (124,125)	-	20% of adults (26y/o) with schizophreniform disorder had a previous diagnosis of ADHD in childhood (11-15 y/o) (126).
Comorbid psychosis	Diagnosis of schizophrenia is more frequent in subjects with ASD (OR = 3.55) than in healthy controls (123)	Diagnosis of schizophrenia is more frequent in subjects with a history of ADHD (OR = 4.59) than healthy controls (127) 16% is the estimated population attributable fraction of developing schizophreniform disorder among children and adolescents with a diagnosis of ADHD (126).	-

Note: ASD: Autism Spectrum Disorders; ADHD: Attention-Deficit and Hyperactivity Disorder.

4.4.1. Autism Spectrum Disorders (ASD)

ASD are characterised by child-onset difficulties in social communication and interaction and restricted stereotypical/repetitive behaviours or interests (2,128). Genetic and environmental factors, and their interaction have been associated with increased risk of ASD (128). Up to 10-30% of cases of ASD have been causally related with de novo or inherited genetic variants (129). Environmental risk factors include prenatal (parental age ≥ 35 y/o, white or Asian parental race, gestational diabetes or hypertension, threat of abortion), perinatal (caesarean delivery, foetal distress, induced labor) and postnatal (low weight at birth, postpartum haemorrhage) risk factors (130–132). Prevalence has been estimated to be 0.8% in the general population (109), and comorbidity with other mental disorders is frequent, especially ADHD (124,125) (see table 2). Long-term outcomes (independent living, employment, friendships, and relation-ships) are overall poor, and strongly correlated with levels of reciprocal social interaction (133). Higher intelligence quotient in individuals with ASD is associated with better adaptative functioning and, to a lesser extent, better social outcomes in adulthood (134). The term "high-functioning" autism is used to describe subjects with ASD and an intelligence quotient ≥ 70 (135).

Meta-analytic data supports that subjects with ASD are characterized at cross-section by reduced grey matter volume in the pallidum, putamen, amygdala and nucleus accumbens and decreased cortical thickness in the temporal cortex yet increased cortical thickness in frontal cortex (136). Functional neuroimaging studies have shown reduced connectivity within the DMN in adults with ASD during rest (137,138). In contrast, resting-state fMRI studies encompassing children with ASD have reported overconnectivity relative to healthy controls (139). This has also been documented in new-borns with family risk for ASD (140). Adolescents with ASD present mixed findings in DMN connectivity, although hypo-connectivity remains the most frequently reported finding (141). To explain this shift from overconnectivity in children with ASD to hypoconnectivity in adults with ASD, authors have hypothesized either a progressive reduction of connectivity during neurodevelopment or an insufficient increase in connectivity in adolescents with ASD compared to typically developing youth (142). Both hypotheses are supported by cross-sectional studies evaluating the association between functional connectivity and age in ASD, which

have reported either a negative correlation within the ASD group (143) or the lack of positive correlation exhibited by the typically developing group (144). New-borns with family risk for ASD also lack the positive correlation between age and the connectivity pattern exhibited by controls without family risk (140). Lawrence et al. (145) demonstrated that adolescents with ASD lack the longitudinal changes in connectivity exhibit by their typically developing peers.

4.4.1.1. Autism Spectrum Disorder and Theory of Mind

Impairment in ToM has been widely studied in ASD (94,146) (see table 3) since it was firstly conceptualized by Baron-Cohen (22), and it is considered a core symptom of the disorder (128). Other authors, however, have hypothesized that deficits in social cognition may be secondary to reduced response to social stimuli, within the Social Motivation Theory (147). In any case, ToM is related with poor social functioning in subjects with ASD (148).

Functional neuroimaging studies using ToM tasks in ASD have reported lower brain activation in the TPJ and mPFC in individuals with ASD relative to controls (149,150). These regions have been identified as key in ToM processing in ASD in a meta-analysis (151) (see table 4). However, over-activation in the right TPJ among people with ASD who demonstrated no difficulties in task performance has also been reported (152). Regarding functional connectivity, subjects with ASD have been found not to present the typical increase of connectivity exhibited by healthy subjects within the mentalizing network during ToM tasks (149,152–154). In fact, most studies have reported reduced functional connectivity in people with ASD relative to typically developing controls during ToM, between the TPJ or superior temporal sulcus and different areas of the frontal lobe (149,155,156) (see table 5). Structural neuroimaging studies in ASD have reported a positive association of ToM performance with cortical thickness in right TPJ and right insula, and volume in amygdala and hippocampus (157). Presumably, no fMRI study so far has explored neural correlates of ToM in ASD when combined with ADHD, despite the frequent comorbid presentation, as discussed in the next section.

Table 3. Meta-Analyses summarizing the findings of Theory of Mind (ToM) performance in neurodevelopmental disorders (Autism Spectrum Disorders, ASD; Attention-Deficit and Hyperactivity Disorder, ADHD; Schizophrenia Spectrum Disorders, SCH) and Clinical High Risk for psychosis (CHR) compared to healthy controls (HC), and between disorders.

Age group	Author & year	Sample size	Differences between groups	Effect of age	Effect of sex	Effect of IQ
	ToM performance in ASD vs HC					
Children & adults	Yirmiya et al., 1998 (94) (ASD vs intellectual disability vs HC)	22 studies (only ASD vs HC)	HC > ASD in ToM (d = .88)	Differences between ASD and HC may increase with age	-	-
Adults	Chung et al., 2014 (146) (ASD vs SCH vs HC)	16 studies (only ASD vs HC) n(ASD) = 362 n(HC) = 315	HC > ASD in verbal ToM task (g = 1.05) HC > ASD in visual ToM task (g = .81)	No effects	No effects	No effects
Children & adults	Bliksted et al., 2016 (158) (ASD vs SCH vs HC) in Frith-Happé animated triangle task	11 studies (only ASD vs HC) n(ASD) = 259 n(HC) = 506	HC > ASD in intentionality (SMD = 3.43) ASD > HC in appropriateness (SMD = −2.37)	-	-	-
Adults	Velikonja et al., 2019 (159) (Social and non-social cognition)	39 studies (only ToM) n(ASD) = 2213 n(HC) = 4355	HC > ASD in ToM (g = −1.09)	No effects	No effects	No effects
Children & adults	Wilson, 2021 (160) in Frith-Happé animated triangle task	33 studies n(ASD) = 1530 n(HC) = 1569	HC > ASD in ToM in children (g = −0.62) HC > ASD in ToM in adults (g = −0.56)	No effect (g=0.03; p=0.83)	-	No effect of verbal ability (g=0.01; p=0.95)
	ToM performance in ADHD vs HC					
Children & adults	Bora & Pantelis, 2016 (161) (ASD vs ADHD vs HC)	44 studies (only ADHD vs HC) n(ADHD) = 1998 n(HC) = 1725	HC > ADHD in ToM (d = .45); within children (d = .56) and within adults (d = .04; n.s.) HC > ADHD in REMT (d = .44) HC > ADHD in Happé Stories (d = .56) HC > ADHD in ToM excluding comorbid ASD (d = .37)	Younger age in ADHD was associated with more severe ToM impairment; and more severe ToM impairments were found in child than adult samples.	No effects	IQ differences between ADHD and HC were associated with more severe social cognitive impairment

	ToM performance in SCH vs HC					
Adults	Sprong et al., 2007 (162)	29 studies n(SCH) = 831 n(HC) = 687	HC > SCH in ToM (d = -1.26) HC > SCH in first-order ToM tasks (d = -1.19) HC > SCH in second-order ToM tasks (d = -1.44) HC > SCH in indirect speech ToM tasks (d = -1.04) HC > SCH in intention-inferencing tasks (d = -.96)	No effects	No effects	No effects
Adults	Bora et al., 2009 (163)	36 studies n(SCH) = 1181 n(HC) = 936	HC > SCH in ToM (d = 1.10) HC > SCH in Hinting Task (d = 1.06) HC > SCH in REMT (d = .90) HC > SCH in False Belief sequencing (d = 1.08) HC > SCH in False Belief stories (d = 1.06) HC > SCH in first-order ToM tasks (d = .87) HC > SCH in second-order ToM tasks (d = 1.09)	No effects of age of onset, although those with longer duration of illness tended to be more impaired (β=.03; p = .06)	No effects	Deficits in IQ tended to impact on ToM difficulties in SCH (β=.35; p = .06)
Children & adults	Bora & Pantelis, 2013 (164) (FEP, UHR, GHR vs HC)	8 studies (only FEP vs HC) n(FEP) = 285 n(HC) = 228	HC > FEP in ToM (d = 1.0) HC > FEP (only SCH) in ToM (d = 1.11) HC > FEP in visual ToM (d = .94) HC > FEP in verbal ToM (d = .99)	-	-	-
Adults	Savla et al., 2013 (165)	50 studies (only ToM) n(SCH) = 1536 n(HC) = 1760	HC > SCH in ToM (g = .96)	No effects	No effects	No effects
Adults	Chung et al., 2014 (146) (ASD vs HC vs SCH)	23 studies (only SCH vs HC) n(SCH) = 634 n(HC) = 667	HC > SCH in verbal task (g = .99) HC > SCH in visual task (g = .73)	No effects	No effects	No effects
Adults	Song et al., 2015 (166) (SCH vs HC in Korea)	13 studies n(SCH) = 377 n(HC) = 386	HC > SCH in ToM (d = -1.27) HC > SCH in affective ToM (d = -1.45) HC > SCH in cognitive ToM (d = -1.20) HC > SCH in visual ToM (d = -1.22) HC > SCH in verbal ToM (d = -1.24)	No effects	No effects	No effects
Adults	Bliksted et al., 2016 (158) (ASD vs SCH vs HC in Frith-Happé animated triangle task)	9 studies (only SCH vs HC) n(SCH) = 287 n(HC) = 297	HC > SCH in intentionality (SDM=3.18) SCH > HC in appropriateness (SMD = −1.01)	-	-	-

ToM performance in CHR vs HC						
Children & adults	Bora & Pantelis, 2013 (164) (FEP, CHR, GHR vs HC)	7 studies (only CHR vs HC) n(CHR) = 332 n(HC) = 249	HC > CHR in ToM (d = .45) HC > CHR in visual ToM (d = .40) HC > CHR in verbal ToM (d = .49)	*CHR groups were significantly older than controls (p=0.02)*	-	-
Children & adults	Van Donkersgoed et al., 2015 (167)	7 studies (only ToM) n(CHR) = 348 n(HC) = 267	HC > CHR in ToM (d = .44) HC > CHR in visual ToM (d = .33) HC > CHR in verbal ToM (d = .52)	No effects	No effects	-
Children & adults	Lee et al., 2015 (168)	8 studies (only ToM) n(CHR) = 382 n(HC) = 291	HC > CHR in ToM (g = .42)	No effects	No effects	Lower IQ accounted for more deficits (estimate=−0.098, p= 0.13),
ToM performance comparing neurodevelopmental disorders						
ASD vs SCH: Children & adults	Fernandes et al., 2018 (169)	19 studies n(ASD) = 482 n(SCH) = 558	ASD = SCH in RMET (g = .22; n.s.) ASD = SCH in other ToM tasks (g = −.03; n.s.)	Significant moderator effect only in RMET (β=- .165; better performance by SCH in studies with younger participants)	[differences only reported by one study]	-
ASD vs SCH: Children & adults	Oliver et al., 2021 (170)	18 studies n(ASD) = 510 n(SCH) = 564	ASD = SCH (g = −.13; n.s.) ASD = SCH in RMET (g = .25; n.s.)	No effect	-	-
ASD vs ADHD: Children & adults	Bora & Pantelis, 2016 (161) (ASD vs ADHD vs HC)	17 studies (only ADHD vs ASD) n(ADHD) = 772 n(ASD) = 710	ASD > ADHD in ToM (d = .71)	No effects	No effects	Significant effects on between-group differences [although ToM results remained significant in IQ-matched samples (d = .52)]

Note: ASD: Autism Spectrum Disorders; ADHD: Attention-Deficit and Hyperactivity Disorder; CHR: Clinical High Risk for psychosis; d: Cohen's *d*; g: Hedges' *g*; HC: healthy controls; IQ: Intelligence Quotient; REMT: "Reading-the-Mind-in-the-Eyes" Test; n.s: no significant; SCH: Schizophrenia; SMD: Standardized Mean Difference; SSD: Schizophrenia Spectrum Disorders; ToM: Theory of mind.

Table 4. Meta-Analyses or systematic reviews summarizing the findings of brain activation in functional Magnetic Resonance Imaging (fMRI) during Theory of Mind (ToM) paradigms in neurodevelopmental disorders (Autism Spectrum Disorders, ASD; Attention-Deficit and Hyperactivity Disorder, ADHD; Schizophrenia Spectrum Disorders, SCH) and Clinical High Risk for psychosis (CHR) compared to healthy controls (HC).

Age group	Author & year	Kind of study	Sample size	Main findings
	Neural activation during ToM in ASD			
Children & adults	Sugranyes et al., 2011 (151)	Activation Likelihood Estimation meta-analysis (ASD vs SCH vs HC in facial emotion recognition and ToM)	7 studies (only ToM in ASD vs HC) n(ASD) = 91 n(HC) = 99	**Under-activation** in left medial frontal, right precentral, left anterior cingulate, left amygdala, left middle temporal and left inferior parietal.
	Neural activation during ToM in ADHD			
	No meta-analyses, no studies			
	Neural activation during ToM in SCH			
Adults	Sugranyes et al., 2011 (151)	Activation Likelihood Estimation meta-analysis (ASD vs SCH vs HC in facial emotion recognition and ToM)	9 studies (only ToM in SCH vs HC) n(SCH) = 133 n(HC) = 140	**Under-activation** in left medial frontal, right posterior cingulate, left middle temporal and left thalamus. **Over-activation** in right paracentral lobe and left posterior cingulate.
Adults	Mothersill et al., 2016 (171)	Activation Likelihood Estimation meta-analysis focused on cerebellum	2 studies n(SCH) = 33 n(HC) = 27	Overlap in one cluster in the left vermis.
Adults	Kronbichler et al., 2017 (172)	Voxel-based meta-analysis using Seed-based *d*Mapping	21 studies n(SCH) = 308 n(HC) = 315	**Under-activation** in mPFC, right premotor Cortex, medial Occipito-parietal, right lingual gyrus, left orbito-frontal cortex, left lateral occipito-temporal, left cingulate gyrus. **Over-activation** in bilateral parietal cortex.
Adults	Jáni & Kašpárek, 2018 (19)	Voxel-based meta-analysis using Seed-based *d*Mapping (Emotion recognition and ToM)	16 studies (only ToM) n(SCH) = 262 n(HC) = 279	**Under-activation** in right insula, bilateral superior frontal gyrus, left cuneus, right posterior cingulate, right precentral gyrus. **Over-activation** in superior frontal gyrus, right inferior parietal, left inferior frontal gyrus, right precuneus, and left supramarginal gyrus.

Children & adults	Vucurovic et al., 2020 (173)	Activation Likelihood Estimation meta-analysis	17 studies (only ToM) n(SCH) = 274 n(HC) = 286	**Under-activation** in left temporo-parietal junction.
	Neural activation during ToM in CHR			
Children & adults	Kozhuharova et al., 2020 (174)	Systematic review (social cognition) > only 2 studies about ToM	Brüne et al., 2011 (175): n(CHR) = 10 (SCH) = 22 n(HC) = 26	**Under-activation** in superior and medial frontal gyrus, posterior cingulate cortex and superior temporal gyrus (and in precuneus relative to SCH) **Over-activation** in inferior frontal gyrus, posterior cingulate, temporal and temporo-parietal areas and precuneus (and in inferior frontal gyrus and temporo-parietal areas relative to SCH)
			Takano et al., 2017 (176): n(CHR) = 17 n(SCH) = 16 n(HC) = 20	**Under-activation** in bilateral inferior frontal gyrus (and only in right inferior frontal gyrus relative to SCH) **Over-activation** in left Superior Temporal Gyrus (but under-activation vs. SCH)
Children & adults	Damme et al., 2019 (177)	Single study (self-reference task)	n(CHR) = 22 n(HC) = 20	No differences

Note: ASD: Autism Spectrum Disorders; ADHD: Attention-Deficit and Hyperactivity Disorder; CHR: Clinical High Risk for psychosis; HC: healthy controls; mPFC: medial prefrontal cortex; SCH: Schizophrenia; ToM: Theory of mind.

Table 5. Main studies of intrinsic functional connectivity in task-based and resting-state functional Magnetic Resonance Imaging (fMRI) in relation to Theory of Mind (ToM) in neurodevelopmental disorders (Autism Spectrum Disorders, ASD; Attention-Deficit and Hyperactivity Disorder, ADHD; Schizophrenia Spectrum Disorders, SCH) and Clinical High Risk for psychosis (CHR) compared to healthy controls (HC).

Age group (mean age; [range])	Author & year	Sample size (% female)	Task during fMRI	Main findings
Functional connectivity during ToM in ASD				
Adults (29 y/o)	Castelli et al., 2002 (178)	n(ASD) = 10 n(HC) = 10	Frith-Happé animated triangles	HC > ASD in the ToM vs control condition contrast in the Right Extrastriate Cortex-STS
Adults (27 y/o)	Mason et al., 2008 (155)	n(ASD) = 18 (6%) n(HC) = 18 (11%)	Three-sentences stories	Within network: HC > ASD during ToM in LMFG-RTPJ Between network: HC > ASD in language ROIs – ToM ROIs
Adolescents & adults (25 y/o; [16-36 y/o])	Kana et al., 2009 (152)	n(ASD) = 12 (17%) n(HC) = 12 (0%)	Frith-Happé animated triangles	HC: ToM > Control condition in RTPJ areas ASD: ToM = Control condition HC > ASD in all inter-lobe networks (frontal-parietal-occipital-temporal)
Adults (22 y/o)	Murdaugh et al., 2012 (179)	n(ASD) = 13 (0%) n(HC) = 14 (0%)	Comic strip vignettes	HC > ASD in the dorsal mPFC (within DMN connectivity)
Children & adolescents (14 y/o; [11-17 y/o])	White et al., 2014 (180)	n(ASD) =22 (14%) n(HC) = 11 (9%)	ToM stories	ToM > Control condition in both groups No group effect
Adolescents & adults (22 y/o; [16-34 y/o])	Kana et al., 2014 (156)	n(ASD) = 15 n(HC) = 15	Comic strip vignettes	HC > ASD during ToM in LMTG:LPMv; LPMv:LSPL; LPMv:RMTG; LPMv:RTPJ; SMA:LSPL ASD > HC during Control condition in the LFFG: LMTG; LFFG: RTPJ; left middle occipital gyrus: LMTG; LMTG: RFFG and LPMv: LSPL) Between network: HC > ASD in the ventral premotor network – TPJ network
Children & adolescents (13 y/o; [10-16 y/o])	Kana et al., 2015 (153)	n(ASD) = 13 (15%) n(HC) = 13 (15%)	Frith-Happé animated triangles	HC > ASD during ToM in the frontal-medial, frontal-parietal and medial-cerebellum networks
Adolescents & adults (19 y/o; [14-32 y/o])	Ciaramidaro et al., 2015 (149) (ASD vs SCH vs HC)	n(ASD) = 23 (9%) n(HC) = 23 (17%)	Comic strip vignettes	HC: ToM > Control condition in the (RSTS) with the mPFC, RTPJ, LTPJ, LSTS, right Temporal Pole, RFFG, LFFG, left SMA, LDLPFC and RDLPFC ASD: ToM > Control condition in the (RSTS) with the RTPJ, LTPJ, RFFG, LSTS HC> ASD during ToM in the (RSTS) with the mPFC
Adults (30 y/o)	Cole et al., 2019 (154)	n(ASD) = 20 (40%) n(HC) = 20 (40%)	Action videos	No group or condition effect in the mentalizing system HC: ToM > Control condition in the mPFC-IFG and mPFC-inferior parietal lobe

Functional connectivity during ToM in ADHD				
No meta-analysis, no studies				
Functional connectivity during ToM in SCH				
Adults (34 y/o)	Das et al., 2012 (181)	n(SCH)* = 23 (0%) n(HC) = 22 (0%) *Duration of illness = 9 years	Frith-Happé animated triangles	Between networks: HC > SCH in the insula-DMN, lateral FTN-medial FTN and posterior DMN and medial FTN Functional connectivity in the lateral FTN-medial FTN during ToM was correlated with ToM performance in both groups.
Adults (27 y/o)	Eack et al., 2013 (182)	n(SSD)* = 20 (30%) n(HC) = 20 (35%) *Duration of illness = 5 years	Visual perspective-taking task	SSD > HC during ToM in the anterior CC-RFFG/parahippocampal area (SSD showed positive correlation, and HC showed negative correlation)
Adolescents & adults (23 y/o; [14-32 y/o])	Ciaramidaro et al., 2015 (149) (ASD vs SCH vs HC)	n(SCH)* = 18 (22%) n(HC) = 23 (17%) *Duration of illness = 6 years	Comic strip vignettes	HC: ToM > Control condition in the (RSTS) with the mPFC, RTPJ, LTPJ, LSTS, right Temporal Pole, RFFG, LFFG, left SMA, LDLPFC and RDLPFC SCH: ToM > Control condition in (RSTS) with LTP, LSTS, RFFG, RDLPFC, LIFG SCH > HC during Control condition in (RSTS) with mPFC
Adults (46 y/o)	Martin et al., 2016 (183)	n(SCH)* = 19 (42%) n(HC) = 17 (47%) *Age at onset = 24 y/o	Frith-Happé animated triangles	SCH: during ToM in (LIFG) with LPC, RSFG, RIFG, RMFG, right CC; and (left Caudate) with right Parahipppocampal, right Paracentral lobule, LMTG SCH: during control condition in (LIFG) with right posterior CC, L putamen, R culmen, RSFG; and within left Caudate
Adults (38 y/o)	Mier et al., 2017 (184)	n(SCH)* = 22 n(HC) = 22 *Age at onset = 28 y/o	Afective ToM (statements after facial expressions)	Affective ToM: HC > SCH increased connectivity between RSTS and LSTS from control condition to ToM
Adults (35 y/o; [21-44 y/o])	Okruszek et al., 2018 (185)	n(SCH)* = 25 (48%) n(HC) = 26 (46%) *Duration of illness = 11 years	Biological motion	HC > SCH in RSTS and R Cerebellar Crus II
Adults (32 y/o; [21-44 y/o])	Erdeniz et al., 2017 (186)	n(SCH)* = 23 (39%) n(HC) = 23 (39%) *Duration of illness = 16 years	Resting-state connectivity correlated with ToM (RMET)	Performance in ToM positively correlated (r=.3-.4) with nodal efficiency in left amygdala and right putamen, and nodal degree in LMTG.
Adults (39 y/o)	Mothersill et al., 2017 (187)	n(SCH) = 27 (26%) n(HC) = 25 (32%)	Resting-state connectivity correlated with ToM (RMET)	SCH: Positively correlated with LPC-right middle CC, LPC-RIFG, LTPJ-right calcarine gyrus and LTPJ-right lingual gyrus. Negatively correlated with LPC-right insula, LPC-LSTG.
Adults (range: 15-40 y/o; mean age = 23 y/o)	Choe et al., 2018 (188)	n(FEP) = 26 (54%) n(HC) = 26 (58%)	Resting-state connectivity correlated with ToM (Strange Stories)	SCH: Negatively correlated with within-network connectivity of the Mirror Neuron System.

Adults (mean age = 32 y/o)	Zemánková et al., 2018 (189)	n(SCH)* = 23 (17%) n(HC) = 19 (26%) *Duration of illness = 8 years	Resting-state connectivity correlated with ToM (Faux Pas)	HC: Positively correlated with mPFC-right amygdala, right accumbens, right hippocampus SCH: Negatively correlated with mPFC-subcallosal cortex, left orbito-frontal cortex
Adults (range: 18-53; mean age = 30 y/o)	Bitsch et al., 2021 (190)	n(SCH)* = 31 (32%) n(HC) = 20 (50%) *Duration of illness = 9 years *[Also included schizoaffective disorder]*	Iterated prisoner's dilemma game	HC > SCH in dorsal mPFC and bilateral TPJ
	Functional connectivity during ToM in CHR			
Adolescents & adults (20 y/o; [13-24 y/o])	Vargas et al., 2019 (191)	n(CHR) = 24 (42%) n(HC) = 26 (50%)	Resting-state connectivity correlated with ToM (Short Story Task)	CHR: greater global efficiency in mPFC for those with spontaneous ToM
Adolescents & adults (21 y/o; [16-23 y/o])	Damme et al., 2019 (177)	n(CHR) = 22 (41%) n(HC) = 20 (45%)	Self-reference task and resting-state connectivity correlated with ToM	Task-based: HC > CHR in coactivation between bilateral PCC-right mPFC Resting: CHR > HC in coactivation between bilateral PCC-right mPFC (not significantly correlated with task)

Note: ASD: Autism Spectrum Disorders; ADHD: Attention-Deficit and Hyperactivity Disorder; CC: Cingulate Cortex; CHR: Clinical High Risk; DMN: Default Mode Network; FEP: First Episode of Psychosis; FTN: FrontoTemporal Network; fMRI: functional Magnetic Resonance Imaging; HC: healthy controls; LDLPFC and RDLPFC: left and right dorso-lateral Prefrontal Cortex; LFFG and RFFG: left and right fusiform gyrus; LIFG and RIFG: Left and Right Inferior Frontal Gyrus; LMFG and RMFG: left and right medial frontal gyrus; LMTG and RMTG: left and right middle temporal gyrus; LPC: left Precuneus; LPMv: Left ventral PreMotor cortex; LSPL: left superior parietal lobule; LSTS and RSTS: Left and Right Superior Temporal Sulcus; LTPJ and RTPJ: left and right temporal parietal junction; mPFC: medial Prefrontal Cortex; RMET: "Reading-the-Mind-in-the-Eyes" Test; ROI: Region of Interest; RSFG: right superior frontal gyrus; SCH: Schizophrenia; SMA: supplementary motor area; SSD: Schizophrenia Spectrum Disorders; ToM: Theory of mind; y/o: years old.

4.4.2. Attention Deficit And Hyperactivity Disorder (ADHD)

ADHD, with an estimated prevalence of 7.2% in general population (110), is characterized by age-inappropriate symptoms of inattention, hyperactivity and impulsivity (2). Individuals with untreated ADHD present long-term poorer social functioning than healthy controls and than those receiving treatment (192). ADHD and ASD are frequently comorbid conditions; 30-60% of individuals with ASD are diagnosed with ADHD (124,125), and 12.5% individuals with ADHD are diagnosed with ASD (122) (see table 2).

Genetic and environmental factors have been associated with ADHD, pointing to gene x environment interactions as the pathophysiological mechanisms underlying the development of the disorder (193). Maternal obesity, gestational hypertension or pre-eclampsia, gestational exposure to acetaminophen or smoking, caesarean delivery and childhood eczema have been associated with increased risk of developing ADHD (120,130). Subjects with ADHD have been found to present less grey matter volume in the ventral mPFC, extending to the right caudate, and right insula, in relation to controls (194). In addition, reduced basal ganglia volumes and less cortical thickness in the fusiform gyrus and temporal pole, have also been described in ADHD by meta-analysis (195). Most resting-state fMRI studies have reported reduced functional connectivity within- the DMN in ADHD (196). In contrast, a task-based fMRI meta-analysis has described predominant hyper-activation in areas overlapping with the DMN in subjects with ADHD relative to healthy controls (197). Taking both findings together, the *DMN interference hypothesis* has been the most accepted explanation for ADHD pathophysiology (59). Spontaneous fluctuations of the DMN, probably due to a dysfunction of the salience network, would interfere with the anticorrelation of the DMN with the central executive network, therefore impairing attention and executive functioning (59). It remains unknown whether social deficits in ADHD are secondary to this dysfunction or altered primarily, as discussed in the next section.

4.4.2.1. Attention Deficit and Hyperactivity Disorder and Theory of Mind

ToM is impaired in ADHD, although with less severe deficits than ASD (161) (see table 3). In addition, ToM impairments in ADHD seem to be more significant during childhood and adolescence than in adulthood (161), in contrast with ASD, whose ToM deficits seem to be persistent over the lifetime (160). The different effect size and pattern of age-related changes in ToM impairment between ADHD and ASD (161), despite sharing deficits in other cognitive domains (198), makes it unlikely that the two disorders share a common neural ToM pathway (199). In fact, executive functions and hyperactive/impulsive symptomatology significantly modulate ToM performance in ADHD (200,201), while ToM difficulties in subjects with ASD are more related with core ASD symptomatology (evaluated with the Autism Diagnostic Observation Schedule, Autism Diagnostic Interview-Revised and Social Responsiveness Scale) than with ADHD symptomatology (202). These findings support the hypothesis that neural correlates of social cognitive deficits are likely to differ between the two disorders.

In line with this, electro-encephalographic studies have identified differences in social cognition (measuring facial emotion processing) between ASD, ADHD (203–205) and the ASD+ADHD comorbid condition; with the latter presenting an additive effect in comparison to the single presentation of each disorder (203,204). Two structural neuroimaging studies in ADHD have reported a positive association of ToM performance with volume in amygdala and hippocampus (157) and grey matter volume in mPFC and right angular gyrus (206). Presumably, there are no task-based fMRI studies so far focusing on the neural correlates of ToM in ADHD, aiming to disentangle whether ToM deficits in ADHD, and the ASD+ADHD comorbid condition, are underpinned by similar or different brain functional mechanisms of ASD and to identify the neural mechanisms of ToM in ADHD compared to healthy controls.

4.4.3. Early-Onset Psychosis (EOP)

Psychotic disorders are characterized by the presence of delusions, hallucinations, disorganized thinking, grossly disorganized or abnormal motor behaviour and, especially in schizophrenia, negative symptoms (2). Lifetime prevalence of psychotic disorders has been estimated at 1 % in the general population (111), where schizophrenia and other non-affective psychotic disorders are the most incident diagnosis (108). Peak rates of incidence of non-affective psychosis take place during adolescence (108); and EOP has been proved to have a poorer prognosis than when onset of the disease takes place during adulthood (207,208). Younger age at onset of psychosis has been related with more hospitalizations, more negative symptoms and poorer social functioning (209).

Multifactorial genetic and gene-environment interactions are likely to underlie the aetiology of schizophrenia and related psychoses (210). Socio-demographic factors (black-Caribbean ethnicity in England, ethnic minority and second generation immigrants), obstetric complications (for instance emergency caesarean delivery, low weight at birth or gestational diabetes) or substance abuse (especially cannabis) have been widely studied and reported as risks factors for psychotic disorders and schizophrenia (121,211,212). Early years of life and neurodevelopment have been pointed as the key period of vulnerability to develop schizophrenia (97,98). Therefore, and as mentioned before, schizophrenia spectrum disorders have been conceptualized as neurodevelopmental disorders (97,98), while this remains more controversial for affective psychoses (213,214). Nevertheless, the diagnosis of a clinical high risk state for developing psychosis is the factor with the strongest association with an ulterior diagnosis of a psychotic disorder (121), as will be discussed in the next section.

Schizophrenia has been associated with widespread cortical reductions in thickness and surface, as supported by meta-analytic data (215). Subjects with first episode of psychosis have been found to present reduced grey matter volume in the right superior temporal gyrus and left insula (216), and regarding EOP, reduced volume in hippocampus and increased volume in pallidum have been reported by

meta-analysis, and specifically in early-onset schizophrenia in comparison to affective psychosis (217). Hypoconnectivity of the mPFC within the DMN is the most consistent finding in resting-fMRI studies involving subjects with schizophrenia, as shown by two meta-analyses (218,219). In contrast, some studies have reported over-connectivity (220); while studies encompassing adolescents with EOP have reported mixed findings (both hypo- and hyper-connectivity), as detailed by a recent review (141). Despite the conceptualization of schizophrenia as a neurodevelopmental disorder, most studies have failed to report age effects on functional connectivity in patients with psychosis (189,221). Precuneus connectivity with left inferior frontal cortex and left middle occipital cortex was found to positively and negatively correlate with age, respectively, in adolescents and adults with a first episode of psychosis (222). Dysfunctional within-DMN connectivity, as well as altered connectivity between the DMN and the salience and central executive networks, have been hypothesized to explain symptomatology in schizophrenia, according to the *Triple Network Model* (60,223). Altered connectivity within- and between- these three networks could explain psychotic symptoms (due to the attribution of external source to internal thoughts), executive dysfunction (due to interference of the DMN with activation of the fronto-parietal network during tasks), and deficits in social functioning (due to impaired ToM involving the DMN, as described in further detail in the next section).

4.4.3.1. Clinical High Risk for Psychosis (CHR)

Pre-clinical symptoms usually precede the development of first episodes of psychosis. This earlier phase preceding the psychosis has been described and conceptualized as the *At-Risk Mental State*, *Ultra-High Risk for Psychosis*, *Psychosis Risk Syndrome* or *Clinical High Risk for Psychosis* (CHR) (224–226). Clinical criteria used to identify patients presenting as CHR have been defined as:

- Attenuated positive or negative symptoms of psychosis (227); evaluated with the Structured Interview for Prodromal Symptoms, scored on the Scale of Prodromal Symptoms (SIPS/SOPS) (228).

- Brief limited intermittent psychotic symptoms (227); evaluated with the Structured Interview for Prodromal Symptoms, scored on the Scale of Prodromal Symptoms (SIPS/SOPS) (228).
- First or second degree relative with schizophrenia or a diagnosis of schizotypal disorder, in combination with a significant decline in functioning (229) according to Structured Interview for Prodromal Symptoms, scored on the Scale of Prodromal Symptoms (SIPS/SOPS) criteria (228).

A 22% cumulative risk of transition to psychosis has been estimated in individuals at CHR at 3 years follow-up (230). Although a modest age effect was described in previous investigations, with older participants presenting greater risk of transition to psychosis (231), transition rates in samples encompassing adolescents at CHR have been estimated to be at 23% at 36 months follow-up (232), similar to adult samples.

Structural neuroimaging studies have found both increased (in the median cingulate, right fusiform gyrus, left temporal pole, right thalamus) and decreased (in the right gyrus rectus and bilateral superior frontal gyrus) grey matter volume in subjects at CHR (233); although some meta-analyses have reported no differences in brain structure between individuals at CHR and healthy controls (234). Development of psychosis has been associated with reduced grey matter in the temporal pole and right anterior cingulate cortex (233–235). Similar to schizophrenia and related psychoses, mixed findings have been reported in functional neuroimaging in participants at CHR, with reports of hyperconnectivity (236), hypoconnectivity (237) or both (238). There are also inconsistencies in relation to predicting transition to psychosis in functional studies: both, hyper- and hypo-connectivity during the resting-state in participants at CHR, have been associated to transition to psychosis (239,240).

4.4.3.2.Psychotic Disorders and Theory of Mind

Several meta-analyses have confirmed impaired ToM in schizophrenia (163) (see table 3) and affective disorders (241,242). ToM deficits are more severe in schizophrenia than in bipolar disorder (243); in which it has been hypothesized that the history of psychotic symptoms could mediate ToM impairments, although the evidence is inconsistent (241). ToM presents the highest correlation with quality of life, clinical insight and everyday functioning in schizophrenia (rated by an interviewer and based on independent living skills and social or work functioning), stronger than any other neurocognitive domain (13,14,244). ToM has been associated, not only with level of overall functioning, but also and specifically, with social functioning (245). Meta-analyses and most of the studies evaluating ToM have included adult samples, although social cognitive deficits in schizophrenia may be more severe when the onset of the disorder takes place during adolescence (246). Few studies have focused on evaluating ToM impairments in participants with EOP (247–251), as summarized in table 6. And these studies have reported either no effect of age or have failed to examine age effects in their samples.

Table 6. Summary of previous studies comparing performance in tasks assessing Theory of Mind (ToM) in individuals with early-onset psychosis (EOP) relative to healthy controls (HC). [Adapted from Study II]

Author & year	Sample	Age (years)	Sex (female)	Duration of disease (months)	ToM task	Results	Effect of age	Effect of sex	Effect of IQ
Pilowsky et al., 2000[a] (247)	12 EOSz 12 HC	12.2 (SD=1.7) 8.5 (SD=1.3)	8% 25%		Fact and value belief task, Deception task, False-belief task	Impaired ToM in EOP compared to HC in the false-belief task	-	-	**Arithmetic ability may influence performance on the False-belief task within EOSz*
Korver-Nieberg et al., 2013 (249)	32 EOP 78 HC	17.1 (SD=1.3) 16.3 (SD=1.6)	39% 36%		Perspective-taking task	No significant differences in cognitive ToM	No effect	No effect	Negatively associated to perspective-taking errors
Bourgou et al., 2016 (248)	12 EOSz 12 HC	14.8 (SD=1.7) 14.7 (SD=1.5)	42% 50%	30±6 -	Moving Shapes Paradigm (*Frith-Happé* Animated Triangles)	Impaired ToM in EOP compared to HC.	No correlation	No correlation	(IQ not measured)
Li et al., 2017 (251)	35 EOSz 35 HC	16.5 (SD=1.4) 16.3 (SD=1.2)	43% 43%	16±15 -	Yoni Task, Faux Pas Task	Impaired affective and cognitive ToM in EOP compared to HC.	-	-	(No differences between groups)
Tin et al., 2018[b] (250)	30 EOSz 30 HC	17.5 (SD=1.2) 17.2 (SD=1.0)	37% 30%	27±16 -	Yoni Task, Faux Pas Task	Impaired affective and cognitive ToM in EOP compared to HC.	-	-	(No differences between groups)

Note: HC = Healthy Controls; EOP = Early-Onset Psychosis; EOSz = Early-Onset Schizophrenia; IQ = intelligence quotient; SD = Standard Deviation; ToM = theory of mind; a: A third group with Autism Spectrum Disorder (n=12; 8% female) also included for comparison; b: A third group with Autism Spectrum Disorder (n=30; 23% female) also included for comparison.

Under-activation in frontal regions, such as the mPFC, superior frontal gyrus, or orbito-frontal cortex, are the most frequently reported findings pooled by several meta-analyses of fMRI during ToM tasks in subjects with schizophrenia (19,151,172) (see table 4). Mixed results are described for the posterior cingulate, occipito-parietal and temporo-parietal regions. These meta-analyses only included adult samples, and only a single study has examined the neural correlates of a social cognitive domain in individuals with EOP, documenting abnormal visual and facial emotion processing (252), but not examining ToM. Neuroimaging studies investigating functional connectivity during ToM tasks have reported underconnectivity in subjects with schizophrenia relative to healthy controls between the TPJ, mPFC and other regions typically recruited during performance of ToM tasks (see table 5). Functional connectivity between these areas has also been found to be reduced during resting-state fMRI in adults with schizophrenia relative to healthy controls (253). In fact, given the anatomic overlap of these regions with the DMN, resting-state connectivity has been also correlated with ToM abilities in adults with schizophrenia (189) (see table 5). In addition, intrinsic functional connectivity seems to be a better predictor of social functioning and cognitive performance than task-based fMRI in subjects with schizophrenia spectrum disorders (254). Structural studies have also reported a correlation between reduced grey matter volume in mPFC with poor ToM performance in young adults with schizophrenia (255). Although during adolescence there is a confluence of the critical period for brain development (70) and the development of ToM skills (48), presumably no studies so far have assessed the neural correlates of ToM in youth with EOP, and have evaluated the effect of age.

4.4.3.3.Clinical High Risk for Psychosis and Theory of Mind

Similarly to schizophrenia, three meta-analyses have reported ToM deficits in CHR (164,167,168), although with smaller size effects, as shown in table 3. When looking at studies individually, findings are mixed, even when examining the same task (such as the "Reading-The-Mind-in-the-Eyes" Test, as shown in table 7). These discrepancies could be related to age differences in the samples (which usually encompass both adolescents and adults), or with the subsample of participants who later transition to psychosis. Only one study has reported reduced correlation between ToM performance and age in participants at CHR relative to healthy controls assessed cross-sectionally (45); although in this study transition outcome was not considered. Only three longitudinal studies have reported data on ToM performance according to transition outcome: 1) Shaakel et al. (256) found that individuals at CHR who transition to psychosis at follow-up (CHR-t) lacked the improvement in ToM performance exhibited by those who did not transition (CHR-nt); and 2) Healey et al. (257) and Zhang et al. (258) reported that poorer ToM performance at baseline predicted transition to psychosis. The three studies encompassed adolescents and adults, but neither of them explored the effect of age (256–258). Therefore, presumably, no study to date has explored whether deficits in ToM performance in individuals at CHR-t are influenced by age.

Table 7. Summary of previous studies evaluating performance in Reading-the-Mind-in-the-Eyes Test (RMET) to assess Theory of Mind (ToM) in individuals with clinical high risk for psychosis (CHR) relative to healthy controls (HC) [Adapted from Study III](257,259–262).

Author & year	Sample	Age (years)	Sex (female)	Results	Effect of age	Effect of sex	Effect of IQ
Couture et al., 2008[a] (259)	88 CHR 41 HC	18.9 (SD=4.6) 23.0 (SD=5.9)	43% 7%	No significant differences	-	No influence	-
Szily et al., 2009[b] (260)	26 CHR (with MDD) 50 HC	22.0 (SD=8.7) 21.1 (SD=6.3)	58% 62%	HC > CHR on the recognition of negative social emotions	-	-	-
Stanford et al., 2011[c] (261)	63 CHR 24 HC	19.6 (SD=3.6) 21.0 (SD=3.6)	21% 38%	No significant differences	No influence	No influence	RMET performance positively associated with IQ
Healey et al., 2013 (257)	147 CHR (> 29 CHR-t[e]) 85 HC (> 5 transition to psychosis)	19.8 (SD=4.7) 19.4 (SD=4.1)	42% 48%	No significant differences between HC and CHR (both groups improved significantly over time) > Transition: poor ToM performance predicted transition to psychosis	-	-	RMET remained a significant predictor of transition to psychosis when controlling by IQ
Zhang et al., 2018[d] (262)	84 CHR 95 HC	19.2 (SD=4.6) 20.3 (SD=4.9)	42% 51%	HC > CHR on performance and time consumption	-	-	Visual and verbal learning (and attention) predicted RMET performance within CHR
Zhang et al., 2018 (258) *[Longitudinal analysis from previous Zhang et al., 2018 (262)]*	> 26 CHR-t > 57 CHR-nt 90 HC	18.8 (SD=2.8) 19.3 (SD=5.1) 20.3 (SD=1.7)	50% 39% 59%	HC > CHR-nt > CHR-t on performance	-	-	Correlation of ToM performance with neurocognition within CHR-t

Note: CHR = participants at Clinical High Risk; CHR-t = participants at Clinical High Risk for psychosis who transition to psychosis; CHR-nt = participants at Clinical High Risk for psychosis who did not transition to psychosis; HC = Healthy Controls; IQ = Intelligence Quotient; MDD = Major Depressive Disorder; RMET = Reading-the-Mind-in-the-Eyes Test; SD = Standard Deviation; *a*: A third group with familial risk for psychosis without psychotic symptoms (n=13; 38% female) also included for comparison; *a*: A third group with schizophrenia (n=26; 12% female) also included for comparison; *b*: A third group with Major Depressive Disorder (n=42; 64% female) also included for comparison; *c*: A third group with Schizophrenia (n=13; 54% female) and a fourth group of older healthy controls (n=14; 64% female) also included for comparison; *d*: A third group with Schizophrenia (n=66; 53% female) also included for comparison; [e]: data available for 28.

Again, only three studies have explored ToM task-based fMRI in CHR (175–177), and have reported mixed findings concerning the activation of mentalizing regions (such as under and over-activation in posterior cingulate, temporal and frontal areas) relative to healthy controls and subjects with schizophrenia; or even no differences (177); as shown in table 4. Again, these discrepancies could be related with the subsample of participants who later transition to psychosis, a factor which was not explored in the mentioned studies. Similarly to task-based fMRI studies, only two studies have explored resting-state functional connectivity correlates of social cognition in CHR (177,191) as shown in table 5. Vargas et al.(191) found that greater global efficiency in the mPFC within the mentalizing network in individuals at CHR was associated with better ToM performance. Damme et al. (177) reported reduced functional connectivity during a self-reference task and increased functional connectivity during the resting-state, in individuals at CHR, between the mPFC and precuneus. The four mentioned neuroimaging studies reporting neural correlates of ToM in CHR (175–177,191) mixed adolescents and adults, did not explore the potential effect of age, and did not report on transition-to-psychosis outcome. Despite evidence suggesting that changes in brain connectivity associated with ToM in psychosis take place early on and may interact with typical development, no study to date has evaluated the neural correlates of ToM in individuals at CHR according to transition to psychosis and assessed the effects of age on these findings.

In summary, there is a large body of evidence supporting that subjects with neurodevelopmental disorders, especially ASD and ADHD, present deficits in ToM. This is also the case for schizophrenia, in which ToM impairments appear to be more severe when the first episode of psychosis takes place at younger ages, and with a potential onset of these deficits before clinical emergence of the disorder (as shown in table 3). Research findings about ToM performance in subjects with the comorbid presentation of ASD and ADHD are conflicting; as are the results from studies regarding the effect of age on the acquisition of ToM in adolescents within the spectrum of psychosis.

There is a fair amount of evidence concerning the neural deficits underlying ToM impairment in subjects with ASD and adults with schizophrenia. However, there are no fMRI studies evaluating the neural correlates of ToM in subjects with ADHD or ASD+ADHD comorbidity, in adolescents with EOP, or in adolescents at CHR according to transition to psychosis. Within the psychosis spectrum, the potential effect of age on the neural correlates of ToM has not been studied, either.

Therefore, the impact that some neurodevelopmental disorders occurring during youth exert on brain functional connectivity underlying ToM, and whether there is a cross-disorder overlap in neural pathways, or whether they differ between neurodevelopmental disorders (263), remain unanswered questions. There is a need to tailor interventions targeting these deficits, and a better understanding of the neural correlates of ToM in these disorders would contribute to this end. The aim of this thesis is to explore the neural correlates underlying ToM impairment in youth with ADHD, the ASD+ADHD comorbid condition, EOP and at CHR.

5. HYPOTHESIS

5.1. Main

- [1] Young adults with ADHD would display worse ToM performance than healthy controls, but better than young adults with ASD or ASD+ADHD.
- [2] Young adults with comorbid ASD+ADHD would display worse ToM performance than those with ASD, with ADHD or healthy controls.
- [3] Youth with EOP and adolescents at CHR-t would display worse ToM performance than healthy controls and adolescents at CHR-nt.
- [4] Young adults with ADHD would present less activation in prefrontal and temporo-parietal areas and lower brain functional connectivity between mentalizing areas than healthy controls, but greater activation and functional connectivity than young adults with ASD or ASD+ADHD.
- [5] Young adults with ASD+ADHD would present less activation in prefrontal and temporo-parietal areas and lower brain functional connectivity in mentalizing areas relative to young adults with ADHD, ASD and healthy volunteers.
- [6] Youth with EOP, or adolescents at CHR-t, would present lower brain functional connectivity in the prefrontal cortex within the DMN relative to healthy controls and adolescents at CHR-nt.
- [7] In all participants ToM performance would positively correlate with brain functional connectivity; therefore, worse performance in the ToM task would correlate with reduced brain functional connectivity.

5.2. Secondary

- [8] Youth with EOP or adolescents at CHR-t would fail to display the age-related improvements in ToM performance and increases in brain functional connectivity exhibited by healthy controls or adolescents at CHR-nt.
- [9] Youth with EOP with schizophrenia spectrum disorders would present more severe ToM impairments and lower brain functional connectivity in the prefrontal cortex within the DMN relative to youth with EOP with affective psychosis.
- [10] Poor ToM performance or lower brain functional connectivity would be associated with higher rates of transition to psychosis within adolescents at CHR.

6. AIMS

2.1.1. Main

- To evaluate ToM in young adults with ADHD, with and without comorbid ASD, and compare them with healthy controls.	➢ Study I
- To evaluate brain activation and functional connectivity while performing a ToM task in young adults with ADHD, with and without comorbid ASD, and compare them with healthy controls.	➢ Study I
- To evaluate ToM in youth with EOP and adolescents at CHR, and CHR according to transition to psychosis, and compare them with healthy controls.	➢ Study II and III
- To evaluate brain functional connectivity in youth with EOP and adolescents at CHR, and CHR according to transition to psychosis, and compare them with healthy controls.	➢ Study II and III
- To evaluate the association between ToM performance and brain functional connectivity in young adults with ADHD, with and without comorbid ASD, youth with EOP, adolescents at CHR and healthy controls.	➢ Study I, II and III

2.1.2. Secondary

- To assess the influence of age on ToM performance and brain functional connectivity within youth with EOP and adolescents at CHR.	➢ Study II and III
- To assess ToM performance and brain functional connectivity in youth with EOP according to whether they have a diagnosis of schizophrenia-related psychosis or affective psychosis	➢ Study II
- To assess the association between ToM performance or brain functional connectivity and transition to psychosis within adolescents at CHR	➢ Study III

7. SCIENTIFIC PUBLICATIONS

7.1. STUDY I:

Neural Correlates of Theory of Mind in Autism Spectrum Disorder, AttentionDeficit/Hyperactivity Disorder, and the Comorbid Condition

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Neural Correlates of Theory of Mind in Autism Spectrum Disorder, Attention-Deficit/Hyperactivity Disorder, and the Comorbid Condition

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Theory of mind (ToM) or mentalizing difficulties is reported in attention-deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD), but the mechanism underpinning these apparently shared deficits is relatively unknown. Eighty-three young adult males, 19 with ASD alone, 21 with ADHD alone, 18 with dual diagnosis of ASD and ADHD, and 25 typically developing (TD) controls completed the functional magnetic resonance imaging version of the Frith-Happé animated-triangle ToM task. We compared neural function during ToM with two non-ToM conditions, random and goal directed motions, using whole-brain and region-of-interest analysis of brain activation and functional connectivity analyses. The groups showed comparable ToM task performance. All three clinical groups lacked local connectivity increase shown by TD controls during ToM in the right temporoparietal cortex, a key mentalizing region, with a differentially *increased* activation pattern in both ASD and comorbid groups relative to ADHD. Both ASD groups also showed reduced connectivity between right inferior lateral prefrontal and posterior cingulate cortices that could reflect an atypical information transmission to the mentalizing network. In contrast, with mentalizing both ADHD groups showed decreasing connectivity between the medial prefrontal and left temporoparietal cortices when compared to TD controls. Therefore, despite the complex pattern of atypical brain function underpinning ToM across the three disorders, some neurofunctional abnormalities during ToM are associated with ASD and appeared differentiable from those associated with ADHD, with the comorbid group displaying combined abnormalities found in each condition.

Keywords: theory of mind (ToM), neurodevelopmental disorder, attention deficit and hyperactivity disorder (ADHD), autism spectrum disoder (ASD), functional magnetic resonance imaging (fMRI)

INTRODUCTION

Autism spectrum disorder (ASD) is characterized by social communication difficulties and stereotypical/repetitive behaviors, while attention-deficit/hyperactivity disorder (ADHD) is characterized by age-inappropriate symptoms of inattention, hyperactivity, and impulsivity (1). Despite the distinct presentations, up to 55% of children and adolescents with the disorders meet both diagnostic criteria (2, 3). Furthermore, reports of a co-occurrence of both disorders in adulthood may indicate its persistence (4–6). Reviews and meta-analyses suggest overlapping cognitive impairments in both disorders including the difficulties in theory of mind (ToM), i.e., the inference of others' mental states or "mentalizing" (7–9), even though ToM deficits have been thought to be ASD-specific [e.g., (10–13)].

In ASD, mentalizing problems are conceptualized as a core symptom (11) or a consequence of diminished social motivation (14). The deficits in ASD are commonly associated with underactivation of temporo- and frontolimbic social brain networks, in medial and ventrolateral prefrontal, temporo-parietal cortices, and amygdala in children [e.g., (15, 16)] and adults [e.g., (17–19)], leading to the "hypo-intentionality" hypothesis of autism (20). However, overactivation of these regions has also been reported in children and adults with ASD (21–24). Reduced activation in the right temporoparietal junction (TPJ) and medial prefrontal cortex (mPFC), particularly, has been shown to correlate with increased autism severity scores (15, 17, 25).

During mentalizing, children and adults with ASD also showed reduced functional connectivity (FC) (17, 20, 21, 26, 27) in the social brain network that is typically increased in TD controls (17, 28, 29). Such FC reduction in ASD has been reported between frontal, especially mPFC, and temporo-parietal regions, particularly on the right hemisphere (20, 26, 30), ventral premotor and sensorimotor areas (25), and among widespread seed regions in the network (21, 27). These findings, together with observation of reduced FC across other cognitive domains (31–33), have led to the theory of domain-general frontal-posterior underconnectivity in ASD (34).

In ADHD, social cognition, and mentalizing deficits are increasingly reported, mostly in children (35–39) but also in adults (40–43), albeit not as consistently as in ASD (8). For the adult age group particularly, recent studies have reported intact mentalizing in ADHD, who are instead impaired in empathy and in their ability for generating solutions for social problems (44, 45). In line with these findings, a review has suggested that social cognition deficits in ADHD are less severe and more heterogeneous than in ASD (8).

In the context of neuroimaging of ADHD, altered orbitofrontal and lateral fronto-striatal activation, which is typicaly linked to executive function deficits (46–48), has been cited as possible mediator for the social cognition deficits in ADHD (49, 50), although, to our knowledge, no fMRI studies have explored neural correlates of ToM in ADHD. Importantly, it is unclear if social cognition and mentalizing deficits are intrinsic to ADHD (41) or reflect co-occuring ASD traits in the population (40).

Comparative fMRI studies involving people with ADHD alone, ASD alone, and/or combined ASD+ADHD could tease apart disorder-differentiating impairments in social brain regions. To date, these studies have been conducted exclusively in children and adolescents with the disorders (51–55). One functional magnetic resonance imaging (fMRI) study has found ASD-specific inferior frontal gyrus underactivation relative to TD and ADHD during emotion identification (51). Furthermore, using resting-state fMRI, ASD-differentiating intrinsic FC impairments were observed in regions typically involved in mentalizing, with increased *local* (i.e., "degree centrality") temporo-limbic FC in the ASD and ASD+ADHD groups relative to TD and ADHD, and shared precuneus overconnectivity across all clinical groups (55). Electroencephalography (EEG) biomarkers for face and eye-gaze processings such as N170 have also been found to be ASD-differentiating relative to ADHD (52–54). These findings suggest that the neural abnormalities underlying social cognition, based on a number of neural and electrophysiological correlates, might be specific to ASD and not ADHD. However, the hypothesis has not been tested during mentalizing specifically.

Therefore, we directly compare hemodynamic response and FC in brain regions during ToM relative to non-ToM conditions across individuals with ADHD, ASD, ASD+ADHD, and typical development. To address the lack of investigation of brain function correlates of comorbidity in the adult population, this study focused on young adults using the Frith-Happé animated-triangle fMRI task that is frequently used for investigating ToM in ASD (21, 24, 27), which has also been shown to detect ToM deficits in ADHD, albeit in children (35). We aimed to investigate if ToM performance deficits are similar or different and are associated with similar or different neural correlates across the three clinical groups. Based on previous findings of neuroimaging (51), FC (55), and EEG (52–54), we hypothesized that abnormalities in the social brain network, e.g., under-activation in right TPJ and mPFC, and reduced fronto-posterior FC during ToM (21, 27, 34) would distinguish the ASD groups, with and without ADHD, from the group with ADHD alone, who would show no neurofunctional impairments.

MATERIALS AND METHODS

Participants

A total of 107 young adult males aged 20–27 years with ASD, ADHD, ASD+ADHD, and TD and full-scale intelligent quotient (FSIQ) ≥70, estimated using the Wechsler Abbreviated Scale of Intelligence (56), took part in the study. Only males were included to increase group homogeneity for these predominantly male-prevalent disorders (57, 58). Handedness was assessed using the Edinburgh Handedness Inventory (59) and did not differ between groups. Excluded were participants with epilepsy,

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; FC, functional connectivity; GD, goal directed movement; fMRI, functional Magnetic Resonance Imaging; TD, typically developing controls; mPFC, medial prefrontal cortex; ToM, Theory of mind; TPJ, temporoparietal junction; rANG, right angular gyrus; RD, random movement; ROI, region-of-interest.

personality disorder, current substance abuse/dependence, lifetime history of bipolar disorder, schizophrenia or head injury, or contraindication for fMRI. The participants completed a larger study involving several fMRI tasks and a neurocognitive task battery (60). After excluding 24 subjects (four with incomplete fMRI data, seven with missing performance data due to technical or compliance issues [these participants answered ≤3 out of 12 questions], 12 with excessive movement (>3 mm) and one with an incidental MRI finding), 83 subjects remained (19 ASD; 21 ADHD; 18 ASD+ADHD; 25 TD). The groups differed in FSIQ, but not age (See **Table 1** for descriptive statistics).

The clinical groups were recruited through specialist adult ASD and ADHD clinics, support organizations, social media, and from a well-characterized population-based cohort of young adults with ASD, the Special Needs and Autism Project (SNAP), who were followed up since 10–12 years and are now young adults (61). Psychostimulant medications, which were withdrawn 48 h before testing, and selective serotonin reuptake inhibitors (SSRIs) prescription, were not exclusion criteria for the clinical groups. Participants with non-stimulant ADHD medications were excluded due to their relatively longer withdrawal periods.

The ASD group consisted of 14 participants with clinical diagnoses (six autism, eight Asperger's syndrome) and five participants with research diagnoses from SNAP [two autism, two atypical autism, and one pervasive developmental disorder (PDD) unspecified], based on the International Classification of Diseases criteria (ICD-10) (62). All but one diagnoses were accompanied by gold-standard research instruments, the Autism Diagnostic Observation Schedule (ADOS) (63) or parent interviews on the Autism Diagnostic Interview-Revised (ADI-R) (64). Where available, current ADOS scores were collected from the examiners. One participant received childhood ASD diagnosis from a specialist neurodevelopmental clinic, supported by an assessment on the Diagnostic Interview for Social and Communication Disorders (DISCO) (65), but had no current scores. None were prescribed medication.

In the ASD+ADHD group, 14 subjects had clinical diagnoses (five autism, six Asperger's syndrome, three atypical autism) and four had research diagnoses of ASD from SNAP (two atypical autism, two PDD unspecified) based on the ICD-10. All but one ASD diagnoses were accompanied by the ADOS or the ADI-R (ADOS score on **Table 1**). One participant's childhood ASD diagnosis from a specialist neurodevelopmental clinic was supported by the DISCO (no current scores). Furthermore, thirteen participants met the criteria for combined and five for inattentive DSM-5 ADHD subtype. Nine had current clinical DSM-5 ADHD diagnoses supported by current assessments on the Diagnostic Interview for Adult ADHD (DIVA 2.0) (66) or the Conners' Adult ADHD Diagnostic Interview for DSM-IV (CAADID) (67). Nine other participants had a significant history of ADHD symptoms assessed through SNAP and met the current ADHD DSM-5 criteria on the Young Adult Psychiatric Assessment (68). Two were prescribed psychostimulants alone [methylphenidate (MPH), dexamphetamine], one SSRIs alone (escitalopram) and one both (MPH, sertraline).

All participants in the ADHD group met the DSM-5 diagnostic criteria: 12 with combined, eight inattentive, and one hyperactive subtype, diagnosed by consultant psychiatrists in specialist adult ADHD clinics. Eighteen diagnoses were supported by the DIVA 2.0 and three by the CAADID. Four were prescribed psychostimulants alone (MPH and lisdexamphetamine), one with SSRIs alone (sertraline) and one with both (MPH and sertraline).

The TD participants were from local communities, were non-medicated, and scored below clinical cut-off on the Conners' Adult ADHD Rating Scale (CAARS) (69) and the Social Responsiveness Scale-2 (SRS-2) (70) for ADHD and ASD traits, respectively. This study was in accordance of the Declaration of Helsinki and had ethical approval from a local National Health Service Research Ethics Committee (NHS REC 13/LO/0373). Each participant gave written informed consent and was given £50 and travel reimbursement.

Clinical Measures

The CAARS ADHD index and the hyperactivity/inattention domain of the Strengths and Difficulties Questionnaires (SDQ) for adults (http://www.sdqinfo.com) indexed ADHD traits, while total algorithm score of SRS-2 indexed ASD traits. The participants completed self-report measures, corroborated by informant (e.g., parents/partner/siblings) for those in the clinical groups.

The Frith-Happé Animated Triangles Task

The block-design fMRI version of the Frith-Happé task was selected as it evokes large effect size of brain activation, which is associated with increased statistical power. The task was also selected based on its frequent use in ToM investigation in ASD children and adult populations (21, 24, 27). A recent study furthermore reported ToM deficits in ADHD children using the same task (35). The task consists of twelve 26–48 s cartoons involving two triangles whose movements express: (1) ToM, e.g., persuading (length = 39.0±2.2s), (2) Goal-directed (GD) interaction, e.g., following (length = 39.5 ± 9.5 s), and (3) Random (RD) purposeless motions, e.g., floating (length = 39.8 ± 1.5 s) (71). Each condition is depicted by four different clips, shown in the same pseudo-randomized block order across participants. Each block consists of 1-s fixation cross (jittered between 0.3–1.9 s), one clip, a 3-s fixation and a visual multi-choice question prompting the participants to identify the movement type shown with a maximum duration of 5 s. The chosen answer is highlighted for 1 s (**Supplementary Figure 1**) before the start of the next block. Response accuracy and response time (RT) were collected during the task.

Outside the fMRI scanning, a subset of the clips (four ToM and four GD) was shown to the participants, followed by the question *"What do you think is happening during the clip?"* Neutral prompts (e.g. "uh-hum") were given by the examiner when the answer was not forthcoming. Responses were transcribed and rated by the first author DI, blinded to the participants' diagnoses, yielding scores for intention attributions (0–5), their appropriateness (0–3), the primary measures; and response length (i.e., number of clauses) and number of prompts, our secondary measure of ToM ability (72). Forty-eight randomly selected transcriptions (12 per group) were independently

TABLE 1 | Group differences in socio-demographic variables and clinical measures.

	TD (n = 25)		ASD (n = 19)		ASD+ADHD (n = 18)		ADHD (n =21)		Group comparison			*Post-hoc*
	M	SD	M	SD	M	SD	M	SD	*F/t*	*df*	*p*	
Age	23.4	1.6	23.0	0.7	23.1	1.3	23.1	2.1	0.22	3, 79	0.88	–
FSIQ	116.8	11.9	105.2	18.9	106.9	14.0	117.8	13.1	4.2	3, 79	0.009	ADHD*, TD* > ASD
Handedness	64.8	70.4	64.7	69.9	71.1	59.0	59.5	70.9	0.09	3, 79	0.96	–
CAARS ADHD index (*t*-scores)												
Self-rated	45.0	7.3	49.4	8.0	58.2	11.3	66.2	6.7	27.9	3, 78	<0.001	ADHD***, ASD+ADHD* > ASD; ADHD***, ASD+ADHD*** > TD; ADHD* > ASD+ADHD
Informant-rated	–	–	46.7	5.1	66.1	11.3	62.5	11.0	21.9	2, 53	<0.001	ADHD***, ASD+ADHD*** > ASD
SDQ hyperactivity/inattention (raw scores)												
Self-rated	1.8	1.4	3.1	2.2	6.6	2.2	7.3	1.6	47.6	3, 78	<0.001	ADHD***, ASD+ADHD*** > ASD; ADHD***, ASD+ADHD*** > TD; ASD† > TD
Informant-rated	–	–	2.8	1.5	7.2	1.7	7.6	1.7	48.8	2, 52	<0.001	ADHD***, ASD+ADHD*** > ASD
ADHD symptom counts[a]												
Inattention	–	–	–	–	7.4	1.2	8.1	1.5	−1.5	1, 32	0.15	–
Hyperactivity/impulsivity	–	–	–	–	4.8	2.7	4.7	2.4	0.03	1, 32	0.98	–
Total SRS-2 (*t*-scores)												
Self-rated	48.2	5.9	61.1	9.7	63.7	10.6	61.5	7.4	16.3	3, 78	<0.001	ASD***, ASD+ADHD***, ADHD*** > TD
Informant-rated	–	–	62.8	6.0	69.5	12.9	58.0	11.3	5.6	2, 53	0.006	ASD+ADHD** > ADHD
ADOS-2 Module 4[b]												
Communication	–	–	1.7	1.9	2.4	2.4	–	–	−1.0	1, 30	0.33	–
Social interaction	–	–	3.3	2.7	4.0	4.2	–	–	−0.60	1, 30	0.56	–
Communication + social interaction	–	–	4.9	4.0	6.4	6.5	–	–	−0.79	1, 30	0.43	–
Stereotyped behaviors and restricted interest	–	–	0.3	.96	1.0	1.4	–	–	−1.7	1, 30	0.10	–

*TD, typical development; ASD, autism spectrum disorder; ADHD, attention-deficit/hyperactivity disorder; M, mean; SD, standard deviation; df, degree of freedom; FSIQ, full-scale intelligence quotient; CAARS, Conners Adult ADHD Rating Scale; SRS, Social Responsiveness Scale version 2; SDQ, Strengths and Difficulties Questionnaires, a version for adults was used. [a]Current ADHD symptom counts were based on the Diagnostic Interview for Adult ADHD (DIVA 2.0) or the Young Adult Psychiatric Assessment, available in 18 participants with ADHD and 16 participants with ASD+ADHD. [b]Current Autism Diagnostic Observation Schedule (ADOS-2) scores were available in a subset of 18 individuals with ASD and 14 participants with ASD+ADHD. Post-hoc significant threshold: *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, and †$p < 0.1$ with Tukey–Kramer multiple comparison correction.*

rated by the second author SL, achieving good interrater agreement for ratings of intention attribution (weighted κ =.71; weighted agreement = 92.8%), appropriateness (weighted κ =.69; weighted agreement = 88.6%), response length [intra-class correlation coefficient (ICC) = 0.97], and number of prompts (ICC = 0.99). Behavioral data were analyzed in STATA 14.0 (73) using (Group × Condition) repeated measures ANOVA, with *post-hoc* analyses corrected using the Tukey–Kramer method, accounting for unequal sample sizes across groups.

Neuroimaging Data Acquisition

Data were acquired using a General Electric (GE) MR750 3T scanner (General Electric, Boston, MA, United States) at the Center for Neuroimaging Sciences, King's College London. The scanner's body coil was used for RF transmission, while an eight-channel head coil was used for signal reception. An echo planar image (EPI) gradient-echo pulse sequence (TR/TE = 2,000/30 ms, flip angle = 80°, FOV = 19.2 × 19.2 cm, 64 × 64 matrix, in-plane resolution = 3 mm, slice thickness/gap = 3/0.3 mm) was used to acquire 40 slices of T2*-weighted MR images angled at 20° up from inter-commissural plane, prescribed consecutively top-to-bottom, covering the entire brain. The 10-min, 14-s task produced 307 volumes in time series. A whole-brain high resolution structural T1-weighted scan (Sagittal ADNI-GO/2 ACC MPRAGE), co-registered with individual activation maps during pre-processing, was acquired in the inter-commissural plane with TE = 3.016 s, TR = 7.312 s, 196 slices, FOV = 27 cm × 27 cm, 256 × 256 matrix, and slice thickness of 1.2 mm.

Neuroimaging Analyses

fMRI data were corrected for slice timing, realigned, co-registered to the individual T1-weighted scan, segmented, normalized to the Montreal Neurological Institute EPI template,

and smoothed using an 8-mm Gaussian kernel. Statistical analyses were completed in two steps on the Statistical Parametric Mapping (SPM8). At the subject-level analyses, BOLD response was predicted using a vector of onsets and durations convolved with the canonical hemodynamic response function (HRF). Six nuisance motion regressors [x-, y-, z-translations, rotations, and additional regressors for each motion spike (>1 mm)] controlled for volume-to-volume head motion and abrupt movements. A high-pass filter was applied at the cut-off of 128 s and a first-order autoregressive model corrected for time series correlation. Investigations were carried out in the orthogonal contrast ToM > RD, typical of past studies (21, 27, 74–76), and separately in ToM > GD, a higher-level contrast investigated in a recent study (72).

Both contrasts were entered to second-level analyses. Within-group activations were analyzed with a cluster extent threshold of p <.05, family-wise error corrected (FWE_{cor}), and a cluster-forming voxel threshold of $p < 0.001$ (**Figure 2**). Between-group activation was modeled with group as predictor, covarying for total frame-wise head displacement to control for residual motion variation. The group differences were analyzed, first, using an exploratory whole-brain analysis (voxel threshold $p < 0.05$, FWE_{cor}) and, second, using a hypothesis-driven region-of-interest (ROI) analyses, by means of small-volume correction, using 10-mm radius spherical ROIs in the bilateral inferior frontal gyrus (IFG), bilateral medial prefrontal cortex (mPFC), bilateral posterior cingulate cortex (PCC), bilateral angular gyrus (ANG), and bilateral temporo-parietal junction/superior-temporal sulcus (TPJ/STS). The ROIs were centered on independently derived coordinates from a whole-brain activation map of ToM > RD [http://neurovault.org/images/3180 (77)], following Kana et al. (27). Mean beta weights of BOLD data were extracted for *post-hoc* pairwise group comparisons, applying Tukey–Kramer correction, and for correlational analyses with primary trait and task performance measures, applying false-discovery rate [FDR] correction. Logarithmic transformations were applied to normalize skewed data distribution as appropriate.

To compare FC between task conditions, we investigated the synchronization of BOLD activation time series across regions to facilitate comparison with previous studies [e.g., (21, 26, 27, 78)]. Activation time-series were first extracted from the spherical ROIs for everyone. The activation time series in ipsilateral TPJ and STS were combined by averaging due to regional overlap, yielding eight seed regions for the subsequent FC analyses. To control for artifacts, six orthogonal head motion parameters, head movement spikes, white matter, and cerebrospinal fluid signal plus their derivatives were regressed out. Artifact-corrected time-series were segmented pertaining to each video clip and those representing the same movement condition were concatenated into a condition-specific time series (27). These time series were correlated pairwise between ROIs, yielding altogether 28 unique correlation coefficients per movement condition (i.e., ToM, GD, and RD), which were then Fisher's z-transformed using an inverse hyperbolic tangent function to produce a FC strength index. They were then analyzed using multilevel mixed-effects linear regression models with group, condition, and group × condition as fixed effects and individual factor as random effects. Model fit was first examined for the overall averaged FC, calculated by averaging z-scores from the 28 pairwise correlations between ROIs. Further examination of model fit then took place in each pairwise FC. Group × condition interaction effects and main effects of group and condition were explored in models with significant fixed-effect model fit. Then, significant *post-hoc* simple effect testing was performed and corrected for multiple testing using the FDR method. Analyses were repeated, covarying for FSIQ and medications in each model to assess their influence in each model. Finally, Pearson's correlations assessed the relation between FC strength, primary measures of clinical traits, and task performance during ToM, corrected for multiple testing with the FDR method.

RESULTS

Task Performance Results

In the performance data from the out-of-scanner task, there were no significant group × condition interactions (**Supplementary Table 1**). No group differences were found in ratings of intention attributions [$F(3, 77) = 2.09$, $p = 0.1$] and their appropriateness [$F(3, 77) = 0.88$, $p = 0.5$]. A group effect was found on the length of description [$F(3, 77) = 2.73$, $p < 0.05$] and prompts required [$F(3, 77) = 3.48$, $p = 0.02$; **Figure 1A**, **Supplementary Table 1**]. *Post-hoc* t-tests showed that the ASD group gave the shortest ToM descriptions (ps < 0.01), despite receiving more prompts than the ADHD ($p < 0.01$) and TD groups ($p < 0.05$). An effect of condition was found on the intentionality scores [$F(1, 77) = 239.0$, $p < 0.0001$], appropriateness scores [$F(1, 77) = 33.3$, $p < 0.0001$], length of description [$F(1, 77) = 117.3$, $p < 0.0001$] and prompts [$F(1, 77) = 184.3$, $p < 0.0001$]. *Post-hoc* t-tests suggested that intentionality scores and length of description were higher in ToM than GD across all groups ($p < 0.001$); appropriateness scores were lower in ToM than GD in the TD, ASD, and ADHD groups ($p < 0.001$); and more prompts were needed during ToM than the GD condition ($p < 0.0001$).

During the fMRI task, a participant with ADHD answered eight out of 12 questions (others answered ≥11 questions), which could reflect ToM difficulties. The participant was included in all analysis. There were no significant group × condition interactions (**Supplementary Table 1**). A trend-level group effect [$F(3, 79) = 2.49$, $p = 0.07$] and a significant effect of condition [$F(2, 158) = 42.3$, $p < 0.0001$] were found for motion type identification (**Figure 1B**, **Supplementary Table 1**). *Post-hoc* t-tests showed GD motion were identified more accurately by the ADHD than the ASD and ASD+ADHD groups ($p < 0.01$), and that RD and ToM motions were identified more accurately than GD motions ($p < 0.001$) by the TD, ASD and ASD+ADHD groups. RT comparisons showed a trend effect of group [$F(3, 79) = 2.60$, $p = 0.06$], with the clinical groups being slower than the TD group, although this was only statistically significant in RD and ToM conditions for the ASD+ADHD group ($p < 0.05$) and in GD for the ASD and ADHD groups ($p < 0.05$) when tested *post-hoc*.

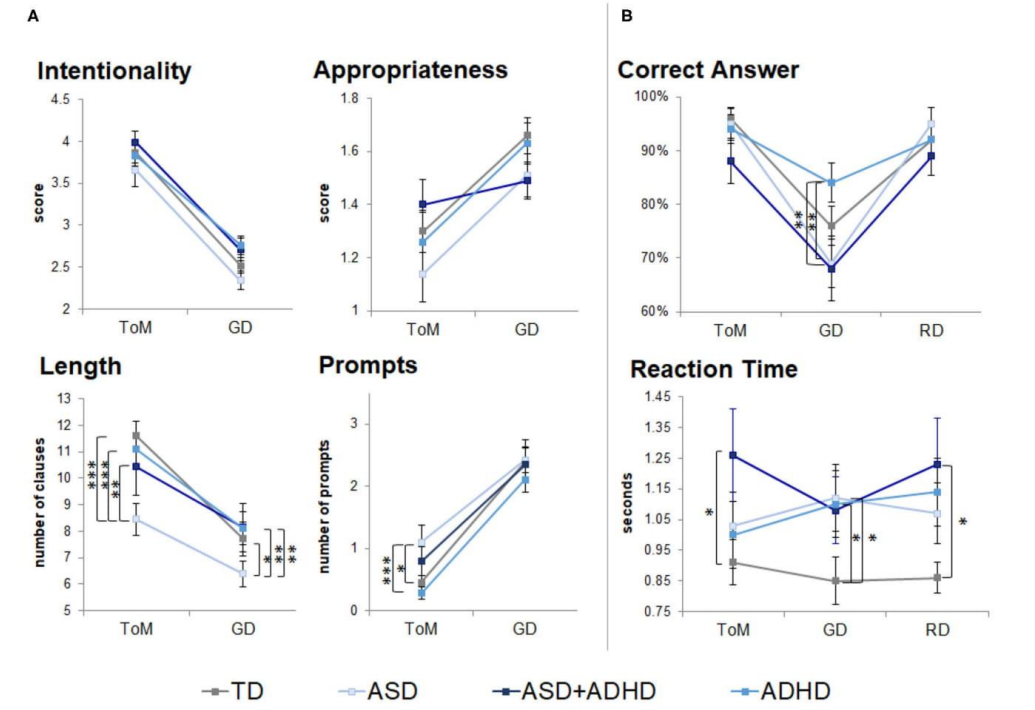

FIGURE 1 | Behavioral performance outside (neuropsychological task) and during fMRI scanning (fMRI task). TD, typical development; ASD, autism spectrum disorder; ADHD, attention-deficit/hyperactivity disorder; GD, goal directed; RD, random movement; ToM, theory of mind. Only pairwise group differences are highlighted although an effect of condition was found in scores for intentionality, appropriateness, length of descriptions and number of prompts during neuropsychological task. An effect of condition was also found for correct identification of motion (correct answers) during the fMRI task. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$, with Tukey–Kramer multiple comparison correction. Error bars represent standard error of the mean. **(A)** Neuropsychological task behavioral results. **(B)** fMRI task behavioral results.

Motion

Total volume-to-volume head movement in the x, y, and z rotation and translation did not differ across groups [$F(3, 79) = 0.74$, $p = 0.53$].

Within-Group Brain Activation

For the ToM > RD contrast, TD controls showed increased activation in ToM relative to RD condition in a region extending from inferior/middle occipital gyri (IOG/MOG) to posterior inferior temporal gyri (ITG) (BA19/37). In ASD, increased activation for ToM > RD was observed in bilateral IOG/MOG/ITG, in precuneus/posterior cingulate (BA7/23), and in bilateral supramarginal/ANG/posterior superior temporal gyrus (STG), extending to right middle temporal gyrus (MTG)/temporal pole (BA 22/21/38). In ADHD, increased activation for ToM > RD was found in right occipital pole, while in ASD+ADHD, the increased activation extended from bilateral IOG/MOG/ITG to right fusiform and lingual gyri, and from bilateral posterior MTG to right posterior STG/supramarginal gyrus/ANG (BA42/39/21/22) (**Figure 2**).

For the ToM > GD contrast, the TD and ADHD groups showed no clusters of increased activation at the chosen threshold. In ASD, increased activation was observed in right supramarginal/ANG/posterior STG (BA 42/41/40/22/48) and right IOG/MOG reaching into fusiform gyrus. In ASD+ADHD, increased activation was found in right IOG/MOG/lingual gyri (**Figure 2**).

Between-Group Brain Activation

Whole-brain analysis revealed no group effect for the contrast of ToM > GD. A group effect was observed for ToM > RD in the rANG [$p = .005$, $F = 12.5$, (x = 60, y = −54, z = 34), *cluster size* = 40 voxels]. *Post-hoc* pairwise comparisons revealed lower right ANG activation in the ADHD than the ASD ($p < 0.001$)

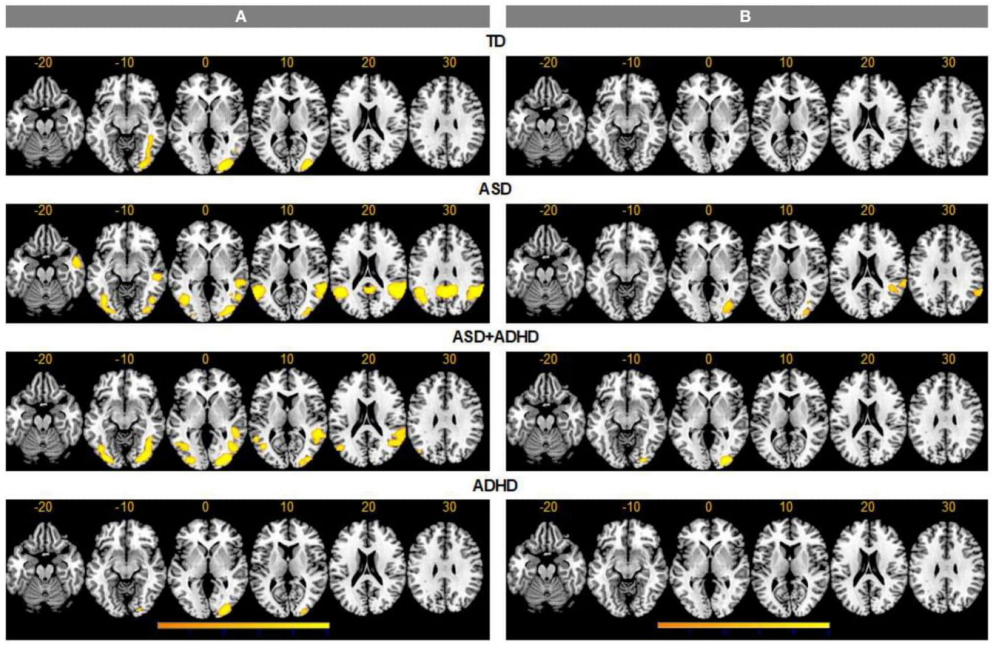

FIGURE 2 | Activation clusters for theory of mind (ToM) over random (RD) and goal-directed (GD) motion experimental conditions. TD, typical development; ASD, autism spectrum disorder; ADHD, attention-deficit/hyperactivity disorder. **(A)** ToM > RD, **(B)** ToM > GD.

and ASD+ADHD ($p = 0.009$) groups, and a trend-level increase in ASD relative to TD ($p = 0.058$; **Figure 3A**, **Table 2**).

Between-group ROI analyses of ToM > RD revealed a group effect in rTPJ/STS [$p < 0.001$, $F = 10.1$, (x = 58, y = −52, z = 30), k = 78 voxels] and rANG [$p = .026$, $F = 5.6$, (x = 50, y = −60, z = 34), k = 49 voxels]. *Post-hoc t*-tests revealed significant higher activation in ASD than ADHD ($ps \leq 0.016$) in both regions and a trend-level increase in rANG in ASD+ADHD relative to ADHD ($p = 0.070$). Corresponding analyses of ToM > GD contrast showed a trend-level group effect in rTPJ/STS [$p = 0.069$, $F = 5.5$, (x = 54, y = −54, z = 28), k = 25 voxels] and rANG [$p = 0.063$, $F = 5.0$, (x = 52, y = −60, z = 32), k = 4 voxels], with higher activation in ASD than ADHD ($ps \leq 0.004$) for both regions, and a higher increase in ASD+ADHD than ADHD in rTPJ/STS ($p = 0.025$) and a trend-level increase rANG ($p = 0.067$; **Figure 3B**, **Table 2**).

In all analyses, the effects of FSIQ ($ps \geq 0.34$), prescription of SSRI alone ($ps \geq 0.38$), psychostimulant alone ($ps \geq 0.49$), and all medication together ($ps \geq 0.17$) were non-significant.

In the TD group, RT to ToM clips showed significant positive correlation with ROI-based activation, for the ToM > RD and ToM > GD contrasts, respectively, in rANG ($r = 0.59$, $p = 0.008$, $r = 0.46$, $p = 0.021$) and rTPJ/STS ($r = 0.55$, $p = 0.014$, $r = 0.52$, $p = 0.016$) and in the whole-brain analysis based rANG cluster for ToM > RD ($r = 0.66$, $p = 0.002$). In the ASD group, the number of prompts during ToM was significantly positively correlated with activation in rANG ($r = 0.58$, $p = 0.022$), and at trend-level, in the whole-brain rANG cluster ($r = 0.44$, $p = 0.071$) in the ToM > RD contrast; and with ROI activation in rANG ($r = 0.63$, $p = 0.020$) and, at a trend-level, in rTPJ ($r = 0.45$, $p = 0.093$) for the ToM > GD contrast.

None of the activation clusters correlated with the severity of ASD or ADHD traits ($ps \geq 0.26$).

Functional Connectivity

Analyses of overall averaged FC revealed significant effects of condition [$\chi^2(2) = 7.79$, $p = 0.02$] and of group × condition interaction [χ^2 (6) = 16.3, $p = 0.012$] but not group. *Post-hoc t*-test showed increased overall FC during ToM relative to RD or GD in TD controls only ($ps \leq 0.001$), although the pattern of findings subtly differed for the individual FC pairs.

Among the ROI pairs, a significant mixed-effect model fit was found between rIFG and PCC, [$\chi^2(11) = 46.6$, $p < 0.0001$); and trend-level significance between mPFC and lTPJ [$\chi^2(11) = 27.7$, $p = 0.051$]; and between rANG with lTPJ [$\chi^2(11) = 24.9$, $p = 0.076$] and rTPJ [$\chi^2(11) = 24.5$, $p = 0.076$] (see **Figure 4**). Between rIFG and PCC, there was a significant effect of condition [$\chi^2(2) = 36.4$, $p < 0.0001$], qualified by increased

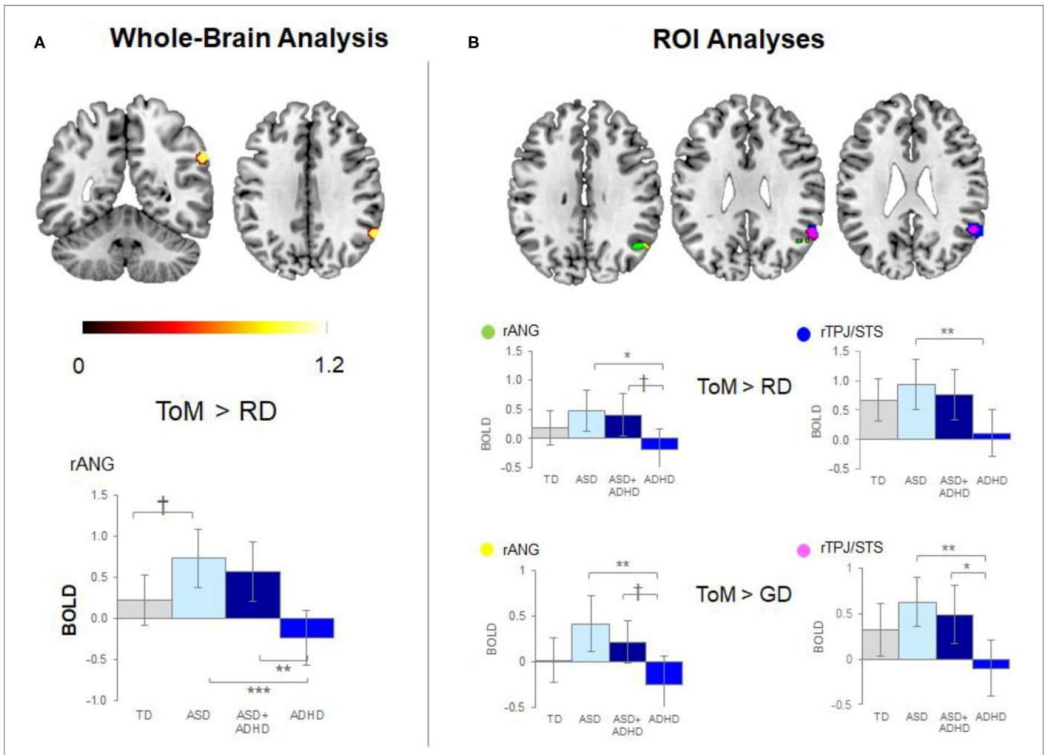

FIGURE 3 | Significant peak activation by clusters and bar graphs showing within pairwise comparisons. **(A)** Whole-brain analysis and **(B)** Region of interest (ROI) analyses. TD, typical development; ASD, autism spectrum disorder; ADHD, attention-deficit/hyperactivity disorder; BOLD, blood-oxygen-level dependent; GD, goal directed; RD, random movement; ToM, theory of mind; rANG, right angular gyrus; rTPJ/STS, right temporoparietal junction/superior temporal sulcus $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$, $^{\dagger}p < 0.1$ with Tukey–Kramer multiple comparison correction.

FC during ToM relative to RD or GD in the TD ($ps \leq 0.0004$) and the ADHD groups ($ps \leq 0.04$). Between mPFC and lTPJ, a significant group × condition interaction [$\chi^2(6) = 14.5$, $p = 0.024$) and a significant group effect [$\chi^2(3) = 9.3$, $p = 0.025$) were found. *Post-hoc* analyses for the interaction showed FC increase in TD controls and decrease in ASD+ADHD and ADHD ($ps \leq 0.007$) during ToM relative to RD; and comparable FC during ToM and GD in TD controls, and FC decrease during ToM relative to GD ($ps \leq 0.045$) in ASD+ADHD and ADHD. *Post-hoc* analyses for the group effect showed increased FC in ADHD relative to TD controls during RD condition ($p = 0.024$), and relative to ASD during the GD condition ($p = 0.024$). Between rANG and bilateral TPJ, there was a significant effect of condition [rANG-lTPJ: $\chi^2(2) = 10.2$, $p = 0.006$; rANG-rTPJ $\chi^2(2) = 15.8$, $p = 0.0004$] due to increased FC in TD controls during ToM relative to RD or GD ($ps \leq 0.025$) between rANG and rTPJ; and during ToM relative to GD ($p = 0.002$) between rANG and lTPJ. No other effects or interactions were significant.

The FSIQ ($ps \geq 0.10$), SSRIs alone ($ps \geq 0.72$), psychostimulants alone ($ps \geq 0.42$), and all medications together ($ps \geq 0.38$) exerted non-significant effects in the models.

The FC strength neither correlated with the severity of ASD and ADHD traits ($ps > 0.39$) nor task performance measures ($ps > 0.11$).

DISCUSSION

To our knowledge, this is the first study to investigate brain activation and FC associated with ToM in young adult males with ASD, ADHD, ASD+ADHD, and TD. Despite comparable task performance, ASD adults with and without ADHD had increased activation relative to ADHD alone during mentalizing in a key temporo-parietal ToM region,

TABLE 2 | Significant peak activation by cluster for the contrasts theory of mind (ToM) over random (RD) and goal-directed (GD) motion in the whole-brain and region-of-interest (ROI) analyses.

	Voxels	MNI coordinates			*F*	Z_{score}	$p_{FWEcorr}$	*Post-hoc*
		x	y	z				
Contrast ToM > RD								
Whole-brain analysis								
rANG	40	60	−54	34	12.5	4.76	0.005	ASD***, ASD+ADHD** > ADHD; ASD† > TD
ROI analyses								
rTPJ/STS	78	58	−52	30	10.1	4.24	<0.001	ASD** > ADHD
rANG	49	50	−60	34	5.58	2.95	0.026	ASD*, ASD+ADHD† > ADHD
		44	−62	36	5.34	2.86		
Contrast ToM > GD								
Whole-brain analysis								
–								
ROI analyses								
rTPJ/STS	25	54	−54	28	5.49	2.91	0.069	ASD**, ASD+ADHD* > ADHD
		58	−52	30	5.31	2.85		
rANG	4	52	−60	32	4.98	2.72	0.063	ASD**, ASD+ADHD† > ADHD

*TD, typical development; ASD, autism spectrum disorder; ADHD, attention deficit/hyperactivity disorder; ToM, theory of mind; RD, random movement; rANG, right angular gyrus; rTPJ/STS, right temporo-parietal function/superior temporal sulcus. MNI, Montreal Neurological Institute; ***$p < 0.001$, **$p < 0.01$, * $p < 0.05$, and †$p < 0.1$, with Tukey–Kramer multiple comparison correction.*

which was trend-wise increased relative to TD in the ASD group without ADHD. In FC, during mentalizing, there were mixed patterns of findings with all clinical groups sharing the lack of increased average FC over all connectivity pairs when compared to TD, which was particularly significant when considering the individual FC pairs in posterior temporo-parietal regions. Furthermore, underconnectivity between right inferior frontal and posterior cingulate cortices was found in the ASD groups, with and without ADHD, while the decreasing FC in medial frontal cortex and left temporo-parietal junction with mentalizing was found only in the ADHD groups, with and without ASD.

Increased temporoparietal activation in rANG during mentalizing appears to differentiate adults with ASD, with or without ADHD, from those with ADHD alone, and at a trend-level from TD controls. Therefore, we show for the first time that this overactivation is ASD-specific relative to the ADHD. This finding was significant in whole-brain analyses of ToM > RD contrast, and either significant or at trend-level in ROI analyses of both mentalizing contrasts. Previous studies have shown reduced rANG activation in children and adults with ASD relative to controls (15, 17–19). However, some studies have also found overactivation in the social brain regions during mentalizing in children and adults with ASD relative to TD (21–24), typically concomitant with unimpaired mentalizing task performance. The present findings could reflect increased processing effort in ASD to perform mentalizing as well as the TD controls and ADHD group [e.g., (23, 24)]. Supporting this interpretation was the positive correlation between rANG activation and the increased prompts for describing ToM movement in ASD, and between rANG activation and RT for classifying ToM clips in TD controls.

Discrepancies of findings were observed across contrasts (ToM > GD *vs.* ToM > RD) and analysis types (e.g., whole brain *vs.* ROI). Specifically, the ToM > GD contrast, relative to ToM > RD in whole-brain and ROI analyses, reduced some brain activation differences to non-significance. Thus, GD motion seems to evoke temporoparietal activation at intermediate level between RD and ToM, which could express parametric modulation of right temporoparietal activation when observing interaction based on goal pursuit alone compared to interaction involving the attribution of mental states in others.

Overall, the clinical groups showed a lack of increased FC during ToM compared to TD controls. The underconnectivity between rANG and bilateral TPJ/STS in particular seemed in line with the findings of anterior and posterior TPJ dysconnectivity between ASD and ADHD during resting state (79). The right-lateralized local rANG-rTPJ/STS underconnectivity during ToM is interesting, given the strong evidence of a positive association between BOLD activation and local FC density during mentalizing (80). Specifically, the rANG activation in both ASD groups, with and without ADHD, exhibited opposite effect to what is expected from a *reduced* local temporoparietal connectivity between rANG and rTPJ. This supports the atypical brain hypothesis [e.g., (21–24, 27)], instead of the hypo-intentionality hypothesis of ASD (20), which now extends to the comorbid group.

The lack of increased connectivity in rIFG-PCC during ToM, was found in ASD and ASD+ADHD but not in ADHD or TD controls. As well as implicated during mentalizing, the rIFG is part of the mirroring networks and is implicated in action processing and social attention. The rIFG is hypothesized as a gateway into the mentalizing networks (81, 82), which include the PCC. Thus, the rIFG-PCC underconnectivity may reflect

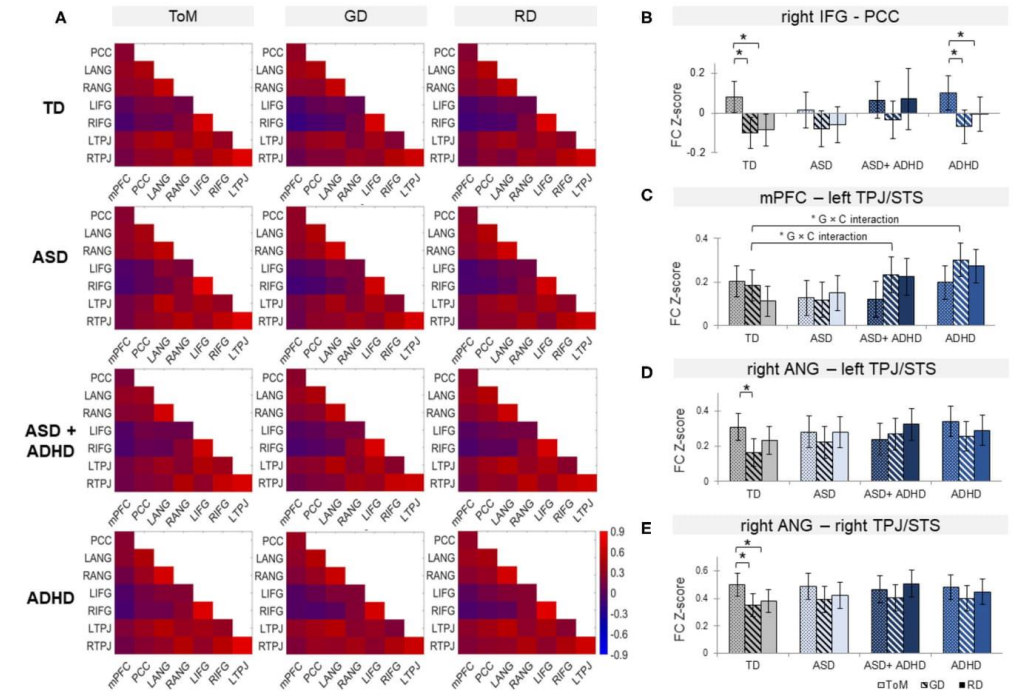

FIGURE 4 | (A) Functional connectivity (FC) matrices within each group for theory of mind (ToM), goal-directed (GD), and random (RD) movement among medial Prefrontal Cortex (mPFC), posterior cingulate cortex (PCC), bilateral angular gyrus (ANG), bilateral inferior frontal gyrus (IFG), and bilateral temporoparietal junction (TPJ), combined with superior temporal sulcus (STS). Bar graphs of FC for right IFG-PCC **(B)**, mPFC-left TPJ/STS **(C)**, right ANG with left **(D)**, and right TPJ/STS **(E)** by group and condition. *G × C represents significant group by condition interaction. Error bars represent 95% confidence interval. TD, typically developing controls; ASD, autism spectrum disorder; ADHD, attention-deficit/hyperactivity disorder. *$p < 0.05$ with false-discovery rate multiple comparison correction.

information transmission failures across the two networks (26, 30), which is ASD-differentiating.

Relative to TD controls, ADHD and ASD+ADHD showed decreasing FC between mPFC and lTPJ with increasing ToM. Functional coupling between mPFC and the temporal cortices occurs bilaterally during mentalizing [e.g., (28, 75, 82, 83)]. While it has not been discussed as much as the rTPJ in the context of mentalizing, the lTPJ is implicated in explicit ToM in meta-analytic connectivity modeling (84), and lesions in the region impaired spontaneous ToM in adults (85, 86). Those specific subdomains of ToM difficulties could perhaps be investigated further in ADHD.

The findings of the study should be viewed with its strengths and limitations. Firstly, the sample size was relatively small, which may have reduced statistical power to detect small effects and increased probability of false positives. The inclusion of young adult males only enhanced the group homogeneity at the expense of the finding's generalizability to other population groups, including female, children, and older adults with the conditions. The absence of correlations between primary ToM measures and brain activation and connectivity also constrained the interpretation of findings. There was limited variance of task performance across all participant groups, which could have reflected reduced symptom severity in non-clinically referred participants (87) or a lack of sensitivity of the simplistic animated-triangle fMRI task for detecting differences between groups. Finally, it is also possible that ToM impairments are present in ADHD in a subtle form that was undetectable by the animated triangle task. Future studies could investigate clinically referred participants, using more complex and naturalistic mentalizing tasks [e.g., (18, 26)].

To summarize, despite evidence of reduced connectivity in all three clinical groups relative to TD controls during ToM, a differentially increased activation pattern was found in both ASD and comorbid groups relative to ADHD in right temporoparietal cortex, which is a key mentalizing region. Both ASD and comorbid groups also showed reduced right inferior frontal and posterior cingulate coupling, which

may reflect an atypical information transmission to the mentalizing network. In contrast, both ADHD and comorbid groups showed decreasing connectivity between medial prefrontal and left temporoparietal cortices with increasing ToM when compared to TD controls. These findings denote a complex pattern of atypical brain function underpinning mentalizing in these three conditions in young adult males, with some evidence of ASD- and ADHD-differentiating features and a combined neurofunctional atypicality in the comorbid group.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found at: https://osf.io/nrj8g/.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by National Health Service Research Ethics Committee (NHS REC 13/LO/0373). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SL, KR, and ES conceptualized the study. CMM, KA, and VS contributed to recruitment. SL conducted the recruitment and data collection. SL, DI, OO'D, and CM contributed to the analysis of the data. SL and DI drafted the manuscript. DL, CMM, CM, KA, VS, KR, and ES contributed to the manuscript preparation. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2020.544482/full#supplementary-material

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The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

7.2. STUDY II:

The relationship between performance in a theory of mind task and intrinsic functional connectivity in youth with early onset psychosis

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The relationship between performance in a theory of mind task and intrinsic functional connectivity in youth with early onset psychosis

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ABSTRACT

Psychotic disorders are characterized by theory of mind (ToM) impairment. Although ToM undergoes maturational changes throughout adolescence, there is a lack of studies examining ToM performance and its brain functional correlates in individuals with an early onset of psychosis (EOP; onset prior to age 18), and its relationship with age. Twenty-seven individuals with EOP were compared with 41 healthy volunteers using the "Reading-the-Mind-in-the-Eyes" Test, as a measure of ToM performance. A resting-state functional MRI scan was also acquired, in which the default mode network was used to identify areas relevant to ToM processing employing independent component analysis. Group effects revealed worse ToM performance and less intrinsic functional connectivity in the medial prefrontal cortex in EOP relative to healthy volunteers. Group by age interaction revealed age-positive associations in ToM task performance and in intrinsic connectivity in the medial prefrontal cortex in healthy volunteers, which were not present in EOP. Differences in ToM performance were partially mediated by intrinsic functional connectivity in the medial prefrontal cortex. Poorer ToM performance in EOP, coupled with less medial prefrontal cortex connectivity, could be associated with the impact of psychosis during a critical period of development of the social brain, limiting normative age-related maturation.

1. Introduction

Social cognition refers to the ability of human beings to interact with others by recognizing their emotions and thoughts. Various psychological processes are considered to be involved in social cognition: facial emotion processing and "theory of mind" (ToM) are the most frequently studied, among others such us empathy, or humor (Uekermann et al., 2010). ToM (Premack and Woodruff, 1978) or *mentalization* (Frith et al., 1991) is the capacity of understanding that others present independent beliefs, intentions or desires, and of attributing their mental states to predict their reactions and behaviour. The processes involved in social cognition are considered to play a key role in successful social interactions (Wade et al., 2018; Yager and Ehmann, 2006). Deficits in ToM have been historically associated with autism spectrum disorders (Baron-Cohen et al., 1985; Yirmiya et al., 1998), however in the last decades it has been suggested that impairments in ToM also underlie social difficulties observed in other mental health conditions (Korkmaz, 2011). Several meta-analyses have confirmed impaired ToM in schizophrenia (Bora et al., 2009) and affective disorders (Bora et al., 2016; Bora and Berk, 2016), with possibly more severe deficits in the former (Mitchell and Young, 2016). Recent reports have shown that ToM presents the highest correlation with everyday functioning in schizophrenia; stronger than any other neurocognitive domain (Bora, 2017; Fett et al., 2011).

Abbreviations: DMN, Default Mode Network; EOAff, early onset affective disorders; EOP, early onset psychosis; EOSz, early onset schizophrenia; fMRI, functional Magnetic Resonance Imaging; gIQ, Global Intelligence Quotient; ToM, theory of mind.

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In typically developing individuals, ToM performance improves with age during childhood, and peaks during adolescence (Valle et al., 2015; Wellman et al., 2001; Wilde Astington and Gopnik, 1991). The medial prefrontal cortex and bilateral temporo-parietal junction, which are the areas of the brain which are most consistently activated during performance of tasks assessing ToM during functional resonance imaging scanning (Schurz et al., 2014), are considered to undergo important functional and structural changes during adolescence (Blakemore, 2008). A study in adults with schizophrenia has suggested that earlier onset of the disorder is associated with greater social cognitive deficits (Linke et al., 2015), suggesting that age of onset may modulate later cognitive function. Studies examining ToM in adolescents with early onset psychosis (EOP; when first psychotic episode takes place before age 18) (Bourgou et al., 2016; Korver-Nieberg et al., 2013; Li et al., 2017; Pilowsky et al., 2000; Tin et al., 2018), summarized in Table 1, have confirmed ToM deficits in this population, although they have reported either no effect of age on the findings or have failed to provide this information. A single study has examined the neural correlates of a social cognitive domain in individuals with EOP, in which the authors documented abnormal visual and facial emotion processing in relation to their healthy counterparts (Seiferth et al., 2009). However, to our knowledge, no studies so far have assessed the neural correlates of ToM in subjects with EOP.

In adult patients with schizophrenia, resting-state connectivity (hereafter referred to as "intrinsic connectivity") between areas of the brain which are typically recruited during performance of ToM tasks, has been found to be decreased (Schilbach et al., 2016). This network of brain areas overlaps with the Default Mode Network (DMN) (Schilbach et al., 2012), which conforms a set of brain regions which activate together during rest and which usually deactivate during goal-directed tasks (Greicius et al., 2003). In addition, intrinsic functional connectivity of the DMN has been related with ToM abilities in both healthy individuals (Li et al., 2014) and in adults with schizophrenia (Zemánková et al., 2018). In fact, intrinsic connectivity has been suggested to be a better predictor of social functioning and cognitive performance than task-based functional Magnetic Resonance Imaging (fMRI) (Viviano et al., 2018).

There is a lack of consensus concerning changes in connectivity of the DMN characterizing psychotic samples: a small number of studies have reported over-connectivity of the DMN during the resting-state in psychosis (Tang et al., 2013), while a recent meta-analysis has documented less intrinsic functional connectivity within the DMN in both schizophrenia (Dong et al., 2018; Kühn and Gallinat, 2013) and bipolar disorder with psychotic features (Syan et al., 2018). In contrast, some studies have reported less connectivity in schizophrenia compared to bipolar disorder, regardless of psychotic symptoms, in which values of intrinsic functional connectivity were intermediate relative to controls (Argyelan et al., 2014; Öngür et al., 2010; Skåtun et al., 2016), while others have found similar deficits in both conditions (Khadka et al., 2013).

From a developmental perspective, a recent meta-analysis focusing on the DMN in healthy individuals has demonstrated greater connectivity in adults compared to children (Mak et al., 2017). The single study reporting an effect of age on seed-based connectivity of the DMN in participants with a first episode of early-onset schizophrenia (Jiang et al., 2015) reported that intrinsic connectivity between a seed located in the precuneus and the left inferior frontal cortex was positively associated with age, while connectivity between a seed in the left middle occipital cortex and the precuneus was negatively associated with age. In contrast, there were no age effects in intrinsic connectivity of the DMN in patients with an adult onset of schizophrenia (Jiang et al., 2015). This study excluded subjects with affective psychosis and did not explore the association between brain imaging measures and social cognitive performance.

In this context we set out to evaluate performance during a ToM task and its relationship with intrinsic functional connectivity during resting-state fMRI, in individuals with EOP compared to healthy volunteers, and to examine the effect of age on these measures. Our hypotheses were: 1) patients with EOP would display worse ToM performance than healthy volunteers; 2) patients with EOP would exhibit less intrinsic functional connectivity within the DMN compared to healthy volunteers; 3) patients with EOP would fail to display the age-related improvements in ToM performance and increases in DMN connectivity exhibited by healthy volunteers; and 4) Differences in ToM performance would be mediated by intrinsic functional connectivity within the DMN.

2. Materials and methods

This is a cross-sectional case-control study carried out at the Department of Child and Adolescent Psychiatry and Psychology of Hospital Clinic of Barcelona (Spain), approved by the local Ethical Review Board.

Table 1
Summary of previous studies comparing performance in tasks assessing theory of mind in individuals with early onset psychosis relative to a control group.

Author and year	Sample	Age (years)	Sex (female)	Duration of disease (months)	ToM task	Results
Pilowsky et al., 2000***a***	12 EOSz	12.2 (SD = 1.7)	8%		Fact and value belief task, Deception task, False-belief task	Impaired ToM in EOP compared to HV in the false-belief task [No report on age effects]
	12 HV	8.5 (SD = 1.3)	25%			
Korver-Nieberg et al., 2013	32 EOP	17.1 (SD = 1.3)	39%		Perspective-taking task	No significant differences in cognitive ToM. No effect of age in the model.
	78 HV	16.3 (SD = 1.6)	36%			
Bourgou et al., 2016	12 EOSz	14.8 (SD = 1.7)	42%	30 ± 6	Moving Shapes Paradigm (*Frith-Happe* Animated Triangles)	Impaired ToM in EOP compared to HV. No correlation with age.
	12 HV	14.7 (SD = 1.5)	50%	–		
Li et al., 2017	35 EOSz	16.5 (SD = 1.4)	43%	16 ± 15	Yoni Task, Faux Pas Task	Impaired affective and cognitive ToM in EOP compared to HV. [No report on age effects]
	35 HV	16.3 (SD = 1.2)	43%	–		
Tin et al., 2018***b***	30 EOSz	17.5 (SD = 1.2)	37%	27 ± 16	Yoni Task, Faux Pas Task	Impaired affective and cognitive ToM in EOP compared to HV. [No report on age effects]
	30 HV	17.2 (SD = 1.0)	30%	–		

Note: HV = Healthy Volunteers; EOP = Early Onset Psychosis; EOSz = Early Onset Schizophrenia; ToM = theory of mind; ***a***: A third group with Autism Spectrum Disorder (n = 12; 8% female) also included for comparison; ***b***: A third group with Autism Spectrum Disorder (n = 30; 23% female) also included for comparison.

2.1. Sample

Twenty-seven participants with EOP were consecutively included. Diagnosis of first episode of psychosis was established at first contact with mental health services and defined as the presence of positive psychotic symptoms of less than 6 months duration with an onset between the ages of 12 and 17 (for details on baseline recruitment and assessment see Castro-Fornieles et al., 2007). Exclusion criteria consisted of: 1) presence of a concomitant disorder that could account for the psychotic symptoms such as autism spectrum disorders, post-traumatic stress disorder or drug-induced psychoses (occasional substance use was not an exclusion criterion); 2) intellectual disability according to DSM-IV-TR criteria; 3) neurological disorders or history of head trauma with loss of consciousness; 4) pregnancy and 5) medical or technical counterindications for the MRI (i.e. metal implants, brain aneurysms, etcetera).

For the current study, all individuals with EOP were assessed 2 years after the diagnosis of their first episode of psychosis; thus, duration of disease was homogeneous and current age and age at onset were highly correlated ($r = .98$; $p < .0001$). Forty-one age and sex matched healthy volunteers were recruited from schools or community settings from the same geographical area as individuals with EOP. Additional exclusion criteria for healthy volunteers were as follows: 1) any current or lifetime Axis I disorder; 2) any psychotic disorder in 1st and 2nd degree relatives. All participants provided written informed assent, and parents or legal guardians gave written informed consent before the study began.

2.2. Clinical assessment

Demographic data, including age, sex and race, was collected; socioeconomic status was classified according to the Hollingshead-Redlich scale (Hollingshead AB, 2007), where the highest parental educational and employment status was recorded.

All participants were assessed 2 years after the first episode by mental health professionals (psychiatrists and psychologists) with experience diagnosing and evaluating children and adolescents with semi-structured interviews, clinical scales and neuropsychological tests. Diagnoses were re-assessed using the Kiddie-Schedule for Affective Disorders and Schizophrenia, Present and Lifetime version (Kaufman et al., 1997) in its Spanish version (Ulloa et al., 2006) according to DSM-IV-TR criteria (American Psychiatric Association, 2000). Clinical severity in individuals with EOP was evaluated using the Positive and Negative Syndrome Scale (PANSS), which is a 30-item scale organized in 3 subscales: positive and negative symptoms and general psychopathology; with each item scored between 1 and 7, from absent to extreme (Kay et al., 1987). Detailed medication history was recorded for each participant; doses of antipsychotic drugs were transformed into chlorpromazine equivalents (Leucht et al., 2014) and cumulative chlorpromazine equivalents over time were calculated for each individual at the moment of scanning.

Theory of mind was evaluated using the child version (Baron-Cohen et al., 2001a) of the "Reading-the-Mind-in-the-Eyes" Test (Baron-Cohen et al., 2001b), which presents 28 images of multiple expressions of different subjects' eyes. It includes a control condition, where participants are asked to identify the sex of poser, and an experimental condition testing emotion identification between a 4-option-multiple choice question.

Neurocognitive level was measured using the Vocabulary, Similarities, Block Design and Matrix Reasoning subtests of the Spanish version of the Wechsler Intelligence Scale for Children - Fourth Edition (WISC-IV) (Wechsler, 2003) or Wechsler Adult Intelligence Scale–III, revised (Wechsler, 2011). The General Ability Index (referred to as Global Intelligence Quotient; gIQ), derived from the Verbal Comprehension and Perceptual Reasoning indices, was used as an index of intelligence level (Flanagan and Kaufman, 2008).

2.3. Statistical analyses

Statistical analysis was performed in Stata v.13.1 using *t*-test and chi-square for demographic and clinical information. Behavioural performance during the ToM task was compared using multilevel mixed-effects linear regression models with group, condition and group by condition interaction as fixed effects and including individual factor as random effect; applying Bonferroni correction for multiple pairwise comparisons. gIQ, sex, age, socio-economic status and group by age interaction were added as covariates when achieving significance level $p \leq .05$. Linear regression models for each condition, control and experimental, were built for assessing the effect of age on behavioural measures including the group by age interaction. Again, gIQ, socio-economic status and sex were added as covariates when significant ($p \leq .05$). Effect sizes were calculated for significant post-hoc paired *t*-tests (Cohen's *d*) and linear regression models (ω^2). Within the EOP group, additional analyses were conducted to assess the relationship between symptom severity and age, and the effect of symptom severity on ToM performance.

2.4. Neuroimaging acquisition

An 8-min resting-state fMRI sequence was acquired on a 3 T Siemens Magnetom Trio Tim (Siemens Medical Systems, Germany) scanner at the Magnetic Resonance Image Core Facility of IDIBAPS, Centre for Image Diagnosis, Hospital Clínic of Barcelona. Participants were instructed to keep their eyes closed, remain as still as possible for the duration of the scanning session. A technician engaged in conversation with the participant before and after the resting-state session to guarantee that they did not fall asleep. Acquisition parameters were as follows: 240 volumes, TR = 2000 ms; TE = 29 ms; matrix size = 480 × 480; slice thickness = 4 mm, acquisition matrix = 80 × 80 mm, 32 slices, voxel size 3 × 3 × 4 mm.

2.5. Neuroimaging preprocessing

A DARTEL algorithm was applied to the segmented T1-structural volumes to generate a sample-specific template. Resting-state fMRI images were realigned, co-registered to the individual T1-weighted scan (segmented using the sample specific template), normalized to the Montreal Neurological Institute (MNI) space and smoothed using a 6-mm Gaussian kernel in SPM12. One healthy volunteer and three participants with EOP were excluded from further neuroimaging analyses due to excessive motion (mean Framewise Displacement >.2 mm) (Power et al., 2017, 2012; Yan et al., 2013); these individuals did not differ in age, sex or socio-economic status from those included in the analysis ($ps \geq .31$).

2.6. Functional connectivity analysis

The component corresponding to the DMN was identified with independent component analysis using the GIFT toolbox v3.0b for SPM12 running on Matlab R2017b. Independent component analysis decomposes fMRI data into spatially independent patterns, which include both functional networks and sources of noise (such as motion or cerebrospinal fluid), thus allowing to minimize the influence of artefact on the findings (Pruim et al., 2015; Salimi-Khorshidi et al., 2014). Furthermore, the fact that it is a data-driven approach, which allows to avoid the potential bias of pre-determined regions of interest, is an additional advantage given the novelty of the study design. The DMN was identified by visual inspection and confirmed through the highest correlation with the template ($r = .61$), and included the prefrontal cortex, precuneus and bilateral temporo-parietal junction [spatial map representation in figure A1 of appendix]. The spatial maps of the DMN component of each subject were compared in a whole brain *t*-test analysis in SPM, introducing group, age, group by age interaction and

sex as regressors within an inclusive DMN mask created with the mean sample template. Only results surviving family-wise error correction are reported. Next, mean values of intrinsic functional connectivity within each significant cluster were extracted for each individual, and linear regression models were conducted in Stata v.13.1, in which the effects of gIQ, sex, age and socio-economic status were examined. These covariates were included in the model when significant ($p \leq .05$). The potential effect of antipsychotic medication and symptom severity on resting-state fMRI measures (cumulative chlorpromazine equivalents; Leucht et al., 2014) was also evaluated within the EOP group. In order to assess whether the differences in ToM performance between healthy volunteers and EOP were associated with intrinsic functional connectivity within the DMN, a mediation analysis was carried out for clusters showing age-associated differences. The proportion of total effect mediated by functional connectivity was calculated based on standardised beta-values obtained from linear regression models.

For secondary analyses, cases were classified according to diagnosis at two-year assessment into early onset schizophrenia (EOSz) and early onset affective disorders (EOAff). Group, and group by age effects in ToM performance and intrinsic functional connectivity within the DMN were tested in these subgroups [See Supplementary Material].

3. Results

3.1. Sample

Socio-demographic and clinical information are presented in Table 2. There were no group differences in age, sex or race distribution. Individuals with EOP showed significantly lower gIQ ($p = .0005$) and socio-economic status ($p = .017$) than healthy volunteers. Diagnoses at 2 years within the case group were: schizophrenia (n = 9), schizoaffective disorder (n = 7), major depressive disorder with psychotic features (n = 3), bipolar spectrum disorders (bipolar I, n = 4; bipolar no otherwise specified, n = 2) and psychosis not otherwise specified (n = 2).

3.2. Theory of mind task

There were significant group by condition ($X^2 = 6.8$; $p = .009$), group ($X^2 = 10.2$; $p = .001$) and condition ($X^2 = 533.2$; $p < .0001$) effects. Post-hoc analysis revealed significant differences in the experimental condition of the "Reading-the-Mind-in-the-Eyes" Test ($p < .001$; Cohen's $d = .79$), whereby individuals with EOP showed poorer performance, while no between group differences were observed in the control condition ($p = 1.0$) [Fig. 1A]. Linear regression models showed a significant group by age effect only in the ToM condition ($p = .014$; $\omega^2 = .21$), where ToM scores and age were positively associated in healthy volunteers ($\beta = .53$; $p = .017$), but not in the EOP group ($\beta = -.35$; $p = .207$) [Fig. 1B]. gIQ was included as covariate only in the linear regression model ($p = .052$); sex and socio-economic status had no significant effect in either model. A negative correlation was found between the total PANSS score and age of illness onset ($r = -.44$; $p = .02$). Therefore, within the EOP group, the effect of severity of symptoms (PANSS: total score and subscales) on the age by ToM performance model was tested; these analyses failed to achieve significance ($\beta s \leq |.13|$; $ps \geq .13$).

Table 2
Socio-demographic and, clinical characteristics of the sample.

	HV (n = 41)	EOP (n = 27)	*p* value
Socio-demographic			
Age (years) [range]	17.8 (SD = 1.6) [15.0–20.9]	18.1 (SD = 1.6) [15.7–20.1]	*.374*
Sex (% female)	56.1%	59.3%	*.796*
Race (% caucasian)	92.7%	81.5%	*.161*
Socio-economic Status	48.9 (SD = 16.0)	39.1 (SD = 15.0)	*.017**
Clinical variables			
Global Intelligence Quotient	104.1 (SD = 9.8)	92.8 (SD = 15.7)	*.0005**
PANSS (total score)	–	49.6 (SD = 16.2)	–
- Positive Subscale	–	10.1 (SD = 3.8)	–
- Negative Subscale	–	15.4 (SD = 6.5)	–
- General Subscale	–	24.4 (SD = 8.6)	–
Age of onset (years)	–	15.9 (SD = 1.5)	–
Duration of disease (months)	–	27 (SD = 3)	–

Note: HV = Healthy Volunteers; EOP = Early Onset Psychosis; PANSS = Positive and Negative Syndrome Scale; SD = Standard Deviation; * $p < .05$.

3.3. Intrinsic functional connectivity

During resting-state fMRI, there was an effect of group in the medial prefrontal cortex within the DMN (cluster 1: [x = 6, y = 59, z = 6]; voxel count = 54; $p^{FWE-corr} = .036$), whereby EOP participants exhibited less connectivity compared to healthy volunteers [Fig. 2A]. A second cluster in the medial prefrontal cortex showed a significant group by age interaction (cluster 2: [x = 3, y = 35, z = −2]; voxel = 66; $p^{FWE-corr} = .017$): whereby connectivity was positively associated with age in HV ($\beta = .23$; $p = .001$), while the effect was the opposite in individuals with EOP ($\beta = -.29$; $p = .001$) [Fig. 2B]. There was no significant effect of socio-economic status, sex or gIQ for either of the clusters, thus these factors were excluded from the model. Within the EOP group, severity of symptoms (PANSS: total score and subscales) showed no significant effect when introduced in the model assessing age in cluster 2 ($\beta s \leq |.03|$; $ps \geq .16$). In individuals with EOP, cumulative chlorpromazine equivalents were not correlated with the mean extracted values of intrinsic functional connectivity in either of these clusters ($rs \leq |.05|$; $ps \geq .83$).

Mediation analysis showed that intrinsic functional connectivity in the medial prefrontal cortex (cluster 2) within the DMN accounted for 16.7% (95%IC: 9.6%–39.6%) of the differences in ToM performance exhibited by the participants with EOP [Fig. 3; table A1 of the Supplementary Material].

Secondary analyses, dividing the sample by diagnostic groups, showed that only participants with EOSz exhibited impaired performance during the "Reading-the-Mind-in-the-Eyes" Test compared to EOAff and healthy volunteers ($ps \leq .008$; Cohen's $d \geq |1.03|$). In contrast, group differences in intrinsic functional connectivity in cluster 1 ($ps \leq .005$) and the group by age interaction in cluster 2 ($ps \leq .001$) remained significant for both patient subgroups compared to healthy volunteers [see table A2 and figures A3-A4 in Supplementary Material].

4. Discussion

Our study evaluating ToM performance and resting-state fMRI in individuals with EOP has found that:

(1) Patients with EOP performed significantly worse than healthy volunteers in a task assessing ToM. There was a positive association between task performance and age in healthy volunteers, which was absent in individuals with EOP.
(2) Patients with EOP exhibited less intrinsic connectivity in the DMN, specifically in the medial prefrontal cortex, than healthy volunteers. Connectivity in this region and age were positively associated in healthy volunteers and negatively associated in EOP.
(3) Differences in performance in the ToM task were partially mediated by intrinsic functional connectivity in the medial prefrontal cortex within the DMN.
(4) Patients with EOSz performed significantly worse than individuals with EOAff and than healthy volunteers in the ToM task, while there were no differences between diagnostic groups in DMN connectivity.

In this sample of patients with EOP, we observed worse performance

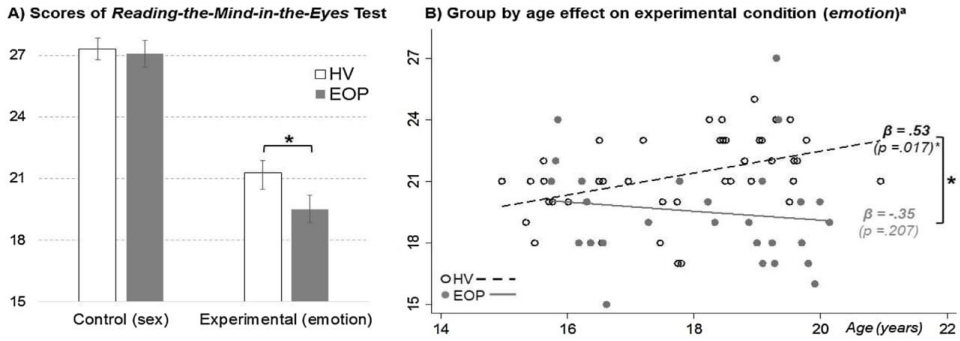

Fig. 1. Bar graphs representing mean least squares (95% confidence intervals) of performance in the control and experimental conditions of the "Reading-the-Mind-in-the-Eyes" Test (A) and group by age effect on experimental condition (B) for the healthy volunteer (n = 41) and early onset psychosis groups (n = 27).
Note: HV = Healthy Volunteers; EOP = Early Onset Psychosis; [a]: model also including global intelligence quotient ($p = .052$) as covariable; * $p < .05$.

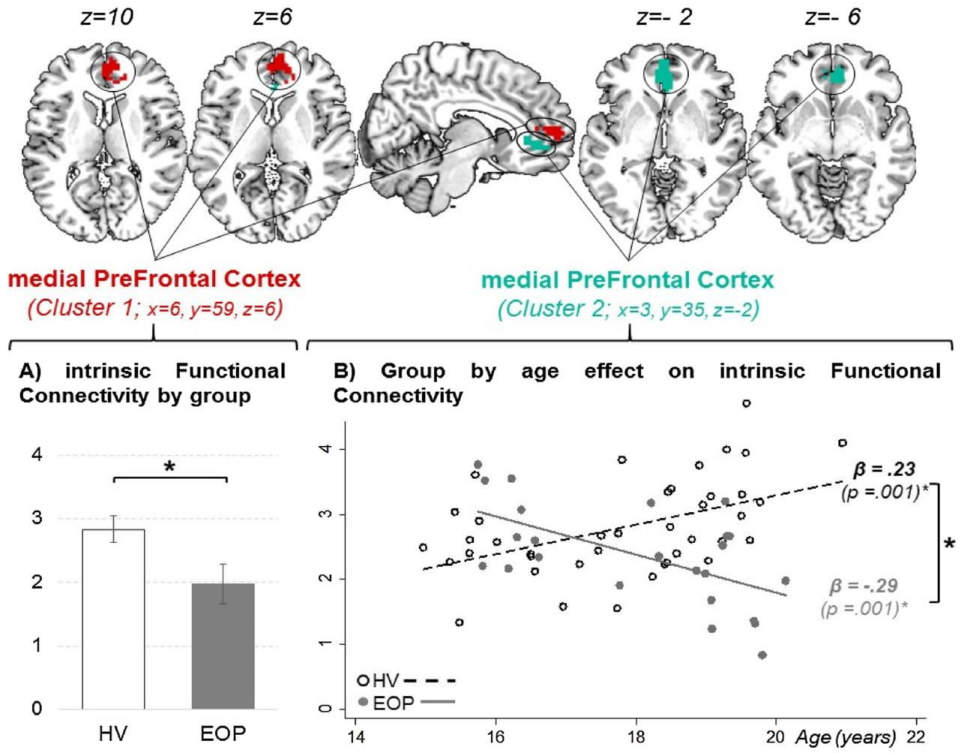

Fig. 2. Clusters within the Default Mode Network showing significant group effect (A) and group by age interaction (B) in intrinsic functional connectivity between participants with early onset psychosis (n = 24) compared to healthy volunteers (n = 40).
Note: HV = Healthy Volunteers; EOP = Early Onset Psychosis; * $p < .05$.

in a task assessing ToM in patients relative to healthy volunteers, despite controlling for differences in global intelligence between groups. Our findings concerning ToM impairment in individuals with EOP are in line with both a meta-analysis of adult samples with schizophrenia (Bora et al., 2009), and several studies encompassing youth with EOP (Bourgou et al., 2016; Korver-Nieberg et al., 2013; Li et al., 2017; Pilowsky et al., 2000; Tin et al., 2018). Our results reflect both a cross-sectional deficit and lack of age-related gain in ToM performance in EOP compared to healthy volunteers. Similar to our findings, the few studies evaluating ToM in participants with EOP so far have also failed to observe a contribution of age on ToM performance in EOP patients (Bourgou et al., 2016; Korver-Nieberg et al., 2013; Pilowsky et al.,

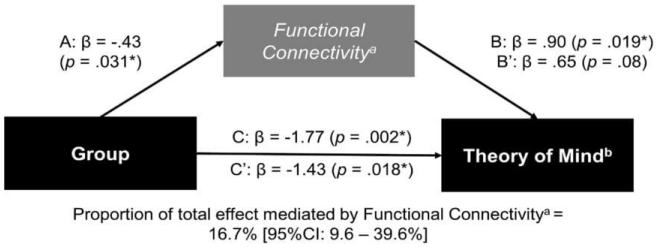

Fig. 3. Mediation analysis illustrating the relationship between intrinsic functional connectivity in the medial Prefrontal Cortex, within the Default Mode Network, with performance in the "Reading-the-Mind-in-the-Eyes" Test.
Note: [a] = Functional connectivity in the medial Prefrontal Cortex (cluster 2; [x = 3, y = 35, z = −2]); [b] = performance in the experimental condition of the "Reading-the-Mind-in-the-Eyes" Test; * $p < .05$.

2000), nor was this observed in a meta-regression with age of onset in a meta-analysis of adult schizophrenia samples (Bora et al., 2009). In addition, we ruled out that greater symptom severity, associated with earlier onset of psychosis in ours and other samples (Vyas et al., 2011), could have contributed to the ToM deficits documented in our sample. In this regard, a recent meta-analysis assessing performance in the "Reading-the-Mind-in-the-Eyes" Test in individuals with autism spectrum disorders showed that ToM scores were positively correlated with age in the control group (Peñuelas-Calvo et al., 2018) -similar to our findings in healthy volunteers-, but not in the group with autism spectrum disorders. Of note, similar performance deficits have been reported in the "Reading-the-Mind-in-the-Eyes" Test between adults with autism spectrum disorders and with schizophrenia (Couture et al., 2010; Craig et al., 2004; Lugnegård et al., 2013; Murphy, 2006). Despite the cross-sectional design, our results point towards a potential developmental discontinuation in the acquisition of ToM skills in EOP. Although the current study design does not shed light on the timing of this process, previous studies have documented ToM impairments in individuals at ultra-high risk for psychosis, who displayed intermediate performance between healthy controls and individuals with schizophrenia (Bora and Pantelis, 2013); reflecting that social cognitive deficits may have an onset prior to clinical disease (Zhang et al., 2018). The emergence of prodromal symptoms and/or a psychotic disorder during adolescence, coinciding with the time in which social cognition and function consolidate (Valle et al., 2015; Wellman et al., 2001), is likely to have an impact on ToM performance. In sum, ToM impairment in individuals with EOP, which appears to be independent of symptom severity or deficits in global intelligence, could be related to a lack of developmental gain in abilities usually acquired during childhood and adolescence, and should be taken into account when tailoring interventions for youth with an EOP (Turner et al., 2018).

We observed less intrinsic functional connectivity in the medial prefrontal cortex within the DMN in individuals with EOP, which is in line with findings from a meta-analysis of resting-state fMRI studies in schizophrenia (Dong et al., 2018; Kühn and Gallinat, 2013). Studies of resting-state fMRI in typically developing youth have shown that networks are built from early childhood: global efficiency and the strength of intrinsic functional connectivity within networks increase over development, with a mean maximum connectivity at age 22 years (Cai et al., 2018; Dosenbach et al., 2010). Specifically, the medial prefrontal cortex is the region with the greatest number of connections correlating with age in the DMN (Sato et al., 2014). Our cross-sectional study of adolescents and young adults up to 20 years of age confirms this increase in connectivity within the DMN in typically developing youth, in contrast to youth with EOP, in whom intrinsic functional connectivity in the medial prefrontal cortex was negatively associated with age. The only study reporting a significant effect of age in functional connectivity in EOP to date employed a node-based analysis, and found that in patients with early onset schizophrenia, connectivity decreased with age between the occipital cortex and the left precuneus, while it increased between the right precuneus and inferior frontal gyrus, which contrasted with findings in healthy controls (Jiang et al., 2015). These results support the notion that abnormal age-related changes in brain functional connectivity may characterize youth with early onset schizophrenia, however the different methodological approach makes it difficult to directly compare to our study. The combination of cross-sectional deficits, together with age-negative associations in connectivity, raises the possibility that illness effects may play a role in the loss of previously developed connections. However, taking into account that duration of illness was similar across all participants, our findings of less hypoconnectivity within the DMN in younger EOP could also support the possibility of greater plasticity or capacity to recover from illness-related disruption at earlier ages. Together with the fact that the medial prefrontal cortex has been shown to be especially sensitive to developmental deviation, our findings support the view that medial prefrontal DMN connectivity may be more responsive to intervention at younger ages.

Our findings suggest a partial contribution of intrinsic functional connectivity in the medial prefrontal cortex to differences in ToM performance. Connectivity between the medial prefrontal cortex and temporo-parietal junction has been reported to play a role during ToM in task-based fMRI studies (Li et al., 2014); and hypoconnectivity of these brain regions has been described in resting-state fMRI studies in schizophrenia (Schilbach et al., 2016). ToM is one of the most consistent and stable dimensions identified during mind-wandering, which is considered to take place during the resting-state (Diaz et al., 2013). Several studies have documented significant correlations between ToM performance and connectivity during resting-state fMRI in adults with schizophrenia (Choe et al., 2018; Erdeniz et al., 2017; Mothersill et al., 2017; Zemánková et al., 2018). In a study in patients with chronic schizophrenia, performance in the "Reading-the-Mind-in-the-Eyes" Test positively correlated with connectivity between the left precuneus and right middle cingulate/right inferior frontal gyrus, and between the left temporo-parietal junction and right calcarine gyrus/right lingual gyrus; and negatively correlated with connectivity between the left precuneus and right insula and left superior temporal gyrus (Mothersill et al., 2017). Zemankova et al. also reported that empathy scores were positively and negatively associated with functional connectivity between the medial prefrontal cortex and other frontal regions in patients with schizophrenia, while they observed no significant association between affective ToM scores and functional connectivity in the medial prefrontal cortex in healthy volunteers (Zemánková et al., 2018). Our findings extend this evidence to a younger population, nearer to illness onset, and add to the notion that connectivity of the medial prefrontal cortex may exert an influence on ToM performance in EOP. Brain-based measures are likely to be more sensitive to biological processes underpinning psychosis than cognitive tasks, therefore suggesting a potential role for DMN connectivity as treatment target and/or means for monitoring treatment response in individuals with EOP.

While both patient groups exhibited reduced intrinsic functional connectivity within the DMN compared to healthy volunteers, only EOSz exhibited impaired performance during the "Reading-the-Mind-in-the-Eyes" Test. A majority of comparative studies have shown greater ToM impairment in schizophrenia relative to bipolar disorder (Caletti

et al., 2013; Guastella et al., 2013; Thaler et al., 2013), in line with our results. Previous studies have supported that hypo-connectivity within the DMN may be specific to schizophrenia (Dong et al., 2018; Kühn and Gallinat, 2013) and to bipolar disorder with psychotic features in adults (Brady et al., 2017; Khadka et al., 2013; Meda et al., 2016), and adolescents (Zhong et al., 2018). In this context, our findings add support that hypo-connectivity of the DMN, specifically in the medial prefrontal cortex, may form part of a psychosis phenotype common to both affective and non-affective presentations of psychotic disorders, while ToM impairment may be specific to schizophrenia spectrum disorders.

The main limitation of our study is the sample size, especially in the secondary analyses presented in supplementary material when subdividing the EOP group by schizophrenia spectrum disorders and affective disorders, which may have resulted in lower statistical power, therefore limiting our capacity to detect statistically significant findings. However, the fact that the sample is composed of an understudied population –EOP-, and that it is homogeneous and clinically well characterised - all individuals have been followed-up since illness onset-, must also be taken into account when assessing the characteristics of the study. Although patients had a short illness duration, we cannot fully rule out that ToM deficits and lower connectivity of the DMN result solely from processes exerting an effect after illness onset, and not surrounding the illness onset. The fact that we do not find a relationship with exposure to antipsychotic medication, for example, argues against this; however, this should ideally be examined in a prospective design including pre-clinical adolescent cases. In contrast, the evaluation of participants 2 years after the first episode of psychosis has the advantage of capturing clinical diagnosis with greater stability (Castro-Fornieles et al., 2011), allowing to sub-classify the sample of EOP patients into schizophrenia and affective spectrum disorders. With regards the technique, the risk of sleep drifts are intrinsic to resting-state fMRI acquisition (Tagliazucchi and Laufs, 2014), although measures were put in place in order to minimize this. As mentioned, this is not a task-based fMRI study, thus clinical and neuroimaging correlations should be taken cautiously. However, it is worth noting that the cluster of hypo-connectivty we have found in the medial prefrontal cortex overlaps with a cluster identified in another study of resting-state fMRI in schizophrenia, in which regions-of-interest were selected according to their overlap between the DMN and brain areas recruited during tasks assessing social cognition (including ToM and excluding emotion recognition), in task-based fMRI designs (Schilbach et al., 2016, 2012). On the other hand, resting-state fMRI carries a number of advantages in relation to replicability (simpler instructions and less potential confounders), making it more comparable with other studies and easier to translate to clinical daily practice, especially considering cost and equipment requirements (Fox and Greicius, 2010). This is particularly relevant when considering the feasibility of scanning youth with EOP. Furthermore, one study has demonstrated that resting-state connectivity has shown to predict social functioning and cognitive performance better than task-based fMRI in schizophrenia (Viviano et al., 2018). Moreover, a study evaluating social skills training in adults with schizophrenia showed a correlation between improvement in social cognitive performance and connectivity of the DMN (Sestini et al., 2016), suggesting that specific interventions in patients with psychosis may have an impact on their social functioning which could potentially be mediated by changes in the underlying neural correlates of social cognition.

4.1. Conclusions

To conclude, our study provides evidence of ToM impairments and less intrinsic connectivity in the DMN in youth with EOP, and a lack of the age-positive or presence of age-negative association in each domain, in contrast to observations in healthy volunteers. Our data increases understanding of the neural underpinnings of social cognitive deficits in psychotic disorders, suggesting medial prefrontal cortex, within DMN connectivity, as a potential brain-based marker for identifying and monitoring social cognitive deficits. It also provides a plausible explanation for reports of greater social cognitive deficits in patients with an earlier age of onset of psychosis, suggesting the need to prioritize interventions targeting social cognition during adolescence.

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Declaration of Competing Interest

No conflicts declared.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.dcn.2019.100726.

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7.3. STUDY III:

Theory of mind performance and prefrontal connectivity in adolescents at clinical high risk for psychosis

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Theory of mind performance and prefrontal connectivity in adolescents at clinical high risk for psychosis

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ABSTRACT

Theory of mind(ToM) impairment is a key feature of psychotic disorders and has been documented in individuals at clinical high-risk for psychosis (CHR), suggesting that it may predate illness onset. However, no study to date has examined brain functional correlates of ToM in individuals at CHR during adolescence. The "Reading-the-Mind-in-the-Eyes" test was used to measure ToM performance in 50 CHR youth, 15 of whom transitioned to psychosis (CHR-t) at follow-up (12 ± 6 months) and 36 healthy volunteers. Resting-state functional MRI was acquired to evaluate functional connectivity within the default mode network. Group by age interaction revealed an age-positive association in ToM performance in healthy volunteers, which was not present in adolescents at CHR-t. Intrinsic functional connectivity in the medial prefrontal cortex was reduced in adolescents at CHR-t relative to those who did not transition and to healthy volunteers. Survival analyses revealed that participants at CHR with lower medial prefrontal cortex connectivity were at greatest risk of developing psychosis at follow-up. We demonstrate that lack of age-related maturation of ToM and reduced medial prefrontal cortex connectivity both precede the onset of psychosis during adolescence. Medial prefrontal cortex connectivity holds potential as a brain-based marker for the early identification of transition to psychosis.

1. Introduction

Theory of mind (ToM) (Premack and Woodruff, 1978) is the ability to understand that others present independent beliefs, intentions or desires, and to infer their mental states in order to predict their reactions and behaviour. ToM acquisition typically takes place during childhood and adolescence. The earliest signs of ToM have been described in 15-month-old children (Onishi and Baillargeon, 2005), although more evident ToM abilities start to arise around 4 years of age (Barresi and Moore, 1996; Wellman et al., 2001). Cognitive ToM (intentions and beliefs) develops earlier than affective ToM (emotions), which continues to develop during late adolescence and into early adulthood (Sebastian et al., 2012; Vetter et al., 2013). ToM performance improves with age (Wellman et al., 2001) and is considered a key process for successful social development leading into adulthood (Yager and Ehmann, 2006). Impaired ToM performance, which has been traditionally described in autism spectrum disorders (Baron-Cohen et al., 1985; Yirmiya et al., 1998), is also present in schizophrenia (Bora et al., 2009). ToM difficulties in schizophrenia have been associated with general intelligence deficits and with duration of disease (Bora et al., 2009; Thibaudeau et al., 2020). However, the conceptualization of schizophrenia as a neurodevelopmental disorder (Murray and Lewis, 1987) has raised the

Abbreviations: DMN, default mode network; CHR, participants at clinical high risk for psychosis; CHR-nt, participants at clinical high risk who did not transition to psychosis; CHR-t, participants at clinical high risk who transitioned to psychosis; HV, healthy volunteers; RMET, reading-the-mind-in-the-eyes test; fMRI, functional magnetic resonance imaging; gIQ, global intelligence quotient; ToM, theory of mind.

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possibility that ToM impairments may start early on in the developmental pathway, during childhood and adolescence. In fact, an earlier onset of schizophrenia is associated with more pronounced social cognitive deficits in adults (Linke et al., 2015); and impaired ToM performance in adolescents with early-onset-schizophrenia has been described in IQ-matched samples (Li et al., 2017; Tin et al., 2018). We recently examined ToM using the "Reading-the-Mind-in-the-Eyes" test, and documented poorer performance in adolescent patients two years after psychosis onset compared to healthy peers (Ilzarbe et al., 2019). These patients also failed to show the physiological positive association between ToM performance and age. Together, these findings suggested a potential developmental deficit in the acquisition of ToM skills during the early stages of psychosis. In the current study we aimed to examine this issue in a younger, independent sample of participants considered at clinical high risk for psychosis, evaluated before the onset of the disease.

So far, two meta-analyses have described impaired ToM in cohorts at clinical high risk for psychosis (CHR) (Bora and Pantelis, 2013; Van Donkersgoed et al., 2015), suggesting that ToM deficits may predate psychosis onset. Yet when looking at studies individually, ToM findings are mixed; even when examining the same task, for instance the "Reading-the-Mind-in-the-Eyes" test [summarized in Table S1 of supplementary material]. Discrepancies in the literature may be related to differences in the age of participants, with samples usually mixing adolescents and adults, which is an important aspect given potential differences in social cognition specific to developmental stage. Another feature is the availability of longitudinal assessments providing information on outcome. For instance, Davidson et al. (2018) reported a reduced correlation between ToM performance and age in participants at CHR relative to healthy volunteers assessed at cross-section; although in this report there was no information available on transition to psychosis at follow-up in individuals at CHR. Measuring changes over time longitudinally, Shakeel et al. (2019) reported that individuals at CHR who transitioned to psychosis at follow-up (CHR-t) lacked the improvement in ToM performance exhibited by those who did not transition (CHR-nt), but in this case the influence of age was not considered. Similarly, in a 24-month longitudinal study, Healey et al. (2013) reported that poor ToM performance at baseline predicted transition to psychosis, suggesting that the mixed ToM findings in the CHR literature could also be due to differences that are specific to the subsample of individuals who later transition to psychosis (Tor et al., 2017). However, to our knowledge, no study to date has explored whether deficits in ToM performance in CHR individuals who later transition to psychosis are influenced by age.

The medial prefrontal cortex and bilateral temporo-parietal junction are the brain areas most consistently activated during the performance of ToM tasks in functional magnetic resonance imaging (fMRI) studies (Schurz et al., 2014), and they overlap with the Default Mode Network (DMN) (Schilbach et al., 2012). Connectivity between these areas during the resting-state has been correlated with ToM performance (Zemánková et al., 2018) and has been found to be reduced in adult patients with schizophrenia (Schilbach et al., 2016). Our group recently found that adolescents two years after a first psychotic episode presented reduced functional connectivity and a negative association between connectivity in the medial prefrontal cortex and age, suggesting an impact of psychosis on the development of DMN connectivity during adolescence. Furthermore, functional connectivity in the medial prefrontal cortex partially mediated the impairments observed in ToM performance (Ilzarbe et al., 2019).

Evidence concerning connectivity within the DMN during the resting-state in psychotic disorders is inconsistent: a small number of studies have found over-connectivity (Tang et al., 2013), while recent meta-analyses have reported reduced functional connectivity in schizophrenia (Dong et al., 2018; Kühn and Gallinat, 2013). Similar inconsistencies characterise findings in CHR cohorts, with authors reporting either hyperconnectivy (Shim et al., 2010), hypoconnectivity (Pelletier-Baldelli et al., 2018) or both (Du et al., 2018). To our knowledge only two studies have explored resting-state functional connectivity correlates of social cognition in CHR. Vargas et al. (2019) found that in individuals at CHR, better performance in a mentalizing task conducted outside the scanner was associated with greater global efficiency in the medial prefrontal cortex within the mentalizing network. Global efficiency is defined as the average inverse shortest path length between nodes, and serves as an approach to measure integrated processing within a network. Damme et al. (2019) reported reduced functional connectivity during a self-reference task and increased functional connectivity during the resting-state in individuals at CHR between the medial prefrontal cortex and precuneus. Both samples mixed adolescents and young adults without distinguishing those who later transitioned to psychosis. Other ToM task-based fMRI studies found reduced prefrontal cortex activation in individuals at CHR relative to healthy volunteers (Brüne et al., 2011; Marjoram et al., 2006), but also failed to explore the relationship with transition to psychosis. Despite evidence suggesting that changes in brain connectivity associated with ToM in psychosis take place early on and may interact with normal development, no study to date has evaluated the neural correlates of ToM in individuals at CHR according to transition to psychosis and assessed the effects of age on these findings (Cao et al., 2018).

In this context we set out to evaluate ToM performance and its relationship with intrinsic functional connectivity during resting-state fMRI in adolescents at CHR for psychosis, comparing those who transitioned to psychosis (CHR-t) over the follow-up period with those who did not (CHR-nt) and to healthy volunteers, as well as to examine the effect of age on these measures. Our hypotheses were: 1) participants at CHR-t would display worse ToM performance than healthy volunteers and than those at CHR-nt; 2) participants at CHR-t would exhibit less intrinsic functional connectivity in the medial prefrontal cortex within the DMN compared to healthy volunteers and to those at CHR-nt; 3) participants at CHR-t would fail to display the positive association with age in ToM performance and DMN connectivity exhibited by healthy volunteers or CHR-nt; and 4) ToM performance would be associated with intrinsic functional connectivity within the DMN. As a secondary aim, we set out to evaluate the capacity of ToM performance or intrinsic functional connectivity within the DMN to predict transition to psychosis within the CHR group.

2. Materials and methods

2.1. Sample

Participants were recruited as part of the Children and Adolescents Psychosis Risk Syndrome (CAPRIS) study (Dolz et al., 2019): 50 help-seeking adolescents (aged 12–17) meeting criteria for CHR (attenuated positive or negative symptoms or brief limited intermittent psychotic symptoms (Cornblatt et al., 2003) scored using the SOPS (Miller et al., 2003); or with a 1st/2nd degree relative with schizophrenia or a diagnosis of schizotypal disorder, plus a decline in functioning (Klosterkötter et al., 2005) according to SIPS criteria (Miller et al., 2003)); 36 healthy volunteers matched by age and sex, recruited from schools or community settings from the same geographical area. Clinical assessments were carried out at baseline, 6, 12 and 18 months for participants at CHR, and at baseline and 18 months for healthy volunteers. The study was approved by the local Ethical Review Board, and all participants provided written informed assent, and parents or legal guardians gave written informed consent prior to study participation. Further details about the recruitment procedure can be found elsewhere (Dolz et al., 2019). Clinical and neuropsychological assessments and resting state fMRI neuroimaging acquired at baseline were included in the analyses.

2.2. Clinical assessment: baseline

Demographic data, including age, sex and race were collected; socio-

economic status was classified according to the Hollingshead-Redlich scale (Hollingshead and Redlich, 2007), where the highest parental educational and employment status was recorded. All participants were assessed by child and adolescent mental health professionals (psychiatrists and psychologists). CHR criteria were assessed with the Structured Interview for Prodromal Symptoms, scored on the Scale of Prodromal Symptoms (SOPS) (Miller et al., 2003); and global functioning was assessed with the Children's Global Assessment Scale (CGAS) (Shaffer et al., 1983). Cannabis use and detailed medication history were recorded for each participant; doses of antipsychotic drugs were transformed into chlorpromazine equivalents (Leucht et al., 2014) and cumulative chlorpromazine equivalents over time were calculated for each individual at the time of scanning. Neurocognitive function was measured using the General Ability Index (referred to as Global Intelligence Quotient; gIQ) (Flanagan and Kaufman, 2008), derived from the Wechsler Intelligence Scale for Children – 4th Edition (WISC-IV) (Wechsler, 2003). The "Reading-the-Mind-in-the-Eyes" Test (Baron--Cohen et al., 2001) was used to evaluate ToM. The task comprises 28 images that reproduce the eyes of different individuals expressing a range of emotions. Participants were asked to identify the gender of the individual (control condition) and the emotion (experimental condition), selected among 4 possible answers.

2.3. Clinical assessment: follow-up

The only information gathered from the longitudinal assessment related to transition to psychosis. This was available for 39 participants at CHR (78 %) and 27 healthy volunteers (75 %), with no differences in age, sex, race, gIQ, socio-economic status, cannabis use or group in relation to the drop-outs. Fifteen adolescents at CHR developed a psychotic episode (30 %) during the follow-up period (mean time to transition: 12.2 (SD = 6.1) months).

Socio-demographic and clinical information are presented in Tables 1 and S2.

2.4. Statistical analyses: socio-demographic and clinical data

Statistical analyses were performed in Stata v.13.1 using *t*-test, ANOVA and chi-square tests for demographic and clinical information. In order to account for both the control and the experimental conditions, performance during the ToM task (% of correct answers) was assessed using a multilevel mixed-effects linear regression model, with group, condition and group by condition interaction as fixed effects, including individual factor as random effect; replicating the methods from our previous article (Ilzarbe et al., 2019). gIQ, sex, age, socio-economic status, cannabis use or baseline clinical severity (total SOPS score, CGAS) were added as covariates to the model when exerting a significant effect ($p \leq .05$). A linear regression model was also used to assess the effect of age on ToM performance, including group, age and group by age interaction. Again, gIQ, sex, socio-economic status, cannabis use or clinical severity (total SOPS score, CGAS) were added as covariates when significant ($p \leq .05$). Bonferroni correction was applied for multiple pairwise comparisons.

2.5. Neuroimaging acquisition and preprocessing

An 8-min eyes-closed resting-state fMRI sequence was acquired in a single session on a 3 T scanner at baseline. Acquisition parameters are detailed in Supplementary material. Resting-state fMRI images were realigned, co-registered to the individual T1-weighted scan, normalized to the Montreal Neurological Institute (MNI) space and smoothed using a 6-mm Gaussian kernel in SPM12. One healthy volunteer (drop-out) and three participants at CHR (one CHR-t, one CHR-nt and one drop-out) were excluded from further neuroimaging analyses due to excessive motion (absolute movement > 3 mm or mean Framewise Displacement >.2 or more than 20 % frames with Framewise Displacement >.3) (Power et al., 2017, 2012; Yan et al., 2013). There were no differences in age, sex, race, gIQ, socio-economic status or cannabis between those excluded due to movement and the rest of the sample. There were no significant differences in the mean Framewise Displacement between CHR and healthy volunteers; or between the three groups (CHR-t, CHR-nt and healthy volunteers).

2.6. Functional connectivity analysis

The component corresponding to the DMN was identified among 20 components estimated by independent component analysis using the GIFT toolbox for SPM12 running in Matlab R2019a. The network was identified by visual inspection and confirmed through the highest correlation with the template (r = .57) [spatial map representation in Fig. S1 of supplementary material]. Replicating the methods from our previous article (Ilzarbe et al., 2019), the spatial maps of the DMN component of each subject were compared in a whole brain analysis in SPM, introducing group, age, group by age interaction, sex and mean framewise displacement as regressors within an inclusive DMN mask created with the mean sample template. Only results surviving family-wise error correction are reported. Next, mean values of intrinsic functional connectivity within each significant cluster were extracted for each individual, and linear regression models were conducted in Stata v.13.1, in which the effects of gIQ, sex, socio-economic status or

Table 1
Baseline socio-demographic and clinical characteristics of the sample subdivided according to transition to psychosis at follow-up.

	CHR-t (n = 15)	CHR-nt (n = 24)	HV (n = 27)	*p* value	*Post-hoc (Bonferroni)*
Socio-demographic					
Age (years) [range]	15.2 (SD = 1.3) [12.6–17.2]	15.7 (SD = 1.7) [12.0–17.9]	15.6 (SD = 1.7) [12.9–18.3]	*.640*	
Sex (% female)	66.7 %	62.5 %	70.4 %	*.838*	
Race (% caucasian)	100.0 %	79.2 %	92.6 %	*.094*	
Socio-economic Status	48.1 (SD = 19.8)	39.2 (SD = 16.2)	50.7 (SD = 14.5)	*.061*	–
Clinical variables					
Global Intelligence Quotient	105.8 (SD = 12.4)	98.6 (SD = 13.7)	107.8 (SD = 12.3)	*.038**	*HV > CHR-nt*
Scale of Prodromal Symptoms (total score)	32.8 (SD = 10.6)	28.9 (SD = 11.0)	1.7 (SD = 2.3)	*<.0001**	*CHR-t = CHR-nt>HV*
- Positive Subscale	9.0 (SD = 4.1)	7.8 (SD = 3.9)	.4 (SD = .8)	*<.0001**	*CHR-t = CHR-nt>HV*
- Negative Subscale	8.5 (SD = 4.7)	10.6 (SD = 5.5)	.4 (SD = .6)	*<.0001**	*CHR-t = CHR-nt>HV*
- Disorganized Subscale	4.4 (SD = 2.8)	3.6 (SD = 2.5)	.3 (SD = .7)	*<.0001**	*CHR-t = CHR-nt>HV*
- General Subscale	10.6 (SD = 3.4)	7.5 (SD = 4.3)	.9 (SD = 2.0)	*<.0001**	*CHR-t > CHR-nt>HV*
Children's Global Assessment Scale	36.0 (SD = 18.2)	50.2 (SD = 16.6)	84.4 (SD = 6.9)	*<.0001**	*HV > CHR-nt > CHR-t*
Reported cannabis use					
- Occasionally - monthly	26.7 %	12.5 %	33.3 %	*.241*	
- Weekly - diary	13.3 %	20.8 %	3.7 %		
Time to transition (months)	12.2 (SD = 6.1)	–	–		

Note: HV = Healthy Volunteers; CHR-t = participants at Clinical High Risk for psychosis who transitioned to psychosis; CHR-nt = participants at Clinical High Risk for psychosis who did not transition to psychosis; SOPS = Scale of Prodromal Symptoms; SD = Standard Deviation; * $p < .05$.

cannabis use were included as covariates in the model when significant ($p \leq .05$). Bonferroni correction was applied for multiple pairwise comparisons. The potential effect of antipsychotic medication on resting-state fMRI measures (cumulative chlorpromazine equivalents (Leucht et al., 2014)) was also evaluated. Correlations between ToM performance and intrinsic functional connectivity were estimated to evaluate their association.

2.7. Survival analysis

In order to account for time to transition in the prediction of psychosis, a survival analysis was performed within the CHR group using Stata v.13.1. Performance in the ToM task and functional connectivity in the clusters showing significant group effects were assessed as predictive variables using Cox proportional hazards models to compute Hazard Ratios. Liu's method (Liu, 2012) for empirical estimation of a diagnostic cut-off point (Area Under the Curve) was used to dichotomize the significant variables, Kaplan-Meier survival curves were then estimated for each group.

3. Results

3.1. Theory of mind task

For the CHR-t, CHR-nt and healthy volunteers contrast, there was no significant group by condition effect ($p = .17$) [Table S3]. However, the linear regression model showed a significant group by age effect between healthy volunteers and CHR-t ($p = .03$; $\omega^2 = .058$); with a positive association between ToM performance and age in healthy volunteers ($\beta = 3.39$; $p = .002$), which was also present at trend-level significance in the CHR-nt group ($\beta = 2.03$; $p = .08$) but not in the CHR-t group ($\beta = -1.37$; $p = .45$) [Fig. 1]. gIQ, sex and socio-economic status were included as covariates in the linear regression model ($ps < .03$) while cannabis use, and ratings in the SOPS and CGAS were excluded, given that they had no significant effect in the model [Table S3].

3.2. Intrinsic functional connectivity

An effect of group was found in the dorsomedial prefrontal cortex within the DMN (cluster 1: [x = -9, y = 47, z = 26]; voxel count = 51; $p^{FWE-corr} = .041$) in the CHR-nt vs CHR-t contrast. Post-hoc analysis with the extracted values showed that CHR-t participants exhibited less connectivity compared to CHR-nt ($p < .001$) and healthy volunteers ($p = .046$) [Figs. 2A and S2A]. A second cluster in the ventromedial prefrontal cortex showed a significant group by age interaction (cluster 2: [x = -12, y = 44, z = -2]; voxel = 50; $p^{FWE-corr} = .044$) in the healthy volunteers vs CHR-nt contrast. Post-hoc analysis with the values extracted from this cluster showed a significant group by age interaction between healthy volunteers and both CHR-t ($p = .001$) and CHR-nt ($p < .001$) groups; where functional connectivity was positively associated with age in healthy volunteers ($\beta = .25$; $p = .001$), while the effect was the opposite in individuals at CHR-nt ($\beta = -.24$; $p = .003$) and CHR-t ($\beta = -.24$; $p = .058$) [Figs. 2B and S2A]. There was no significant effect of socio-economic status, sex, gIQ or cannabis use when included in the models. In individuals at CHR receiving antipsychotic treatment (n = 21), cumulative chlorpromazine equivalents were not correlated with functional connectivity in either of the clusters ($rs \leq |.22|$; $ps \geq .34$).

There was a trend-level correlation between ToM performance and functional connectivity in cluster 2 in healthy volunteers (n = 35; r = .32; $p = .058$) [see Fig. S3], not replicated in the other groups.

A secondary Region-of-Interest (ROIs) analysis was performed based on results from our previous study in a sample of patients with early onset psychosis (Ilzarbe et al., 2019). The two ROIs, defined according to regions showing group and group by age effects in the contrast between patients with early onset psychosis relative to healthy volunteers, were located in the dorsal and ventral areas of medial prefrontal cortex within the DMN, respectively [see Fig. S2A]. CHR-t exhibited reduced functional connectivity relative to healthy volunteers at trend-level ($p = .060$) in ROI1 located in the dorsomedial prefrontal cortex; and there was a significant group by age interaction between healthy volunteers and CHR-nt ($p = .028$) in ROI2 in the ventromedial prefrontal cortex [for further information see supplementary material and Fig. S2B].

For the sake of completeness, we conducted contrasts for CHR vs healthy volunteers for both the theory of mind task and resting state fMRI data, which revealed no significant group or group by age effects in either modality. These analyses are presented in Supplementary Material.

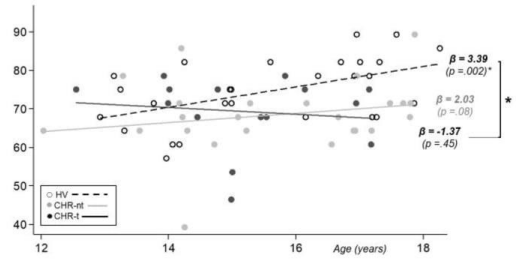

Fig. 1. Scatter-plot representing group by age effects on the experimental condition of the "Reading-the-Mind-in-the-Eyes" Test comparing healthy volunteers vs participants at clinical high risk for psychosis according to transition to psychosis[a].
Note: HV = Healthy Volunteers; CHR = participants at Clinical High Risk for psychosis; CHR-t = participants at Clinical High Risk for psychosis who transitioned to psychosis; CHR-nt = participants at Clinical High Risk for psychosis who did not transition to psychosis; [a]: model also including global intelligence quotient, sex and socio-economic status ($ps < .03$) as covariables; * $p < .05$.

3.3. Survival analysis

Out of 50 participants at CHR, 43 were included in the survival analysis (three excluded due to movement and four with no follow-up). Fourteen participants had experienced transition to psychosis during the follow-up period. Only functional connectivity in dorsomedial prefrontal cortex (cluster 1) (HR = .20; $p = .002$) was associated with less probability to transition to psychosis at follow-up. Further analysis allowed to establish a cut-off point in functional connectivity of dorsomedial prefrontal cortex (cluster 1) (cut-off point = 1.52; area under ROC curve = .83; sensitivity = .79; specificity = .79). Participants with low functional connectivity (under the cut-off point) in dorsomedial prefrontal cortex (cluster 1) exhibited a significantly increased risk of transition to psychosis (HR = 6.29; $p = .005$; 95 %CI: 1.75–22.64) [Fig. 3].

4. Discussion

Our study evaluated ToM performance and resting-state fMRI in adolescents at CHR for psychosis and found:

(1) A positive association between ToM performance and age in healthy volunteers, which was absent in participants at CHR-t.
(2) Reduced intrinsic functional connectivity in the dorsomedial prefrontal cortex within the DMN in participants at CHR-t, relative to CHR-nt and to healthy volunteers. Connectivity in the ventromedial prefrontal cortex was positively associated with age in healthy volunteers, while it was negatively associated with age in both CHR-nt and CHR-t.
(3) An association between reduced intrinsic functional connectivity in the dorsomedial prefrontal cortex within the DMN and higher rates of transition to psychosis in individuals at CHR.

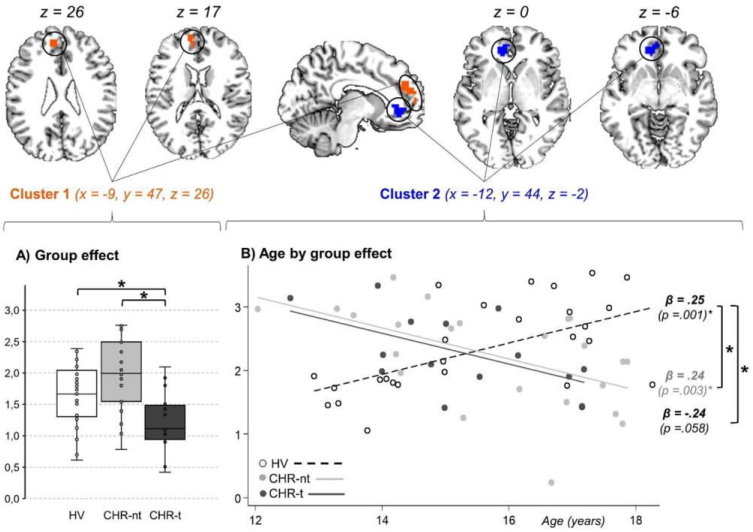

Fig. 2. Clusters within the Default Mode Network showing a significant effect of group (A) and group by age interaction (B) in intrinsic functional connectivity between healthy volunteers and participants at clinical high risk for psychosis divided according to transition to psychosis at follow-up, overlaid on a grayscale brain template.
Note: HV = Healthy Volunteers; CHR-t = participants at Clinical High Risk for psychosis who transitioned to psychosis; CHR-nt = participants at Clinical High Risk for psychosis who did not transition to psychosis; * $p < .05$.

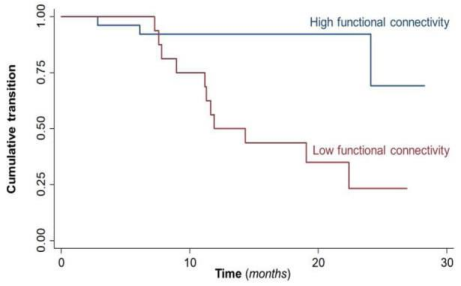

Fig. 3. Kaplan-Meier survival estimates for transition to psychosis within participants at clinical high risk for psychosis divided by functional connectivity ("low" and "high", dichotomized according to the cut-off point of 1.52) in the dorsomedial prefrontal cortex (cluster 1) [x = -9, y = 47, z = 26].

We found no group by condition effects in ToM performance between CHR, CHR-t, CHR-nt and healthy volunteers; contrary to our hypothesis and to findings from the single study examining performance in the same ToM task in individuals at CHR according to transition to psychosis (Healey et al., 2013). Two factors may have contributed to the lack of group effects in ToM performance in our study. First, a potential effect of developmental stage: the sample in the study by Healey et al. (2013) predominantly encompassed adults, while we focused on adolescents. Healthy volunteers in our study exhibited a positive association between ToM performance and age, in line with meta-analytic findings (Peñuelas-Calvo et al., 2019), while participants at CHR who transitioned to psychosis failed to present such association, which coincides with findings by Davidson et al. (2018). This suggests a potential developmental discontinuation of ToM abilities in these individuals, in line with our previous findings in an independent sample of adolescents with early-onset psychosis (Ilzarbe et al., 2019). This would lead to larger ToM impairments in older patients with psychosis, as reflected by the greater effect sizes reported in adult samples with schizophrenia (Bora et al., 2009) than in adolescents with early-onset psychosis (Ilzarbe et al., 2019). Second, effect sizes of ToM impairments in CHR are likely to be smaller in comparison to first-episode psychosis (Bora and Pantelis, 2013) or schizophrenia (Bora et al., 2009; Zhang et al., 2018) given the heterogeneity of CHR samples. Our findings are in line with previous age-related ToM difficulties documented in CHR (Healey et al., 2013; Davidson et al., 2018; Shakeel et al., 2019), and suggest that this lack of age-positive association with ToM performance is due to those individuals at CHR who later transition to psychosis. This is consistent with a recent longitudinal study reporting lack of improvement in ToM performance over time in CHR-t relative to CHR-nt (Shakeel et al., 2019). Our results also expand our previous findings showing a lack of association between age and ToM performance in adolescents with early-onset psychosis (Ilzarbe et al., 2019), suggesting an impaired acquisition in ToM abilities during development, prior to the onset of the psychosis. The emergence of prodromal symptoms and progression to overt psychosis in adolescence, which is a critical period for the maturation of ToM abilities, may explain the greater social cognitive deficits associated with earlier onset of the disease reported in adult samples (Linke et al., 2015).

We observed reduced intrinsic functional connectivity in the dorsomedial prefrontal cortex within the DMN in individuals at CHR who transitioned to psychosis. Similar to our findings, Anticevic et al. (2015) reported hypoconnectivity involving the prefrontal cortex in participants at CHR who transitioned to psychosis relative to healthy volunteers, which is also consistent with the results from two meta-analyses in patients with schizophrenia (Dong et al., 2018; Kühn and Gallinat, 2013). In contrast, Cao et al. (2018) described global hyperconnectivity during the resting-state in participants at CHR who converted to psychosis relative to those who did not. The use of a seed-based-analysis or a ROI-to-ROI analysis, respectively, has been hypothesized to explain the discrepancies between studies (Cao et al., 2018). This group effect is also in line with our previous findings of reduced intrinsic functional connectivity in the medial prefrontal cortex in individuals with early-onset psychosis (Ilzarbe et al., 2019). We have found less connectivity in the CHR-t group compared to healthy volunteers, albeit at trend-level significance (as shown in Fig. S2B), in the same region within the dorsomedial prefrontal cortex as in our earlier article (Ilzarbe et al., 2019). Interestingly, mean values of connectivity were comparable between CHR-t participants and youth with early-onset psychosis, while values in healthy volunteers were higher in our previous study (Ilzarbe et al.,

2019), where participants were overall older. Despite the fact that this is an indirect comparison between two different samples, therefore limiting our capacity to draw conclusions, our findings suggest that youth in the early stages of psychosis may not experience the increase in connectivity in the medial prefrontal cortex typically taking place during adolescence. We indeed found a positive association between connectivity and age in healthy volunteers in the ventromedial prefrontal cortex. In fact, the medial prefrontal cortex is thought to play a key role in the development of the DMN during adolescence, experiencing a sharp increase in connectivity during this period in healthy volunteers (Cai et al., 2018; Dosenbach et al., 2010; Mak et al., 2017; Sato et al., 2014; Truelove-Hill et al., 2020). A meta-analysis reporting greater connectivity within the DMN in adult samples relative to children and adolescents (Mak et al., 2017) suggested that methodological differences between studies could explain discrepant findings in the literature: those using independent component analysis and seed-based analysis tended to find positive correlations with age (Dosenbach et al., 2010; Sato et al., 2014), while those using a ROI-to-ROI approach tended to find negative correlations with age (Marek et al., 2015). In our study, in contrast to the healthy volunteers, both CHR-nt and CHR-t groups showed a negative association between functional connectivity and age. This may suggest a shared neurodevelopmental deficit, as delayed brain maturation has been related with psychopathology (Cropley et al., 2020; Sato et al., 2016). Medial prefrontal cortex disruption has been implicated in several disorders and related with multiple cognitive domains (Hiser and Koenigs, 2018), with regionally specific differences. For instance, ventral areas within the medial prefrontal cortex extending to anterior cingulate cortex (Marusak et al., 2016), as is the case of cluster 2, have been associated with value-based decision-making tasks (Gilbert et al., 2009; Hiser and Koenigs, 2018). On the other hand, dorsal regions of the medial prefrontal cortex, which is where cluster 1 is located, have been related with impaired ToM in schizophrenia (Hiser and Koenigs, 2018). In fact, cluster 1 partially overlaps with significant regions reported by a ToM fMRI-task based meta-analysis in schizophrenia (Sugranyes et al., 2011), and with the prefrontal areas associated with the mentalizing network during resting-state fMRI in schizophrenia (Schilbach et al., 2016) [Fig. S2A]. Besides social cognitive difficulties, disrupted connectivity of the prefrontal cortex in schizophrenia (Zhou et al., 2015) has also been linked with psychotic symptoms (Thoma et al., 2016) and impaired executive functions (Giraldo-Chica et al., 2018); and has been associated with glutamate hypofunction (Limongi et al., 2020). Glutamate levels in the medial prefrontal cortex (overlapping with mentalizing areas) have been associated with resting-state connectivity within the DMN in healthy volunteers (Martens et al., 2020), and positively correlated with better cognitive performance in individuals at high-risk for psychosis (Wenneberg et al., 2020). Our results extend our previous findings of impaired maturation of medial prefrontal cortex connectivity in adolescent-onset psychosis (Ilzarbe et al., 2019), in alignment with the current physiopathological framework for schizophrenia (Howes et al., 2015), and suggest that dysfunction in dorsal and ventral areas of the medial prefrontal cortex is already present in adolescents during the prodromal stage, before the onset of the first episode.

We failed to find an association between ToM performance and functional connectivity in the medial prefrontal cortex, in consonance with a previous study in individuals at CHR (Damme et al., 2019). This dissociation between apparently no impairment in performance in the ToM task and altered functional connectivity of the DMN in participants at CHR who later transition to psychosis, contrasts with our previous finding of a relationship between ToM and functional connectivity within DMN in adolescents with early-onset psychosis (Ilzarbe et al., 2019). An explanation could be that brain disruption may precede ToM deficits in adolescents at CHR who will later develop psychosis. Furthermore, altered connectivity between mentalizing regions may interfere in the acquisition of ToM abilities during development. This could explain why ToM deficits are more pronounced after the onset of psychosis (Ilzarbe et al., 2019), compared to the prodromal stage. If so, functional neuroimaging may be more sensitive towards detecting illness-related changes than behavioural tasks (Ilzarbe et al., 2019; Kim et al., 2009; Malhi et al., 2007), especially during the early stages of the illness. Further, we found that reduced functional connectivity in the dorsomedial prefrontal cortex, overlapping with mentalizing regions in schizophrenia, was a significant marker of transition to psychosis in CHR individuals. Previous studies have also supported the role of functional neuroimaging in detecting risk of transition to psychosis, over the use of clinical variables (Cao et al., 2018); and our findings point to the dorsomedial prefrontal cortex as a potential key region.

The main limitation of our study is the sample size, which may have resulted in lower statistical power, therefore limiting our capacity to detect statistically significant findings, which may have been particularly relevant when assessing ToM performance. Given that earlier age of onset of psychosis has been associated with greater clinical severity (Immonen et al., 2017), differences in clinical severity according to age could have influenced the relationship between age and ToM. Nevertheless, it is worth noting that overall clinical and symptom severity did not exert a significant effect on the estimated statistical models. In contrast, a strength of the study is the fact that our sample is composed exclusively of adolescents (Tor et al., 2017), which allows for the study of CHR individuals during a key period in neurodevelopment (Murray and Lewis, 1987). Furthermore, it also promotes homogeneity of the sample. The evaluation of participants according to their longitudinal outcome is another strength of this study and increases the clinical relevance of our findings. In addition, resting-state fMRI presents advantages in relation to replicability (simpler instructions and less potential confounders), making it more comparable with other studies and easier to translate to clinical daily practice, especially when working with adolescents with mental health disorders, as well as considerations related to cost and equipment requirements (Fox and Greicius, 2010).

4.1. Conclusions

To conclude, our study provides evidence of a lack of an age-positive association in ToM performance and reduced medial prefrontal connectivity in adolescents at CHR who go on to develop a first psychotic episode. Our data increase the understanding of the neural underpinnings of psychosis, suggesting medial prefrontal cortex, within DMN connectivity, as a potential brain-based marker for identifying and monitoring individuals at greatest risk of transition.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.dcn.2021.100940.

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8. DISCUSSION

The present work extends the current knowledge on the neural correlates of ToM in subjects with developmental disorders. The three studies included in this thesis provide evidence of functional neuroimaging in neurodevelopmental disorders, focusing on the neural functioning patterns underlying ToM performance in subjects with ADHD, the ASD+ADHD comorbid condition, EOP and at CHR during adolescence. An overview of the sample, methodology and main findings of each study is presented in the table-Summary in the next page.

This Discussion includes the findings of the three studies in order to frame their main results from a neurodevelopmental perspective. First, behavioural results of ToM performance across the three studies are presented. Second, neuroimaging results and their correlation with the behavioural results are discussed. Third, the conceptualization of neurodevelopmental disorders in consonance with the findings are discussed. Finally, limitations, clinical and research future perspectives are presented, which lead to the Conclusions.

Table-Summary. Comparison of methods and results of the three studies included in the thesis.

	Study I	**Study II**	**Study III**
Location/Institution	London (United Kingdom)/King's College London	Barcelona (Spain)/Hosp. Clínic de Barcelona	Barcelona (Spain)/Hosp. Clínic de Barcelona
Design	Cross-sectional case-control study	Cross-sectional case-control study	Longitudinal case-control study
Subjects	19 **ASD** 21 **ADHD** 18 **ASD + ADHD** 25 **HC**	27 **EOP** (2 years after first episode of psychosis) 41 **HC**	<u>Baseline</u> <u>18-months follow-up</u> 50 **CHR** → 15 **CHR-t** → 24 **CHR-nt** 36 **HC** → 27 **HC**
Ages	22-29 y/o (all males)	15-20 y/o	12-17 y/o
Clinical/neurocognitive eval.	CAARS, SRS-2, SDQ17+, ADOS-2 / WASI-II	PANSS / WISC	SIPS/SOPS, CGAS / WISC
ToM evaluation	**Frith-Happé Animated Triangles**	**Reading-the-Mind-in-the-Eyes Test**	**Reading-the-Mind-in-the-Eyes Test**
> ToM findings	- Comparable ToM performance in all four groups	- EOP performed worse than HC in ToM - EOP performance in ToM lacked the positive correlation with age exhibited by HC	- CHR-t performance in ToM lacked the positive correlation with age exhibited by HC or CHR-nt
Neuroimaging	**Block task-based fMRI (Frith-Happé animated triangles)**	**Resting-state fMRI**	**Resting-state fMRI**
> fMRI findings	- Increased activation in right angular gyrus in ASD and ASD+ADHD relative to ADHD - ASD, ASD+ADHD and ADHD lacked the increased functional connectivity between the right angular gyrus and bilateral TPJ exhibited by HC - ASD and ASD+ADHD lacked the increased functional connectivity between the right inferior frontal gyrus and posterior cingulate cortex exhibited by HC and ADHD - ADHD and ASD+ADHD showed decreased functional connectivity between the mPFC and left TPJ during ToM relative to HC	- EOP showed reduced functional connectivity in the dorsal mPFC within the DMN, relative to HC - EOP showed negative correlation between functional connectivity and age in the ventral mPFC within the DMN, while in HC this correlation was positive - ToM impairments were partially mediated by functional connectivity in the ventral mPFC within the DMN in EOP	- CHR-t showed reduced functional connectivity in the dorsal mPFC within the DMN relative to HC and to CHR-nt - CHR-nt and CHR-t showed negative correlation between functional connectivity and age in the ventral mPFC within the DMN, while in HC this correlation was positive - Reduced functional connectivity in the dorsal mPFC within the DMN was associated with higher risk of transition to psychosis in CHR

Abbreviations. ASD: Autism Spectrum Disorders; ADHD: Attention-Deficit and Hyperactivity Disorder; CAARS = Conners Adult ADHD Rating Scale, CGAS = Children's Global Assessment Scale; CHR-t=participants at Clinical High Risk for psychosis who transition to psychosis; CHR-nt=participants at Clinical High Risk for psychosis who did not transition to psychosis; DMN = Default Mode Network; EOP = Early-Onset Psychosis; fMRI = functional Magnetic Resonance Imaging; HC: healthy controls; mPFC = medial PreFrontal Cortex; PANSS = Positive and Negative Symptom Scale; SDQ17+ = Strengths and Difficulties Questionnaires for age 17 years and above; SIPS/SOPS = Structured Interview for Prodromal Symptoms, scored on the Scale of Prodromal Symptoms; SRS = Social Responsiveness Scale version 2; ToM = Theory of Mind; WAIS = Wechsler Adult Intelligence Scale, WISC = Wechsler Intelligence Scale for Children.

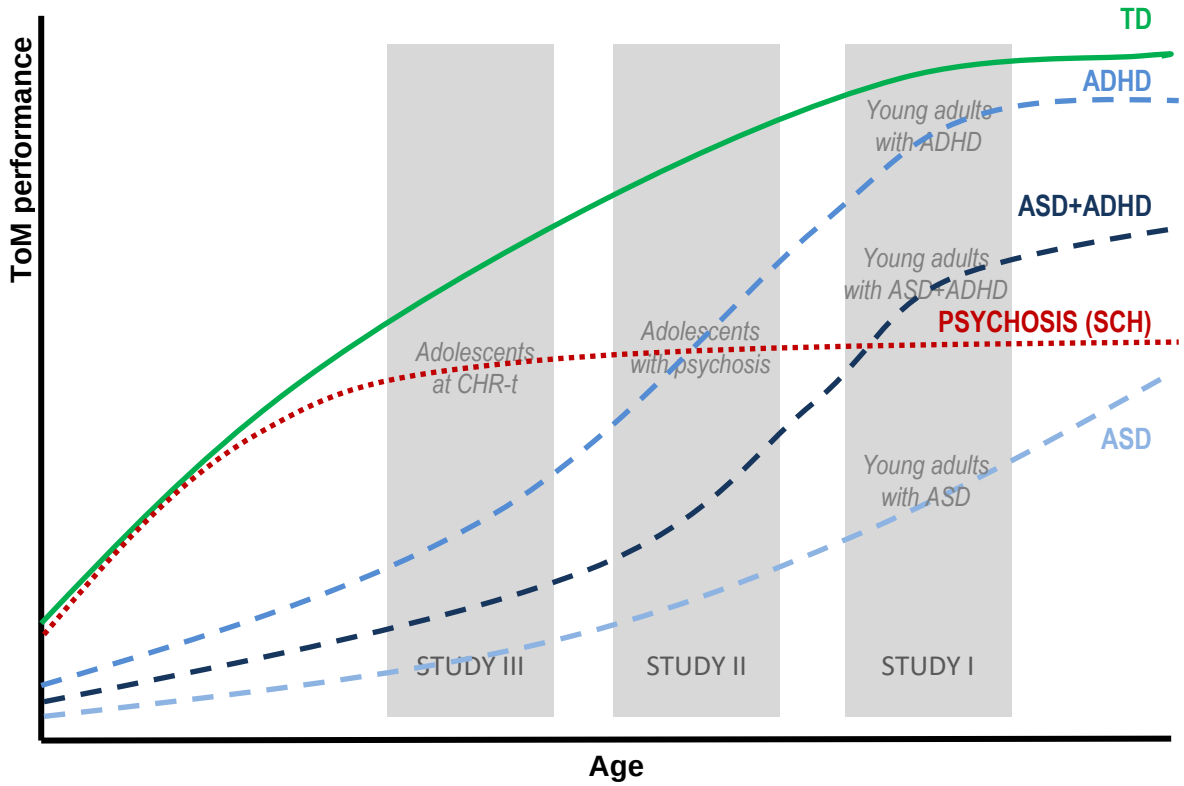
8.1. Theory of Mind in neurodevelopmental disorders: behavioural measures

Study I focused on the neural mechanisms underlying ToM in young adults with ADHD and the ASD+ADHD comorbid condition. Although there were subtle differences in the performance of the ToM task between the clinical groups (ASD, ASD+ADHD and ADHD) and the control group, there were no differences in the main outcomes. Interestingly, the performance in another ToM task, the Strange Stories task, published elsewhere (264) within the same sample of subjects revealed significant impairment in the ASD group relative to the healthy control and ADHD groups; with the ASD+ADHD group achieving an intermediate level of performance between the two other clinical groups. Several factors may be potentially mediating these discrepant results between performance in the two ToM tasks within the subjects with ASD. First, the Frith-Happé animated triangle task may be too simplistic, and previous studies encompassing adults with ASD relative to healthy controls have previously reported conflicting findings using this task: both, significant differences (158) as well as similar performance, have been reported (152). Second, it could be that, as Study I is a population-based study, the included subjects may present less severe ASD features relative to clinically referred samples (265). Third, high functioning adults with ASD may demonstrate less ToM difficulties due to compensatory reasoning skills in low demanding tasks (266,267). The latter possibility could be supported by the neuroimaging findings, with the ASD group showing a relative overactivation in temporo-parietal areas, as discussed in the next section. Livingston and Happé (268) have suggested that compensation may be underlying the behavioural improvement in adulthood exhibited by some subjects diagnosed with ASD since childhood; and recommend research on this topic combining cognitive tasks and biological markers. ToM acquisition in subjects with ASD does not seem to follow the same trajectory exhibited by typically developing individuals during childhood and adolescence (269,270).

Subjects with ADHD did not show significant differences in ToM performance relative to healthy controls in the Frith-Happé animated triangle task, nor was this observed in the Strange Stories task within the same sample (264). These findings may be related with the sample encompassing young adults; given

that the meta-analysis conducted by Bora et al. (161) reported significant deficits in ToM in children and adolescents with ADHD, yet this was not replicated in the adult samples. Taken together, this suggests that ToM could be among the cognitive domains in which subjects with ADHD catch-up with their typically developing peers at adulthood, following a period of neurodevelopmental delay during childhood and adolescence (271). Similar to the discussion concerning the findings in the ASD group, the acquisition of compensatory skills may be also a possibility for adults with ADHD (268). Interestingly, subjects with the ASD+ADHD comorbid condition showed a comparable performance in the Frith-Happé animated triangle task to healthy controls and to the other clinical groups; while in the Strange Stories task, within the same sample, they exhibited intermediate performance between ASD (poorest performance) and the ADHD or control groups (best performance) (264). Brain activation in subjects with the ASD+ADHD comorbid condition during ToM task was also intermediate between the ASD and ADHD groups, suggesting shared neural mechanisms between the two disorders when presenting comorbidly. This finding contrast with the initial hypothesis, since it was expected that the comorbid group would perform the worst in the ToM task and would present the most extreme brain activation pattern. Studies evaluating ToM performance in children with the comorbid condition report a similar or poorer performance in the ASD+ADHD comorbid groups relative to the ASD group (272–274). In contrast, a study encompassing adults and evaluating ToM found comparable ToM performance between ASD, ADHD and the ASD+ADHD comorbid condition (275). In the light of the literature and the findings of this thesis, it may be speculated whether individuals with the combination of ASD and ADHD during childhood exhibit ToM deficits similarly to individuals with ASD alone; and whether there is significant improvement during neurodevelopment in ToM abilities, similarly to ADHD, leading to comparable ToM performance to ADHD and healthy controls in adulthood. Contextualizing the findings of this thesis in the available literature supports differential trajectories of ToM acquisition during childhood and adolescence until adulthood for each neurodevelopmental disorder, raising the need for longitudinal studies in order to fully evaluate these hypotheses. Hypothetical neurodevelopmental trajectories for ToM acquisition abilities in ASD, ADHD and the ASD+ADHD comorbid condition are presented in figure 4.

Figura 4. Hypothetical neurodevelopmental trajectories for ToM acquisition abilities in neurodevelopmental disorders based on previous literature and the findings of this thesis. Grey areas indicate group inclusion and age ranges for each study.



Note: ASD: Autism Spectrum Disorders; ADHD: Attention-Deficit and Hyperactivity Disorder; CHR-t: Clinical High Risk who transition to psychosis; SCH: Schizophrenia; TD: Typically developing subjects; ToM: Theory of mind

Studies II and III provide data on the association between resting-state fMRI and ToM deficits in the spectrum of psychosis during adolescence: in both youth with EOP and at CHR for psychosis. The results of Study II confirmed that patients with EOP performed significantly worse than healthy controls, in line with a meta-analysis of adult samples with schizophrenia (163) and several studies encompassing youth with EOP (247–251). In contrast, Study III revealed no significant differences in ToM performance between adolescents at CHR-t and healthy controls. This finding contrasts with the results from the two studies evaluating performance in the "Reading-the-Mind-in-the-Eyes" Test according to transition to psychosis in youth at CHR (257,258). It is important to bear into account a neurodevelopmental perspective in order to contextualize and explain both findings: the mean ages of the samples by Healey et al. and Zhang et al. are

more than 4 years older than the sample in Study III (257,258). In line with this, Studies II and III found evidence of a significant lack of age-related gain in ToM performance in youth with EOP as well as in adolescents at CHR-t compared to healthy controls and their peers at CHR-nt, Healthy controls in both studies exhibited a positive association between ToM performance and age, similar to meta-analytic findings (43), while participants with EOP and at CHR-t failed to present such association. It may be speculated that adolescents at CHR who will transition to psychosis discontinue the trajectory of typically developing acquisition of ToM abilities, hence the fact that they exhibit age by group differences, although the gap between these adolescents at CHR and their healthy peers is not enough at this time to show group differences. However, over time, the progressive acquisition of ToM abilities in the typically developing subjects and lack of developmental gain in the probands would lead to a growing difference between them. Therefore, by the time the psychotic disorder is established, both the age by group and group effects would become significant. Therefore, this suggests a potential developmental discontinuation of ToM abilities in the psychosis spectrum starting before the onset of the first episode, maintained through the course of the disorder, as hypothesized in figure 4. This would explain the significant group effect found in youth with EOP in Study II, while there was a lack of group effect in the CHR sample in Study III; and also that both groups exhibited a lack of age-positive correlation in the ToM performance when compared with their healthy peers. Davidson et al. (45) also showed a reduced association between age and ToM performance cross-sectionally in the CHR group relative to healthy controls, but failed to provide follow-up data on transition to psychosis. Shakeel et al.'s (256) longitudinal study also supports this interpretation: they found that individuals at CHR-t lacked the improvement in ToM performance over follow-up exhibited by CHR-nt, although they did not consider age in the statistical analysis and did not include a healthy control group. And finally, Healy et al. and Zhang et al. (257,258) did find the mentioned group effect in CHR-t, but the mean age of their sample was 4 years older, and therefore case-control differences in ToM performance may have been larger due to the influence of age on group effects. Furthermore the literature supports larger ToM impairments in older patients with psychosis, as reflected by the greater effect sizes reported in adult samples with schizophrenia (163) than in adolescents with EOP or subjects at CHR, as found in Studies II

and III. The secondary analysis of Study II showed that only participants with early-onset schizophrenia, but not youth with early-onset affective disorder with psychotic symptoms exhibited impaired ToM performance relative to healthy controls. Greater ToM impairment in schizophrenia relative to bipolar disorder and major depressive disorder has been reported in the literature (163,241,242,276–278) in line with the results of this thesis. The higher male:female ratio and more severe neurocognitive deficits in schizophrenia spectrum psychosis may have mediated their greater ToM impairments when compared to affective disorders in Study II, as pointed by meta-analysis (279). Therefore, the emergence of prodromal symptoms and progression to overt psychosis within the schizophrenia spectrum during adolescence, coinciding with the critical period in which social cognition and function consolidate (41,42), may explain the greater ToM deficits associated with earlier onset of the disease reported in adult samples (246) represented in figure 4.

8.2.Theory of Mind in neurodevelopmental disorders: neuroimaging measures

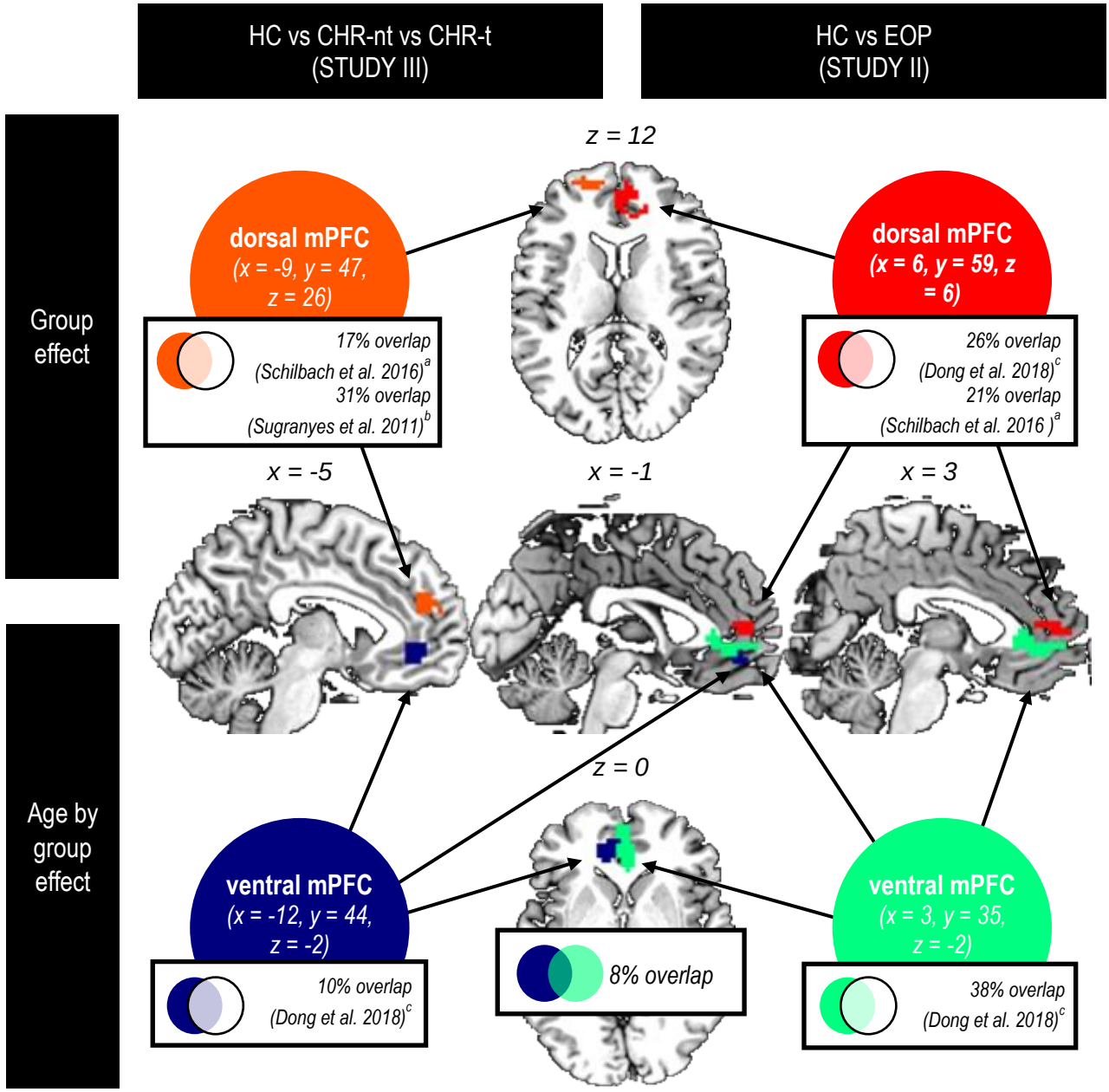
Study I revealed that there were differences in brain activation in the ADHD group relative to the ASD group in the right temporo-parietal regions. The lack of significant group effect between ASD and healthy controls is in consonance with the largest study to date evaluating the Frith-Happé animated triangle task during fMRI in ASD (280). According to the findings of Study I, the ASD group showed an overactivation in temporo-parietal areas relative to the ADHD group and, only at a trend level, to the control group. Some studies have reported overactivation in mentalizing areas in children and adolescents with ASD relative to healthy controls during ToM tasks (152,155,281), which has been hypothesized to act as a compensatory mechanism (266,267). Furthermore, this overactivation could be a marker of neurodevelopmental delay, with adults with ASD showing a pattern of brain activation comparable to typically developing adolescents, who present greater brain activation and comparable ToM performance relative to healthy adults (52). Nevertheless, it was the ADHD group, who exhibited hypoactivation in right temporo-parietal regions, the one showing an opposing pattern of activation to the ASD group; and therefore pointing to a potentially different pattern of brain activation underlying ToM in both disorders. Activity in the right TPJ has been associated with ToM and reorienting attention tasks, and some authors have suggested that the superior temporal sulcus, within the TPJ, plays an integrative role between these functions (282). This co-localization does not imply exactly the same voxel distribution or a common process, as suggested by several meta-analyses about attention and ToM paradigms which have reported regional-specificity within the TPJ for each task (283–285). The pattern of performance and brain activation during ToM in the ASD+ADHD comorbid condition is comparable to the ASD group in young adults, although previous studies in children using electro-encephalographic measures have suggested an additive effect of both disorders in the comorbid condition (203,204), The findings of this thesis support a disorder-specific neural mechanism for ToM in ASD and ADHD. Furthermore, other neuropsychological functions which may show disorder-specific impairment may influence ToM performance, as pointed by previous

studies correlating performance in ToM with executive functions in children with ADHD (286) but not in children with ASD (202).

In addition to this disorder-specific brain activation in Study I, healthy controls presented a ToM-specific pattern of functional connectivity between mentalizing regions relative to non-ToM conditions, which was not replicated in the clinical groups. These findings are consistent with previous literature, which has also reported a lack of typical increase of intrinsic functional connectivity during ToM tasks in subjects with ASD (149,152–154). The common underconnectivity between temporo-parietal regions found in the ASD, ADHD and ASD+ADHD comorbid groups points to a shared endo-phenotype for ToM in both neurodevelopmental disorders, as suggested by resting-state studies (287). In particular, Kernbach et al. (287), found that a brain network factor with the most pronounced between-bilateral temporo-parietal connectivity was associated with ASD and ADHD during the resting state in a data-driven, transdiagnostic analysis. On the other hand, the lack of increased connectivity between frontal and posterior regions during ToM found in ASD and ASD+ADHD, but not in ADHD or healthy controls, points to an ASD-differentiating connectivity pattern. This finding is in line with previous literature reporting underconnectivity in participants with ASD in ToM-task-based fMRI studies (see table 5). Resting-state fMRI studies have also reported ASD-specific altered functional connectivity in similar regions, relative to ADHD and healthy controls (288). Compared to healthy controls, ADHD and ASD+ADHD groups showed decreasing functional connectivity between the mPFC and the left TPJ with increasing ToM, also pointing to an ADHD-specific connectivity pattern. Although there are no previous fMRI studies examining ToM in ADHD, this counterintuitive connectivity pattern (increased during control conditions and reduced during the ToM condition) may be reflecting ADHD core deficits: the TPJ has been related not only with ToM (16) but also with attention (289). In fact, it has been hypothesized that reorienting attention from external to internal stimuli may be underlying ToM processes (shifting to compare/connect other's experience with one's own). The TPJ, as mentioned in the previous paragraph, could play a key role mediating this attention shift (289). A hypothesis for the neural correlates of ToM in ADHD may be that impaired attention could be altering ToM processing. The findings of this thesis add to the literature that subjects with ADHD and the ASD+ADHD

comorbid condition lack the specific ToM pattern in functional connectivity between regions typically present in healthy controls during social cognition, sharing impaired connectivity features with ASD and also presenting ADHD-specific altered connectivity during a ToM task.

Figure 5. Brain location of clusters within the medial Prefrontal Cortex within the Default Mode Network for Studies II and III. [Adapted from Study III – Supplementary Material].

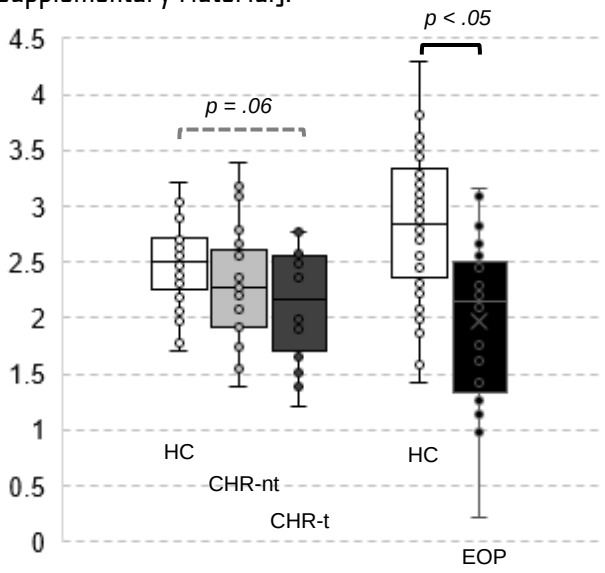


Note: HC=Healthy Controls; CHR-t=participants at Clinical High Risk for psychosis who transition to psychosis; CHR-nt=participants at Clinical High Risk for psychosis who did not transition to psychosis; EOP=participants with Early-Onset Psychosis; mPFC: medial PreFrontal Cortex; ROI=Region-Of-Interest; [a]= 10mm-spheric-ROI (centred at x:-2, y:52 z:14); [b]= 10mm-spheric-ROI (centered at x:-6, y:52 z:30); [c]= 10mm-spheric-ROI (centred at x:0, y:50 z:2)

Studies II and III provide data on resting-state fMRI in adolescents in the psychosis spectrum: youth with EOP and at CHR for psychosis. Youth with EOP and at CHR-t exhibited less intrinsic functional connectivity in the dorsal mPFC within the DMN relative to healthy controls or adolescents at CHR-nt. This area overlaps with a cluster identified in another study of resting-state fMRI in schizophrenia (see figure 5), in which regions-of-interest were selected according to brain areas engaged during tasks assessing social cognition, and belonging to the DMN (82,253). Also, the clusters within the dorsal mPFC found in Studies II and III overlap with the main finding in a meta-analysis of resting-fMRI in schizophrenia (218) and another meta-analysis of ToM task-based fMRI in schizophrenia (151), respectively; as shown in figure 5. Secondary analysis of Study II found shared reduced connectivity in the mPFC in both youth with schizophrenia spectrum disorders and with affective disorders with psychotic features, relative to healthy controls. Functional connectivity in the mPFC is also altered in bipolar disorder (290), and hypo-connectivity within the DMN has been described for bipolar disorder with psychotic features (291–293), and confirmed to be present in adolescent samples (294). Studies assessing connectivity within the DMN in major depressive disorder have revealed conflicting findings: some studies have shown hyperconnectivity (295), while others have shown hypoconnectivity (290). Reduced functional connectivity between the subgenual/mPFC area and hypothalamus have been described in patients with major depressive disorder with psychotic symptoms relative to healthy volunteers, but not in those without psychotic features (296). Findings of Study II add support to the notion that hypo-connectivity of the mPFC within the DMN may be part of a psychosis phenotype common to affective and non-affective presentations of psychotic disorders. This is consistent not only with studies encompassing patients with psychosis, but also with studies in participants at CHR-t relative to healthy controls, in whom Anticevic et al. (240) reported prefrontal cortex hypoconnectivity associated to ulterior transition to psychosis. The single study associating hyperconnectivity and transition to psychosis in participants at CHR (239) used Region-Of-Interest-to-Region-Of-Interest analysis instead of Independent Component Analysis, which is the method used in Studies II and III and in Anticevic et al.'s study (240). These methodological differences have been

hypothesized by Cao et al. to explain the opposite results in connectivity (239). The results were consistent when using the Region Of Interest in dorsal mPFC from Study II to analyse data from Study III, as shown in figure 6. In this post-hoc analysis, reduced connectivity in the CHR-t group was found at trend-level, with mean values of connectivity comparable between CHR-t participants and youth with EOP. Interestingly, the mean values in healthy controls were higher in Study II, where participants were overall older. These findings suggest that youth with psychosis may not experience the typical increase in mPFC connectivity during adolescence, and brain connectivity may "pause" or "slow down its growth" before the onset of the first episode of psychosis. In line with this, Studies II and III found that connectivity in the ventral mPFC and age were positively associated in healthy controls, and negatively associated in youth with EOP or adolescents at CHR-t. The areas in the ventral mPFC found in Studies II and III are coincident and, as before, they are congruent with the main findings of a meta-analysis of resting-fMRI in schizophrenia (218), as shown in figure 5. The mPFC experiences a sharp increase in connectivity during adolescence (70,71,76,77,297) and is the region with the greatest number of connections correlating with age in the DMN in children and adolescents (77), in line with the results in healthy controls in Studies II and III. In contrast, the EOP and CHR-t groups showed a negative association between age and intrinsic functional connectivity in the mPFC within the DMN. Again, these findings suggest that psychosis may have an impact on the

Figure 6. Medial Prefrontal Connectivity in youth with early-onset psychosis, at clinical high-risk and healthy controls from Study II and 3, using Region Of Interest from Study II. [Adapted from Study III – Supplementary Material].



Note: HC=Healthy Controls; CHR-t=participants at Clinical High Risk for psychosis who transition to psychosis; CHR-nt=participants at Clinical High Risk for psychosis who did not transition to psychosis; EOP=participants with Early-Onset Psychosis; HC: healthy controls.

maturation of connections of prefrontal regions within the DMN even before the onset of the first episode of psychosis.

Disrupted connectivity of the prefrontal cortex in schizophrenia (298) has also been linked with psychotic symptoms (299) and impaired executive functions (300). Therefore, ToM deficits in psychosis could be secondary to the impairment in other clinical and neuropsychological domains. Nevertheless, there are task-based fMRI studies showing that impairments of ToM in schizophrenia are associated with an alteration within the dorsal-mPFC (190,301); and the finding of Studies II and III in EOP and CHR-t within the dorsal-mPFC overlaps with the main findings of a ToM-task-based fMRI meta-analysis (151), and resting-state fMRI mentalizing network in schizophrenia (253).

Subtle relationships between ToM performance and neuroimaging findings were found to be associated in the three studies. Results from Study I showed that the number of prompts received by the ASD group correlated with hyperactivation in the right angular gyrus, supporting the interpretation of a compensatory effort in the ASD group (fMRI relative overactivation coupled with comparable ToM performance to healthy controls). Results from Study II showed that functional connectivity in the ventral mPFC within the DMN accounted for 16.7% of the differences in ToM performance exhibited by the youth with EOP; in line with findings by Zemankova et al., who reported that empathy scores were associated with functional connectivity between mPFC and other frontal regions in individuals with schizophrenia (189). Results from Study III showed a trend-level correlation between ToM performance and functional connectivity in the ventral mPFC only in the group of healthy controls. In contrast, the three studies also present a common apparent dissociation between similar to healthy controls performance in the ToM task and altered brain activity or functional connectivity pattern in the clinical groups. In Study I, there were no differences in the main outcomes of the ToM task, while the brain activation pattern significantly differed between groups. In the secondary analysis of Study II, in which cases were subdivided according to their diagnosis, both early-onset schizophrenia and early-onset affective disorders groups exhibited reduced intrinsic functional connectivity within the DMN compared to healthy controls, while only the former

presented significant impaired performance in the "Reading-the-Mind-in-the-Eyes" Test. Thus, the group with early-onset affective disorders present reduced connectivity in fMRI without differences in behavioural performance. In Study III, subjects at CHR-t showed no differences in ToM performance compared to healthy controls, while neuroimaging results replicated the findings of reduced intrinsic functional connectivity within the DMN. The dissociation between task performance and fMRI findings suggest that: 1) the pattern of brain engagement during ToM processing differs between subjects with neurodevelopmental disorders or at CHR and healthy controls (189); and 2) neuroimaging may be more sensitive towards detecting disorder-related neural differences than behavioural tasks (302,303). Findings in Study I suggest persistent atypical neural processing of ToM in ASD, ADHD and the ASD+ADHD comorbid condition in adulthood. Findings in Studies II and III suggest that the brain disruption may precede ToM deficits and may interfere with the acquisition of ToM abilities during development in adolescents at CHR-t. Furthermore, connectivity of the dorsal-mPFC within the DMN may be a marker of transition to psychosis in CHR individuals. This finding supports the notion that functional neuroimaging may play a role in helping to define risk of transition to psychosis, over the use of clinical variables (239).

8.3. Theory of Mind across neurodevelopmental disorders: commonalities & specificities

Neurodevelopmental disorders are frequently comorbid, as presented in table 2, and a previous diagnosis increases the risk of presenting another neurodevelopmental disorder. For example, there is an increased risk of developing psychosis or psychotic symptoms in subjects with a previous diagnosis of ADHD (127) or ASD (304) compared to the general population. Neurodevelopmental disorders also share genetic (305,306) and environmental risk factors (119–121). Furthermore, neurodevelopmental disorders overlap between each other in the clinical presentation and in impairments in some cognitive domains (96), including ToM. ToM is progressively acquired during development (4,41–44), and deficits in ToM are shared by neurodevelopmental disorders since childhood (96). However, the literature and the findings of this thesis suggest different trajectories for each disorder, as hypothesized in figure 4. Impairments in ToM in subjects with ASD seem to be present in childhood and adulthood (94,146,160); although adults with ASD may develop some compensatory skills as showed by the findings of Study I and supported by other studies demonstrating less difficulties in ToM in these individuals (266,267). Impairments in ToM in subjects with ADHD seem to be evident during childhood, but not significantly present in adulthood (161), suggesting that they may catch-up with their typically developing peers following a potential delay of the acquisition of social skills. ToM impairments in adult patients with schizophrenia are comparable with those in ASD, as shown by a meta-analysis (169) of studies directly comparing the two conditions (307). Previous research has suggested that earlier age of onset of the first episode of psychosis is associated with poorer ToM performance (246,307). The findings of this thesis suggest that a discontinuation in the acquisition of ToM abilities in psychosis may start during development, before the clinical onset of the first episode (164,262). Specifically, for ToM impairments in ASD and schizophrenia, a model of disruption due to defect or excess has been hypothesized in the literature. The *diametrical opposed model of Autism-Schizophrenia* proposed a continuum in ToM abilities between the two disorders to explain shared clinical and pathophysiological characteristics (308). On one hand, subjects with ASD would present under-developed ToM, which could explain the social deficit as core in the disorder. On the other, subjects with schizophrenia would present

over-developed ToM, which could explain psychotic and paranoid symptoms due to over-attributing (309). This altered attribution of other's thoughts and emotions would also lead to ToM impairments (309). In line with this model, some studies have found balanced/normalized ToM in patients with psychosis when presenting comorbidly with high autistic traits (310). In contrast, other studies have reported no differences in the percentage of errors related with under-developed or over-developed ToM between ASD and schizophrenia spectrum disorders (311). The findings of this thesis add to the previous body of literature, and suggest a complex picture underlying ToM impairments in neurodevelopmental disorders: where a nuclear and shared endophenotype of social cognitive deficits coexists with particularities which are specific to each domain (depending on the test used to evaluate) and specific to each disorder.

The shared alteration in brain maturation and synaptic pruning during childhood and adolescence has been hypothesized to explain the clinical overlap and frequent comorbidity in neurodevelopmental disorders (312). Furthermore, common genetic features have been reported in ASD, ADHD and psychosis (313); and altered synaptic pruning has been identified in post-mortem studies in both ASD and schizophrenia (314). Several structural studies have highlighted shared neuroanatomical deficits between ASD and ADHD (194), and between ASD and psychosis (315,316). Literature also supports developmentally-altered brain functional connectivity patterns shared trans-diagnostically in some psychiatric disorders (such as ADHD or prodromal symptoms of psychosis) during adolescence (317). Functional neuroimaging studies of neurodevelopment highlight childhood and adolescence as a crucial period of brain maturation, and a window of opportunity to intervene (318).

This thesis adds information about the lack of this specific connectivity pattern during ToM tasks in young adults with ADHD and the ASD+ADHD comorbid condition relative to healthy controls. The neuroimaging findings of Study I support a disorder-specific neural processing of ToM in subjects with ADHD; and a shared ADHD- and ASD-specific neural pattern in subjects with comorbid ASD+ADHD. In addition, this thesis provides evidence of reduced connectivity in the mPFC within the DMN during resting-state fMRI in youth with EOP and those at CHR-t. The association between impaired ToM performance and

reduced functional connectivity in the mPFC in youth with EOP, which is not present in adolescents at CHR-t, suggests that brain functional changes may precede the ToM behavioural deficits detected in patients with psychotic disorders. The main findings in this thesis encompassed the mPFC or TPJ, neural nodes within the DMN or mentalizing network, whose functional connectivity is altered in a number of psychiatric disorders (141,319). The *triple network model*, encompassing within- and between-connectivity of the DMN, salience network and executive network, has been proposed to explain several psychiatric disorders, including schizophrenia, ASD and ADHD (61). Despite each disorder presenting different pathophysiology, the interconnectivity between the networks would explain the overlap of symptomatology, such as ToM deficits. In line with this, a model of cross-disorder connectomics suggests that a combination or interaction of different impaired networks involved in basic neuropsychological processes may lead to similar presentation deficits in more complex neuropsychopathological processes, such as social cognition (102). Either way, both models defend differences in the underlying mechanisms of ToM impairment in each neurodevelopmental disorder, as supported by the results of this thesis. The three studies present data about common and disorder-specific neural patterns correlating or preceding ToM difficulties in youth with ASD, ADHD, psychosis or at CHR-t. The findings of this thesis support differences in the underlying mechanisms of ToM across neurodevelopmental disorders and across neurodevelopment.

8.4. Limitations

Limitations of the studies included in this thesis are detailed in the respective publications. However, the main ones are also summarised and presented comparatively here.

The cross-sectional design to study developmental disorders is a limitation of the three studies; although Study III included longitudinal information about clinical outcome concerning transition to psychosis. Larger sample sizes would have resulted in higher statistical power, and subtle or trend differences may have become significant, especially in Study I. Recruitment for the studies was challenging: Study I identified subjects using a population-based selection, allowing a priori more generalizable outcomes; and the second and third studies focused on a low incident disorder within the target population, requiring a long recruitment period. Regarding sample selection: the inclusion of only young-adult males in Study I, or evaluation of participants 2 years after the first episode of psychosis in Study II, enhanced group homogeneity at the expense generalizability of the findings. The higher prevalence of ASD in males than females (114) and the reported sex differences in brain activation and functional connectivity in ASD and ADHD by previous studies (320), justified the specific sample selection in Study I. In Study II, the evaluation of participants 2 years after the first episode of psychosis allowed to sub-classify the sample of EOP patients into schizophrenia and affective spectrum disorders with greater diagnostic stability (321). In addition, the exposure to psychiatric medication may have exerted an effect on the findings, although this was evaluated in all three studies and no significant relationship was detected between ToM performance and its neural correlates.

ToM-task selection for the studies may have influenced the findings. Frith-Happé animated triangle task, used in Study I, appeared to be too simplistic for some groups of patients with ASD (152); despite being widely referenced in the literature (160) and frequently used in task-based fMRI studies (see table 5). Regarding Studies II and III, some authors have suggested that performance in the "Reading-the-Mind-in-the-Eyes" Test may be related to facial emotion perception more than ToM abilities (322,323) despite a

number of studies having used it for measuring ToM (43), and having been conceptualized as a ToM task when designed (35).

The fact that task-based and resting-state fMRI approaches were both used may be considered to be another limitation. Each technique has advantages and disadvantages for each study. Although the Frith-Happé animated triangles task selected in Study I may have been too simplistic for adults with ASD, task-based fMRI allows to extract stronger conclusions about the brain-based findings. In Studies II and III, clinical and neuroimaging correlations need to be interpreted with caution. However, resting-state fMRI has been considered a better approach than task-based fMRI to study neurodevelopmental changes in functional connectivity (324), it also facilitates replicability (simpler instructions and less potential confounders) and is easier to translate to clinical daily practice (325); especially given that resting-state connectivity has shown to predict social functioning and cognitive performance better than task-based fMRI in schizophrenia (254).

8.5. Future perspectives

8.5.1. Clinical Implications

The findings from this thesis suggest caution when interpreting the lack of ToM impairment in neurodevelopmental disorders or adolescents at CHR. Firstly, there may be some patients/subjects requiring more demanding tasks to detect impaired ToM performance when deficits are subtle or when putting compensatory strategies in place. In addition, an adequate ToM performance does not exclude abnormal neuroimaging findings. fMRI could be a supplementary test in future clinical practice for neurodevelopmental disorders and youth at CHR, as discussed in the next section.

The findings of this thesis suggest that there are different neural mechanisms underlying ToM difficulties in each developmental disorder, and therefore interventions aimed at improving social skills and social functioning should be designed and monitored accordingly. Subjects with ADHD and the ASD+ADHD comorbid condition may benefit from a different treatment approach to those targeting ASD alone. A recent systematic review about social skills training programs in children and adolescents with ADHD found no significant impact on social skills, but a positive improvement in core ADHD symptoms (326). These findings, in consonance with the results of this thesis, suggest that integrative treatment encompassing social skills and targeting attention and behavioural problems in subjects with ADHD would be more effective than adding single interventions for this population (327).

The findings of this thesis in adolescents with EOP and at CHR raise the need for early intervention programs aimed at building social skills before the onset of psychosis. Moreover, a study evaluating social skills training in adults with schizophrenia showed a correlation between improvement in social cognitive performance and connectivity of the DMN (328), suggesting that specific interventions in patients with psychosis may have an impact on their social functioning which could potentially be mediated by changes in the underlying neural correlates of social cognition. Although there is an increasing number of studies reporting on social skill training programs for psychotic patients (329,330), few studies so far have

focused on intervening in first episode (331) or recent onset (332) patients, and none in adolescent population. Therefore, specific treatments targeting subjects at risk for developing psychosis (333) could potentially prevent more severe impairments after the onset of the disorder.

Nevertheless, whether ToM impairments alone are sufficient to predict long-term functioning is still a matter of debate (334–336). As mentioned, studies assessing specific treatments focused on social skills training have reported improvements in symptomatology, such as core-disorder symptoms in ADHD (327) or insight in psychosis (337) but there were no significant findings regarding social functioning. This phenomenon may translate the difficulties to disentangle ToM from other neuropsychological functions that also mediate social cognition (338). Thus, a holistic perspective is required to design personalized and disorder-specific integrative treatments; accounting for brain functional connectivity as a potential marker to monitor efficacy and response.

8.5.2. Research implications

Despite a large body of literature supporting cross-diagnostic ToM impairments in neurodevelopmental disorders, the neural correlates underlying these difficulties remain poorly understood for ADHD, the ASD+ADHD comorbid condition, and the early phases of psychosis during adolescence. The studies included in this thesis have addressed this gap in the literature. Identifying these mechanisms will help to better understand the impact that these neurodevelopmental disorders occurring during youth exert on the brain, in order to build explanatory models which will help to develop tailored treatments and preventive strategies.

Given that the findings of this thesis support differential neural correlates between neurodevelopmental disorders and there is cumulative evidence of differences in ToM impairment over development, research focused on younger age groups and longitudinal designs are necessary (339). Future studies should address the neural processes involved in ToM deficits in ADHD and ASD+ADHD comorbid condition in children and adolescents, as well as in the earlier stages of psychosis, such as youth

with risk factors for psychosis (for instance, offspring of patients with the disease), considered to be in the "pre-prodromal phases" (340). Expanding the study of the neural correlates of ToM to other neurodevelopmental disorders, such as Tourette syndrome, or include environmental factors, such as traumatic experiences or bullying, would help to identify common and specific neurodevelopmental pathways involved in brain maturation and ToM acquisition. Furthermore, expanding the neurocognitive domains (attention, executive functions…) explored would help to clarify whether there are other neuropsychological process influencing the deficits of ToM presented in each disorder.

In addition, task-based and resting-state fMRI studies complement each other in the study of neurodevelopmental disorders. It is important to make progress in the field of neuroimaging research if fMRI is to be incorporated in clinical practice in order to diagnose (for instance evaluating abnormal neural processing of ToM) and/or predict prognosis (for instance risk of transition to psychosis), able to provide information over the use of clinical variables (239).

9. CONCLUSIONS

This thesis aimed to study the neural correlates of theory of mind cross-diagnostically in neurodevelopmental disorders using functional connectivity, focusing on: 1) ADHD and comorbid ASD+ADHD condition, 2) EOP and 3) CHR. The main conclusions of the thesis, derived from Study I (1-3), Study II (4-6), and Study III (7-9) as well as the significance of the results (10) and future lines of research that could be pursued (11-12), can be summarized as follows:

1. Young adults with ADHD, ASD or ASD+ADHD showed comparable performance relative to healthy controls in the ToM task. [In contrast to hypothesis 1 and 2]
2. Young adults with ADHD showed under-activation in the right parieto-temporal regions relative to individuals with ASD or ASD+ADHD comorbid condition, pointing to different brain mechanisms between the two disorders. [In contrast to hypothesis 4 and 5]
3. Young adults with ADHD, ASD or ASD+ADHD comorbid condition did not present the ToM-specific functional connectivity between fronto-parietal and parieto-temporal regions exhibited by typically developing controls; and showed common and disorder-specific connectivity patterns. [In line with hypothesis 4 and 5]
4. Youth with EOP exhibited poorer ToM performance than healthy controls, and a lack of age-related maturation in ToM acquisition exhibited by healthy controls. Within EOP, youth with early-onset schizophrenia presented deficits in ToM performance relative to youth with early-onset affective disorders and healthy controls. Youth with early-onset affective disorders performed no differently than healthy controls. [In line with hypothesis 3, 8 and 9]
5. Youth with EOP showed less mPFC connectivity within the DMN relative to healthy controls; and also presented a negative association between mPFC connectivity and age, which was positively associated within healthy controls. Youth with early-onset schizophrenia and early-onset affective disorders showed less mPFC connectivity within the DMN relative to healthy controls, but without differences between each other. [In line with hypothesis 6 and 8; and in contrast to hypothesis 9]

6. Intrinsic functional connectivity in the mPFC within the DMN was associated with ToM performance in youth with EOP. [In line with hypothesis 7]
7. Adolescents at CHR-t failed to exhibit the normative age-related maturation in ToM acquisition exhibited by healthy controls or participants at CHR-nt. [In line with hypothesis 8]
8. Adolescents at CHR-t showed less mPFC connectivity within the DMN relative to healthy controls and CHR-nt. Both CHR-t and CHR-nt presented a negative association between mPFC connectivity and age; in contrast to healthy controls, in which these were positively associated. [In line with hypothesis 6 and 8]
9. Adolescents at CHR with lower mPFC connectivity presented higher rates of transition to psychosis relative to those with higher mPFC connectivity. [In line with hypothesis 10]
10. Cross-diagnostic examination of the neural correlates of ToM difficulties in youth with neurodevelopmental disorders increases the understanding of the differential underlying brain mechanisms playing a role in ToM in each neurodevelopmental disorder.
11. mPFC connectivity holds potential as a biomarker for predicting transition to psychosis within adolescents at CHR.
12. This new knowledge may help to tailor disorder-specific interventions targeting ToM during youth, and provide potential neuroimaging markers to monitor their efficacy.

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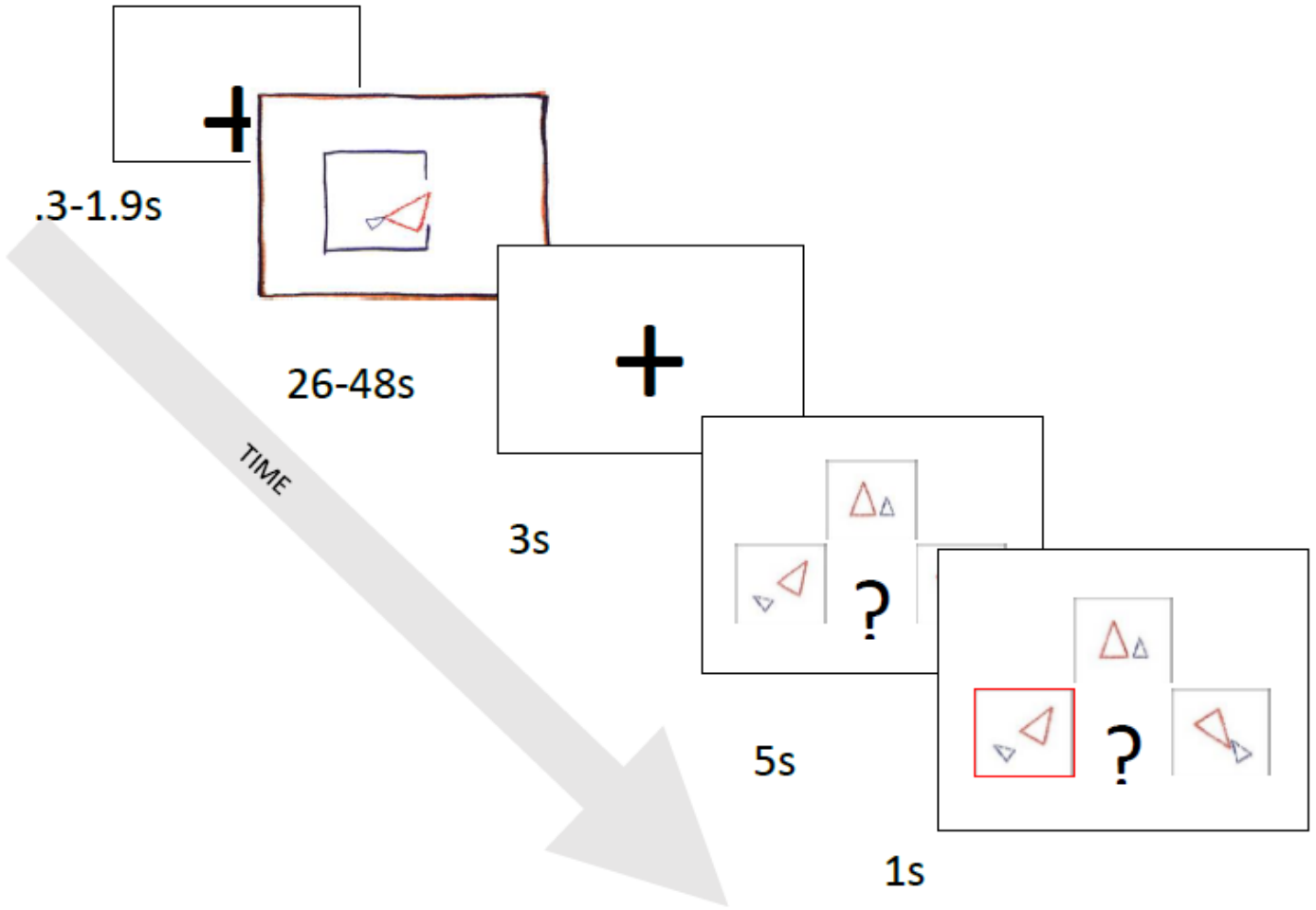
11. APPENDIX 1: Supplementary material from study I

Figure S1. Schematic Diagram of Frith-Happé Animated Triangle Task



The task consists of twelve 26-48s cartoons depicting two triangles whose movement reflect (1) ToM or mentalizing, e.g. persuading, (2) Goal-directed (GD) or physical interaction, e.g. following and (3) Random (RD) purposeless motions, e.g. floating. Each movement condition is represented by four clips, shown in a pseudo-randomised order consistent across participants. A fixation cross of 1-s mean duration (range: 0.3 – 1.9 s) preceded each clip. The clip is then followed by 3-s fixation, followed by a visual multi-choice question asking the participants to identify the movement featured in the clip, i.e. ToM, GD, or RD, that had to be answered within a 5-s interval. The participant's choice is highlighted by a red box around it for a 1-s interval.

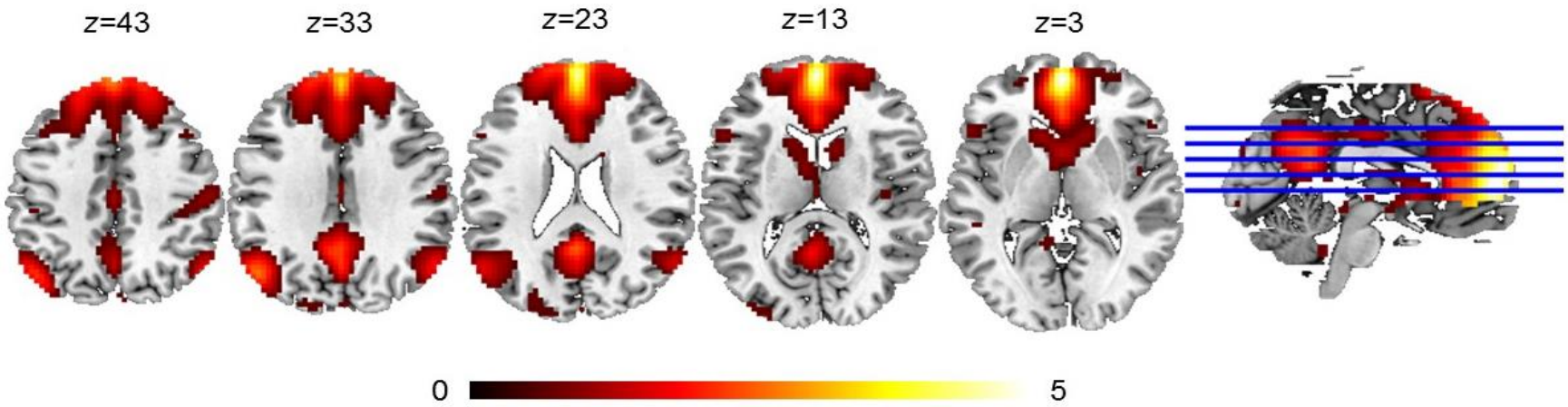
Table S1. Group differences in behavioural data of the neuropsychological task and during functional Magnetic Resonance.

		TD (n = 25)	ASD (n = 19)	ASD+ADHD (n = 18)	ADHD (n =21)	*Group effect*	*Condition effect*	*Condition by group effect*	*Post-hoc*
						F (p value)			
Intentionality	ToM	3.87 (3.60-4.13)	3.66 (3.24-4.08)	3.99 (3.71-4.26)[a]	3.83 (3.56-4.09)[b]	2.09 (*.108*)	239.04 (< *.0001****)	.68 (*.570*)	**TD**: ToM*** > GD **ASD**: ToM*** > GD **ASD+ADHD**: ToM*** > GD **ADHD**: ToM*** > GD
	GD	2.52 (2.34-2.69)	2.34 (2.11-2.57)	2.71 (2.44-2.97)[a]	2.76 (2.53-2.99)[b]				
Appropiatness	ToM	1.30 (1.13-1.47)	1.14 (.92-1.37)	1.40 (1.20-1.60)[a]	1.26 (1.03-1.49)[b]	.88 (.455)	33.25 (< *.0001****)	1.63 (.189)	**TD**: GD*** > ToM **ASD**: GD*** > ToM **ADHD**: GD*** > ToM
	GD	1.66 (1.52-1.80)	1.51 (1.34-1.69)	1.49 (1.34-1.63)[a]	1.63 (1.47-1.78)[b]				
Length	ToM	11.58 (10.44-12.73)	8.45 (7.17-9.72)	10.44 (8.18-12.70)[a]	11.09 (9.8-12.37)[b]	2.73 (< .05*)	117.33 (< *.0001****)	2.70 (.051)	**TD**: ToM*** > GD **ASD**: ToM*** > GD **ASD+ADHD**: ToM*** > GD **ADHD**: ToM*** > GD **/ToM**: ASD** < TD, ASD+ADHD, ADHD **/GD**: ASD* < TD, ASD+ADHD, ADHD
	GD	7.71 (6.40-9.02)	6.38 (5.37-7.39)	8.14 (6.20-10.08)[a]	8.10 (6.80-9.40)[b]				
Prompts	ToM	.45 (.20-.71)	1.10 (.54-1.66)	.79 (.31-1.28)[a]	.28 (.07-.48)[b]	3.48 (.02*)	184.34 (< *.0001****)	1.83 (.149)	**TD**: GD *** > ToM **ASD**: GD *** > ToM **ASD+ADHD**: GD *** > ToM **ADHD**: GD *** > ToM **/ToM**: ASD* > TD, ADHD
	GD	2.42 (1.69-3.15)	2.42 (2.00-2.84)	2.35 (1.76-2.94)[a]	2.11 (1.69-2.53)[b]				
Correct answer during fMRI	ToM	96% (92-100%)	95% (88-100%)	88% (79-96%)	94% (89-100%)	2.49 (.067)	42.29 (< *.0001****)	1.64 (.141)	**TD**: ToM, Rd*** > GD **ASD**: ToM, Rd*** > GD **ASD+ADHD**: ToM, Rd*** > GD **/GD**: ADHD** > ASD, ASD+ADHD
	GD	76% (68-84%)	69% (60-79%)	68% (55-81%)	85% (77-92%)				
	RD	92% (86-98%)	95% (88-100%)	89% (81-97%)	92% (87-98%)				
Reaction Time *(seconds)*	ToM	.91 (.76-1.06)	1.03 (.79-1.26)	1.26 (.95-1.57)	1.00 (.78-1.23)	2.60 (.058)	.74 (.480)	.88 (.515)	**/ToM**: TD* < ASD+ADHD **/GD**: TD* < ASD, ADHD **/RD**: TD* < ASD+ADHD
	GD	.85 (.70-1.01)	1.12 (.90-1.35)	1.08 (.86-1.30)	1.10 (.88-1.32)				
	RD	.86 (.76-.97)	1.07 (.86-1.27)	1.23 (.92-1.54)	1.14 (.91-1.36)				

Abbreviations: TD = Typical development, ASD = Autism Spectrum Disorder, ADHD = Attention Deficit and Hyperactivity Disorder, ToM = Theory of mind condition, GD = Goal Directed condition, RD = Random condition. [a]: n=17; [b]: n=20 Post-hoc significant threshold: * $p < .05$, ** $p < .01$, *** $p < .001$, with Tukey-Kramer multiple comparison correction.

12. APPENDIX 2: Supplementary material from study II

Figure A1. Spatial map of the Default Mode Network for the whole sample (overlaid on a grayscale brain template).



Secondary analysis by diagnostic group.

Methods. For secondary analyses, cases were classified according to diagnosis at two-year assessment, resulting in "early onset schizophrenia" (EOSz), grouping all schizophrenia spectrum disorders (295.x: schizophrenia and schizoaffective disorder) and "early onset affective disorders" (EOAff) (296.x4: major depressive disorders with psychotic symptoms and bipolar spectrum disorders with psychotic symptoms). The two participants with a diagnosis of psychosis not otherwise specified (298.9) were excluded from this secondary analysis due to its low diagnostic stability (Castro-Fornieles et al., 2011). Statistical analyses were repeated to explore differences in task performance and resting-state fMRI by diagnostic group; and Bonferroni correction was applied in all post-hoc pairwise comparisons.

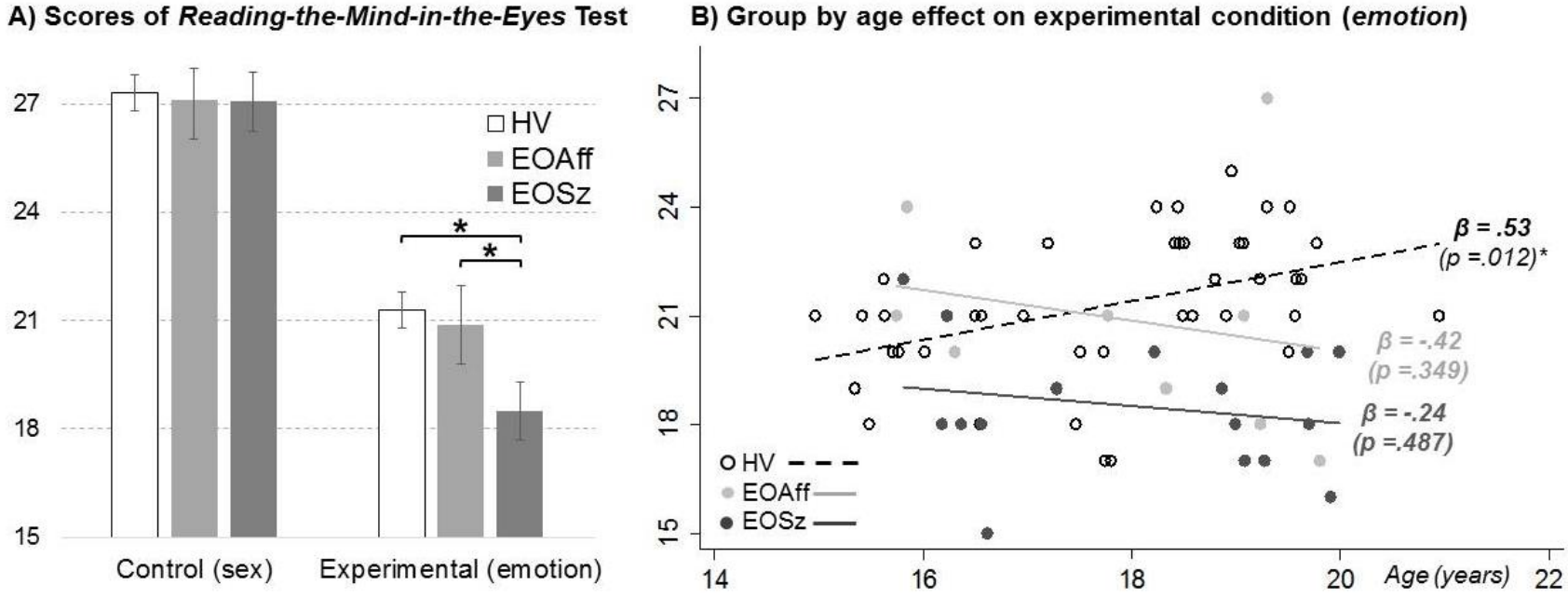
Results. Dividing the sample by diagnostic groups, there were also significant group by condition (X2= 14.7; p = .0006), group (X2= 18.7; p = .0001) and condition (X2= 422.0; p < .0001) effects in the model. Post-hoc analysis revealed significant differences in individuals with EOSz, who showed impaired ToM performance compared to healthy volunteers and to participants with EOAff (ps ≤ .008; Cohen's d ≥ |1.03|). In contrast, there were no differences between individuals with EOAff and healthy volunteers in the ToM condition, or between groups in the control condition (ps = 1.0). There was no significant effect of gIQ, sex, socio-economic status or age, or for the group by age interaction in the linear regression models. Group differences in intrinsic functional connectivity in cluster 1 (ps ≤ .005) and the group by age interaction in cluster 2 (ps ≤ .001) remained significant for both the EOSz and EOAff groups compared to healthy volunteers [see table A1 and figures A2-A3]. Although the correlation between symptom severity (total score of PANSS) and age of onset was not significant in the subgroup of participants with EOSz (r = -.39; p = .13) either with EOAff (r = -.65; p = .06), it was tested whether severity of symptoms may had a role in the regression models accounting for age. There was no significant effect of severity of symptoms (PANSS: total score and subscales) in ToM performance or functional connectivity (cluster 2) (βs ≤ |.26| ; ps > .22) but for the negative subscale of the PANSS on the functional connectivity in medial Prefrontal Cortex (cluster 2) within the group with participants with early onset schizophrenia (β = -.12; p = .014), still being significant the effect of age (β = -.40; p = .005) [This p values are presented uncorrected because it was considered a sensitivity analysis].

Table A1. Socio-demographic and clinical characteristics of the participants and statistical differences between groups.

	HV (n=41)	EOSz (n=16)	EOAff (n=9)	*p* value[a]	Post-hoc (*Bonferroni*)
Socio-demographic					
Age (years)	17.8 (SD=1.6)	18.0 (SD=1.6)	17.9 (SD=1.6)	*.654*	
Sex (% female)	56.1%	50.0%	77.8%	*.396*	
Race (% caucasian)	92.7%	75.0%	88.9%	*.172*	
Socio-economic Status	48.9 (SD=16.0)	34.7 (SD=13.3)	44.9 (SD=15.3)	*.008**	HV > EOSz
Clinical variables					
Intelligence Quotient	104.1 (SD=9.8)	85.8 (SD=12.5)	101.7 (SD=15.2)	*.0001**	HV = EOAff > EOSz
PANSS (total score)	-	55.9 (SD=13.6)	41.6 (SD=17.3)	*.008**	EOSz > EOAff
- Positive Subscale	-	10.7 (SD=3.8)	9.8 (SD=4.1)	*.412*	
- Negative Subscale	-	19.7 (SD=3.8)	9.1 (SD=4.6)	*.0006**	EOSz > EOAff
- General Subscale	-	26.1 (SD=8.5)	22.7 (SD=9.2)	*.113*	
Age of onset	-	15.9 (SD=1.6)	15.6 (SD=1.6)	*.497*	
Cumulative Chlorpomazine Equivalents	-	310827 (141201)	251035 (216508)	*.126*	
Diagnosis		Schizophrenia (n=9) Schizoaffective disorder (n=7)	Major depressive disorder (n=3) Bipolar disorders (type I, n=4; no otherwise specified, n=2)		

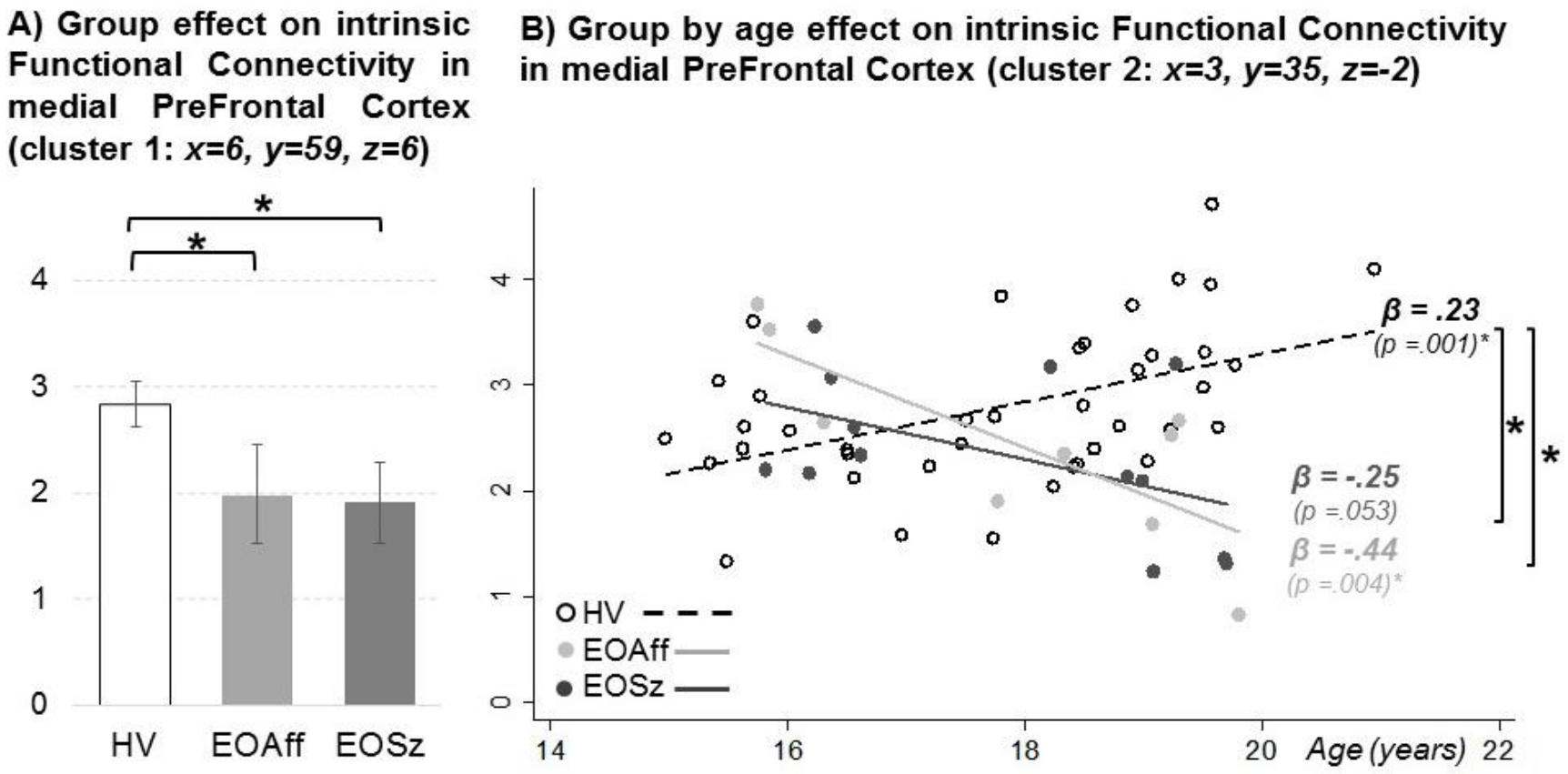
Note: HV = Healthy Volunteers; EOSz = Early Onset Schizophrenia; EOAff = Early Onset Affective disorder; PANSS = Positive and Negative Syndrome Scale; [a]Exact Fisher test or Kruskal-Wallis test for categorical and continuous variables respectively; * $p < .05$

Figure A2. Bar graphs representing mean least squares (95% confidence intervals) of performance in the control and experimental conditions of the "Reading-the-Mind-in-the-Eyes" Test (A) and group by age effect on experimental condition (B) for the healthy volunteers (n=41), the early onset schizophrenia spectrum group (n=16) and the early onset of affective spectrum group (n=9).



Note: HV = Healthy Volunteers; EOSz = Early Onset Schizophrenia spectrum disorders; EOAff = Early Onset Affective spectrum disorders; * $p < .05$

Figure A3. Clusters within the default mode network showing significant group effect (A) and group by age interaction (B) in intrinsic functional connectivity between participants with early onset schizophrenia (n=13), early onset affective disorders (n=9) and healthy volunteers (n=40).



Note: HV = Healthy Volunteers; EOSz = Early Onset Schizophrenia spectrum disorders; EOAff = Early Onset Affective spectrum disorders; * $p < .05$

13. APPENDIX 3: Supplementary material from study III

METHODS

Neuroimaging acquisition

An 8-min resting-state fMRI sequence was acquired on a 3 Tesla scanner at the Magnetic Resonance Image Core Facility of IDIBAPS, Centre for Image Diagnosis, Hospital Clínic of Barcelona. Participants were instructed to keep their eyes closed and remain as still as possible for the duration of the scanning session. A technician engaged in conversation with the participant before and after the resting-state session to guarantee that they did not fall asleep. Acquisition parameters were as follows: 240 volumes, TR = 2000 ms; TE = 29 ms; matrix size = 480 × 480; slice thickness = 4 mm, acquisition matrix = 80 × 80 mm, 32 slices, voxel size 3 × 3 × 4 mm. Seventy-six participants were scanned in a Siemens Magnetom Trio Tim (Siemens Medical Systems, Germany) and 10 participants in the Siemens Magnetom Prisma (Siemens Medical Systems, Germany), due to an upgrade of the scanner during the study at the beginning of 2018.

RESULTS FROM SECONDARY ANALYSES

CHR vs healthy volunteers contrast

Socio-demographic and clinical information are presented in table S2. There was no group by condition effect on ToM performance in the CHR vs healthy volunteers contrast (p = .17); and the linear regression model showed no significant group by age effect (p = .55) [see table S3]. Whole brain analysis comparing intrinsic functional connectivity between CHR vs healthy volunteers yielded no areas of differences surviving family-wise error correction.

Sensitivity analyses

Neuroimaging analyses were repeated including only the participants scanned in the Siemens Magnetom Trio Tim (n=73; three excluded due to excessive movement). Group effects in functional connectivity in cluster 1 between CHR-t, CHR-nt and HV, remained significant (F = 6.12, p = .004); with CHR-t group exhibiting reduced functional connectivity relative to CHR-nt (p = .003) and at a trend level with HV (p = .099). Group by age interaction between healthy volunteers and both CHR-t (p = .013) and CHR-nt (p < .001) remained significant; where functional connectivity was positively associated with age in HV (β = .22; p = .006), while the effect was the opposite in individuals with CHR-nt (β = -.27; p = .002) or CHR-t (β = -.19; p = .18).

The survival analysis was also repeated including participants at CHR scanned in the Siemens Magnetom Trio Tim (n=39), with 12 transitions to psychosis. The functional connectivity of cluster 1 ROI1 (HR = .22 p = .005) was associated

with less probability to transition. Participants with functional connectivity in cluster 1 under the cut-off point of 1.52 (as in the main analysis) exhibited a similar, significantly increased risk of transition to psychosis (HR = 5.16; p = .014; 95%CI: 1.39-19.13).

Regions-of-Interest analysis

Mean values of Regions-of-Interest (ROIs) were extracted from the spatial maps of the DMN component of each subject using the Marsbar toolbox. ROIs were defined based on our previous findings of group and group by age effects in adolescents with early onset psychosis relative to healthy volunteers (Ilzarbe et al., 2019): ROI1 ([x=6, y=59, z=6]; voxel count=54) and ROI2 ([x=3, y=35, z=-2]; voxel count=66), both located in the medial prefrontal cortex within the DMN [see figure S2A].

When comparing CHR-t, CHR-nt and healthy volunteers, there was a group effect which was significant at trend level (F = 2.93, p = .061) in ROI1, with CHR-t exhibiting reduced functional connectivity relative to healthy volunteers (p = .060). There was a significant group by age interaction between healthy volunteers and CHR-nt (p = .028) in ROI2; although functional connectivity was not significantly associated with age in either group [see figure S2B].

Table S1. Summary of previous studies comparing performance in the Reading-the-Mind-in-the-Eyes Test to assess Theory of Mind in individuals with clinical high risk for psychosis relative to a control group (257,259–262).

Author & year	Sample	Age (years)	Sex (female)	Results
Couture et al., 2008[a]	88 CHR 41 HV	18.9 (SD=4.6) 23.0 (SD=5.9)	43% 7%	No significant differences
Szily et al., 2009[b]	26 CHR (with MDD) 50 HV	22.0 (SD=8.7) 21.1 (SD=6.3)	58% 62%	HV > CHR on the recognition of negative social emotions
Stanford et al., 2011[c]	63 CHR 24 HV	19.6 (SD=3.6) 21.0 (SD=3.6)	21% 38%	No significant differences
Healey et al., 2013	147 CHR (29 CHR-t[e]) 85 HV (5 transition to psychosis)	19.8 (SD=4.7) 19.4 (SD=4.1)	42% 48%	No significant differences between HV and CHR (both groups improved significantly over time) **>>** Transition: poor ToM performance predicted transition to psychosis
Zhang et al., 2018[d]	84 CHR 95 HV	19.2 (SD=4.6) 20.3 (SD=4.9)	42% 51%	HV > CHR on performance and time consumption

Note: CHR = participants at Clinical High Risk; CHR-t = participants at Clinical High Risk for psychosis who transitioned to psychosis; HV = Healthy Volunteers; SD = Standard Deviation; [a]: A third group with familial risk of psychosis without psychotic symptoms (n=13; 38% female) also included for comparison; [a]: A third group with schizophrenia (n=26; 12% female) also included for comparison; [b]: A third group with Major Depressive Disorder (n=42; 64% female) also included for comparison; [b]: A third group with Schizophrenia (n=13; 54% female) and a fourth group of older healthy controls (n=14; 64% female) also included for comparison; [d]: A third group with Schizophrenia (n=66; 53% female) also included for comparison; [e]: data available for 28.

Table S2. Baseline socio-demographic and clinical characteristics of the sample.

	CHR (n=50)	HV (n=36)	*p* value
Socio-demographic			
Age (years) [range]	15.4 (SD=1.5) [12.0 – 17.9]	15.9 (SD=1.6) [12.9 – 18.3]	*.197*
Sex (% female)	70.0%	63.9%	*.551*
Race (% caucasian)	86.0%	88.9%	*.692*
Socio-economic Status	40.8 (SD=18.6)	50.3 (SD=14.0)	*.016**
Clinical variables			
Global Intelligence Quotient	99.9 (SD=14.5)	106.9 (SD=11.4)	*.018**
Scale of Prodromal Symptoms (total score)	30.2 (SD=11.2)	1.5 (SD=2.1)	*<.0001**
- Positive Subscale	8.0 (SD=4.0)	.3 (SD=.7)	*<.0001**
- Negative Subscale	10.1 (SD=5.1)	.4 (SD=.6)	*<.0001**
- Disorganized Subscale	3.7 (SD=2.5)	.3 (SD=.7)	*<.0001**
- General Subscale	8.5 (SD=4.2)	.8 (SD=1.8)	*<.0001**
Children's Global Assessment Scale	45.1 (SD=17.1)	85.5 (SD=6.7)	*<.0001**
Reported cannabis use			
- Occasionally - monthly	20.0%	27.8%	*.376*
- Weekly - diary	18.0%	8.3%	

Note: HV = Healthy Volunteers; CHR = participants at Clinical High Risk for psychosis; SOPS = Scale of Prodromal Symptoms; SD = Standard Deviation; * $p < .05$

Table S3. Statistical models for "Reading-the-Mind-in-the-Eyes" Test comparing healthy volunteers vs participants at clinical high risk of psychosis according to transition to psychosis.

	Dependent variable	Adjusted means (95% CI)			Variables (including the interaction term)				Post-hoc (Bonferroni)
HV vs CHR									
		HV	CHR		**Group**	**Condition**	**Group by condition**	**Covariables**	
Multilevel mixed-effects linear regression model	Control condition	97.5% (95.1%-99.9%)	96.1% (94.0%-98.1%)		χ^2= 6.74 (p = .009)*	χ^2= 502.01 (p < .001)*	χ^2= 1.84 (p = .17)	-	Group: HV > CHR Condition: Control > Experimental
	Experimental condition	73.6% (71.2%-76.0%)	69.1% (67.0%-71.1%)						
					Group	**Age[a]**	**Group by age**	**Covariables**	
Linear regression model	Experimental condition				F= .52 (p = .47)	β= 2.07 (p =.037)	β= -1.16 (p =.37)	gIQ: β=.16; (p =.040)*	
HV vs CHR-nt vs CHR-t									
		HV	CHR-nt	CHR-t	**Group**	**Condition**	**Group by condition**	**Covariables**	
Multilevel mixed-effects linear regression model	Control condition	97.5% (94.8%-100.0%)	96.4% (93.5%-99.4%)	96.0% (92.3%-99.6%)	χ^2= 7.51 (p = .023)*	χ^2= 412.82 (p < .001)*	χ^2= 3.51 (p = .17)	-	Group: HV > CHR-nt Condition: Control > Experimental
	Experimental condition	74.6% (71.9%-77.3%)	68.5% (65.6%-71.3%)	69.3% (65.7%-72.9%)					
					Group	**Age[a]**	**Group by age**	**Covariables**	
Linear regression model	Experimental condition				F= 2.29 (p = .11)	β=3.39 (p =.002)*	β(CHRnt)= -1.36 (p =.39) β(CHRt)= -4.76 (p =.026)*	Sex: β(female)= 5.57; (p=.019)* gIQ: β= .23; (p =.021)* SES: β= -.17; (p =.021)*	

Note: HV=Healthy Volunteers; CHR-t=participants at Clinical High Risk for psychosis who transitioned to psychosis; CHR-nt=participants at Clinical High Risk for psychosis who did not transition to psychosis; gIQ=global intelligence quotient; SES=socio-economic status; [a]: healthy volunteers as group of reference; * p < .05

Figure S1. Spatial map of the Default Mode Network for the whole sample (overlaid on a grayscale brain template).

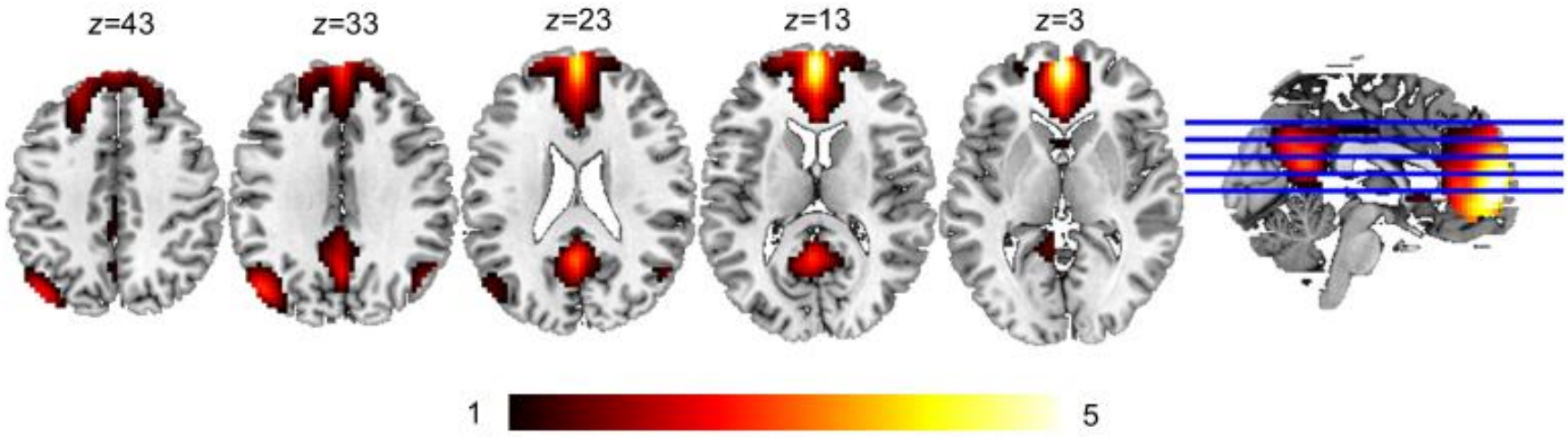
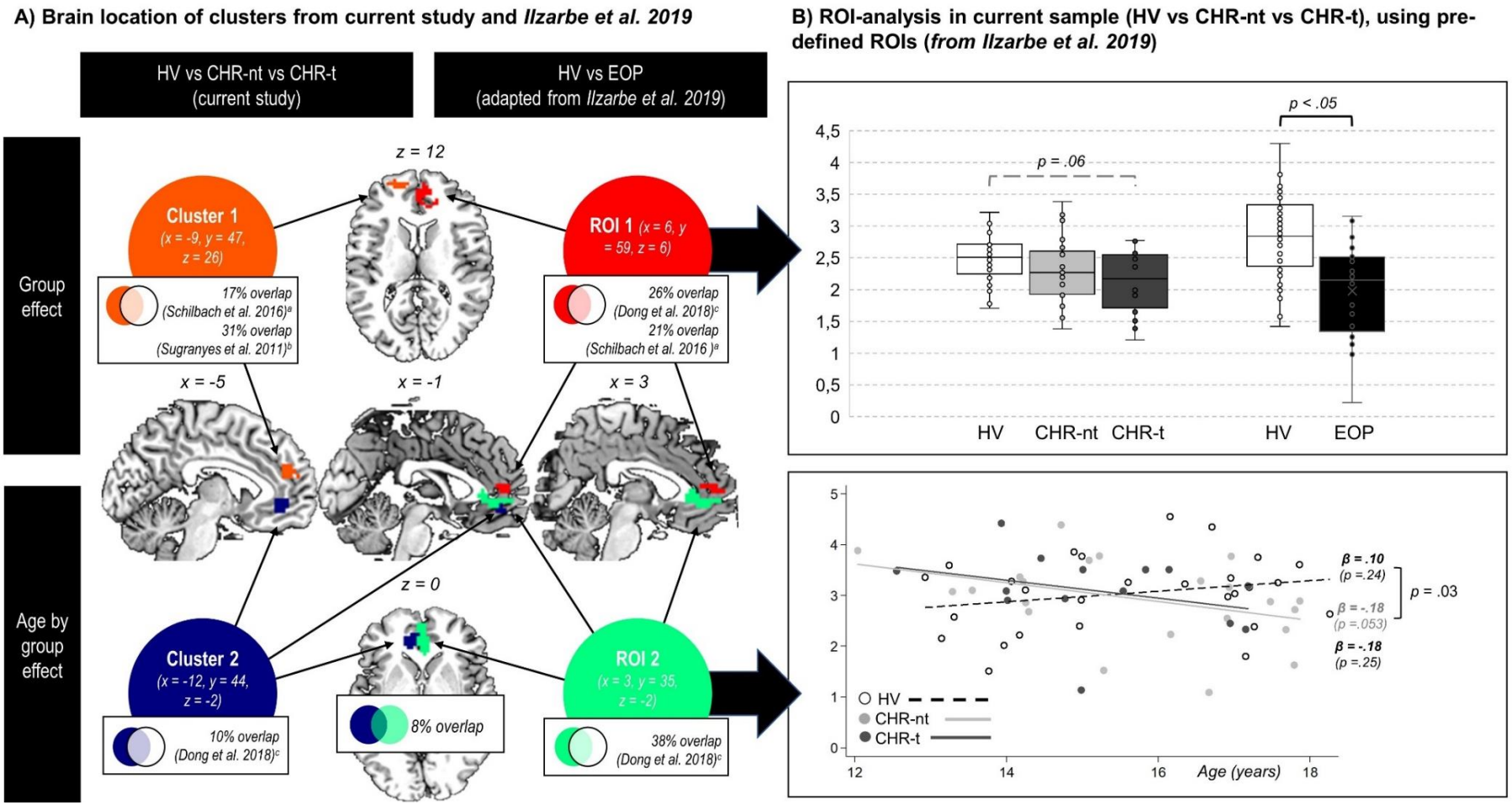
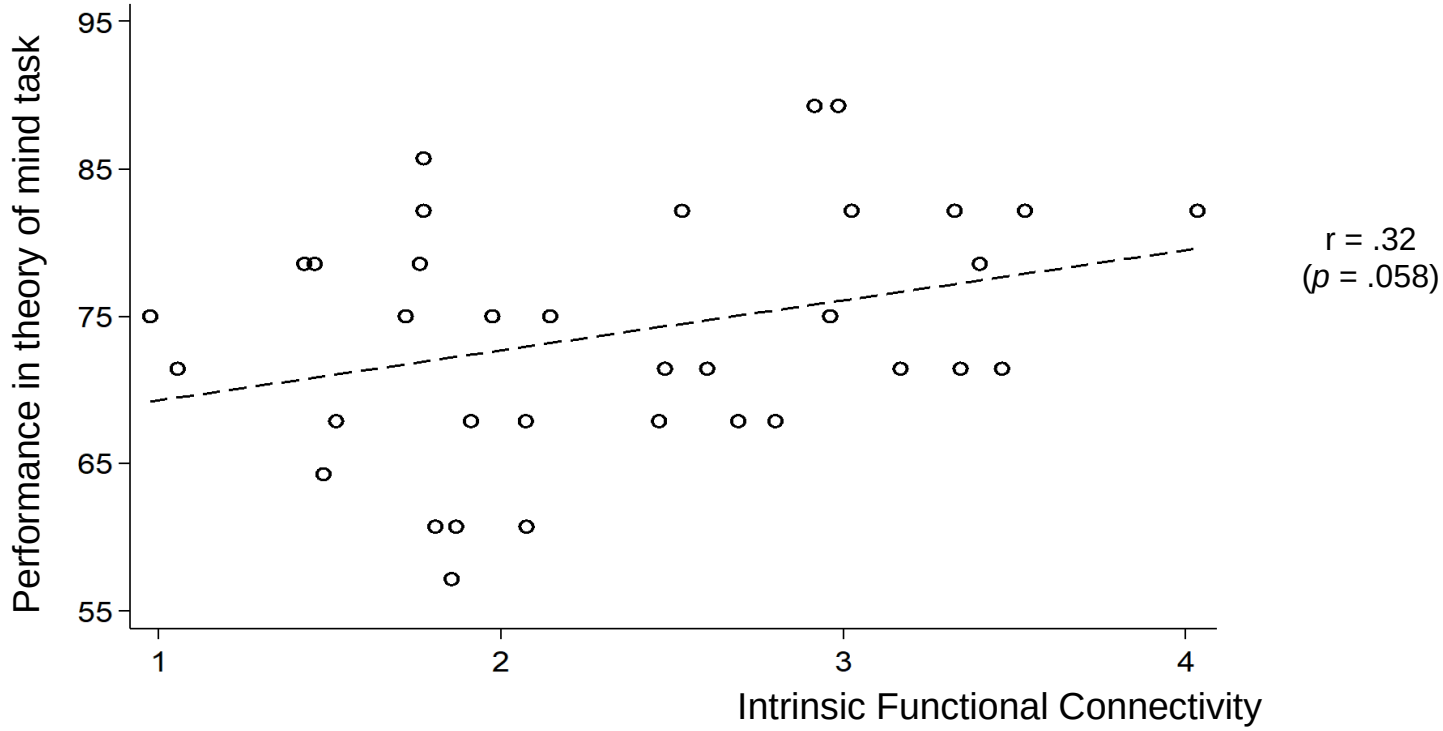


Figure S2. Comparison between current findings (depicted in left column) with regions of interest showing group and group by age effects in a previous study in patients with early onset psychosis (*Ilzarbe et al. 2019*) (depicted in right column) overlaid on a grayscale brain template¥.



Note: HV=Healthy Volunteers; CHR-t=participants at Clinical High Risk for psychosis who transitioned to psychosis; CHR-nt=participants at Clinical High Risk for psychosis who did not transition to psychosis; EOP=participants with Early Onset Psychosis; gIQ=global intelligence quotient;ROI=Region-Of-Interest; SES=socio-economic status;[a]= 10mm-spheric-ROI (centered at x:-2, y:52 z:14); [b]= 10mm-spheric-ROI (centered at x:-6, y:52 z:30); [c]= 10mm-spheric-ROI (centered at x:0, y:50 z:2) * $p < .05$. ¥ Some contents of the figure adapted from Ilzarbe et al. 2019.

Figure S3. Correlation between intrinsic functional connectivity in the medial prefrontal cortex (cluster 2: [x = -12, y = 44, z = -2]; voxel = 50) and performance in the "Reading-the-Mind-in-the-Eyes" Test (% of correct answers) in healthy volunteers (n = 35).



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