HIPERPROLACTINEMIA EN PSICOSIS TEMPRANAS: IMPACTO EN EL RENDIMIENTO COGNITIVO Y LA FUNCIONALIDAD DE LOS PACIENTES

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HIPERPROLACTINEMIA EN PSICOSIS TEMPRANAS:

IMPACTO EN EL RENDIMIENTO COGNITIVO Y LA FUNCIONALIDAD

DE LOS PACIENTES

TESIS DOCTORAL

Dirigida por el Dr. Javier Labad Arias y la Dra. Elisabet Vilella Cuadrada

Departamento de Medicina y Cirugía de la Universitat Rovira i Virgili

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HAGO CONSTAR que el presente trabajo, titulado “Hiperprolactinemia en psicosis tempranas: Impacto en el rendimiento cognitivo y la funcionalidad de los pacientes”, que presenta Itziar Montalvo Aguirrezabala para la obtención del título de Doctor, ha sido realizado bajo mi dirección en el Departamento de Medicina y Cirugía de esta universidad.

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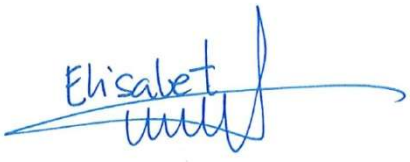
Los directores de la tesis doctoral:



Elisabet Vilella Cuadrada

Javier Labad Arias

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PRÓLOGO

Ésta tesis doctoral incluye 4 artículos científicos. Los dos primeros están publicados, y los dos siguientes están aceptados y en proceso de publicación:

ARTÍCULO 1

Título: Changes in prolactin levels and sexual function in young psychotic patients after switching from long-acting injectable risperidone to paliperidone palmitate.

Autores: Itziar Montalvo, Laura Ortega, Xavi López, Montse Solé, Rosa Monseny, Joan Franch, Elisabet Vilella, Javier Labad

Revista: International Clinical Psychopharmacology

Año: 2013

Volumen: 28

Páginas: 46-49

DOI: 10.1097/YIC.0b013e32835ba832

ARTÍCULO 2

Título: Increased prolactin levels are associated with impaired processing speed in subjects with early psychosis.

Autores: Itziar Montalvo, Alfonso Gutiérrez-Zotes, Marta Creus, Rosa Monseny, Laura Ortega, Joan Franch, Stephen M. Lawrie, Rebecca M. Reynolds, Elisabet Vilella, Javier Labad

Revista: PLoS One

Año: 2014

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ARTÍCULO 3

Título: Sex differences in the relationship between prolactin levels and impaired processing speed in early psychosis.

Autores: Itziar Montalvo, Roser Nadal, Antonio Armario, Alfonso Gutiérrez-Zotes, Marta Creus, Ángel Cabezas, Montse Solé, Maria José Algora, Vanessa Sánchez-Gistau, Elisabet Vilella, Javier Labad

Estado: Aceptado por la revista Australian & New Zealand Journal of Psychiatry. En prensa

ARTÍCULO 4

Título: Improvement in cognitive abilities following cabergoline treatment in patients with a prolactin-secreting pituitary adenoma.

Autores: Itziar Montalvo, Marta Llorens, Laia Caparrós, Montserrat Pamias, Jordi Torralbas, Olga Giménez, Assumpta Caixàs, Diego J. Palao, Javier Labad

Estado: Aceptado por la revista International Clinical Psychopharmacology. En prensa

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ABREVIACIONES

SNC	Sistema Nervioso Central
LH	Hormona Luteinizante
FSH	Hormona Foliculoestimulante
EMAR	Estado Mental de Alto Riesgo
ILD	Inyectable de larga duración (en inglés, LAI: Long Acting Injectable)
PP	Paliperidona Palmitato
MCCB	MATRICS Consensus Cognitive Battery

RESUMEN DE LA TESIS DOCTORAL

Introducción: La hiperprolactinemia es una condición frecuente en la población con un trastorno psicótico cuyas consecuencias más estudiadas han sido las derivadas del hipogonadismo secundario, aunque es una hormona con múltiples efectos a nivel de otros órganos, algunos aún no del todo conocidos. La repercusión que los niveles elevados de prolactina pueden tener sobre las habilidades cognitivas se han estudiado en modelos animales y en diferentes poblaciones no psiquiátricas, observando un efecto negativo en algunos procesos cognitivos. No existen estudios hasta el momento que evalúen dicho efecto en pacientes con un trastorno psicótico, población con alta prevalencia de hiperprolactinemia y de alteraciones cognitivas.

Objetivos: Con este proyecto se estudia la posible relación entre los niveles de prolactina y el rendimiento cognitivo en pacientes con una psicosis incipiente, controlando por posibles variables de confusión como son el estado psicopatológico, el tratamiento con psicofármacos, el uso de sustancias o los niveles de cortisol. Además se analiza si existen diferencias de género en la relación entre los niveles de prolactina y rendimiento cognitivo. Por último, se estudia si la reducción de los niveles de prolactina comporta una mejoría en las habilidades cognitivas en pacientes con un prolactinoma.

Métodos: Esta tesis doctoral consta de cuatro trabajos. El primer y último trabajo son estudios prospectivos de una serie de casos (de 11 y 10 casos respectivamente), el primero de pacientes afectos de un trastorno psicótico que pasaron de risperidona inyectable de larga duración a Paliperidona Palmitato, y el último de pacientes afectos de un prolactinoma que iniciaban un tratamiento con cabergolina. En ambos estudios se midieron los niveles de prolactina a nivel basal y al final del estudio. En el caso del primer estudio se correlacionaron los niveles de prolactina con los cambios en la funcionalidad sexual con el cuestionario ASEX y en la funcionalidad global medida con la escala PSP, y en el último estudio los cambios en los niveles de prolactina se correlacionaron con los cambios en el rendimiento cognitivo de los pacientes con la batería MCCB.

El segundo y tercer trabajo son estudios transversales, con pacientes con una psicosis temprana a los que se les realizó una valoración del rendimiento cognitivo con la batería MCCB y se relacionó con los niveles plasmáticos de prolactina. Se controlaron variables como el estado psicopatológico, el tratamiento con psicofármacos, el uso de sustancias y los niveles de cortisol en plasma. En el tercer estudio se pudo realizar un análisis estratificado por sexos y ver diferencias de género en la relación de los niveles de prolactina y rendimiento cognitivo, ya que la muestra de pacientes era más amplia que en el segundo estudio.

Resultados: En el primer estudio se observó una reducción de los niveles de prolactina a los 3 meses tras el cambio de risperidona inyectable de larga duración a paliperidona palmitato, que no se acompañó de una mejoría de la funcionalidad sexual, pero sí de una mejoría en la funcionalidad global de los pacientes con una psicosis. En el segundo estudio se observó una

correlación entre los niveles de prolactina y rendimiento cognitivo, sugiriendo que los niveles elevados de prolactina pueden afectar negativamente al rendimiento cognitivo, concretamente a la velocidad de procesamiento. En el tercer estudio se vio que existen diferencias de género en esta relación, ya que este efecto de la prolactina está limitado al género masculino principalmente. Por último, en el cuarto estudio observamos una mejoría en el rendimiento cognitivo de los pacientes con un prolactinoma tras la reducción de los niveles de prolactina con cabergolina.

Conclusiones: Los resultados obtenidos sugieren que los niveles elevados de prolactina podrían repercutir negativamente en el rendimiento cognitivo y funcionalidad de los pacientes con una psicosis, principalmente varones. El descenso de los niveles de prolactina tras el tratamiento con cabergolina comporta una mejoría de las habilidades cognitivas en pacientes con hiperprolactinemia secundaria a un prolactinoma, lo que plantea el posible uso de este agonista dopaminérgico como fármaco procognitivo en pacientes con psicosis e hiperprolactinemia crónica.

INTRODUCCIÓN

1. INTRODUCCIÓN

La hiperprolactinemia es una condición frecuente en la población con un trastorno psicótico, cuyas consecuencias no se conocen en toda su amplitud pero que pueden afectar a la salud física y a la calidad de vida de los pacientes y es muchas veces minusvalorada por los clínicos.

La esquizofrenia y los trastornos psicóticos son enfermedades que causan un alto grado de discapacidad. Las alteraciones cognitivas son una característica nuclear de los trastornos psicóticos, presentes en las fases tempranas de la enfermedad incluso antes del primer episodio psicótico franco y son determinantes para la funcionalidad de los pacientes (Schmidt, Grunert, Schimmelmann, Schultze-Lutter, & Michel, 2014).

Esta tesis doctoral pretende esclarecer los efectos que tiene la hiperprolactinemia sobre la funcionalidad global y cognitiva de los pacientes, ya que este conocimiento podría conllevar a desarrollar estrategias eficaces para mejorar la calidad de vida de las personas con trastornos mentales.

1.1. PROLACTINA

La prolactina fue descubierta en 1928 como factor pituitario que podía inducir la secreción de leche en ratas, y en 1933 fue identificada por Riddle et al. en palomas, dándole el nombre de prolactina por su capacidad de estimular la producción de leche. Hasta 1970 se creyó que la forma humana de la prolactina era idéntica a la hormona de crecimiento (GH) y se dudaba de la existencia de la prolactina humana, ya que sólo disponían de métodos para purificar la GH (Henry Friesen, 1995). En 1970 se aisló y se purificó por primera vez la prolactina humana gracias al desarrollo de las técnicas de radioinmunoensayo (RIA) y permitió a Beumont et al. (1974) clarificar su rol en la regulación hormonal. En los años 80 se ampliaron los estudios a estudios animales, estudios in vitro y mediciones bioquímicas refinadas. Todo ello llevó a una definición de la fisiología de la prolactina.

1.1.1. Estructura

La prolactina humana es una hormona polipeptídica de cadena única compuesta por 199 aminoácidos y de un peso molecular de 23 kDa. La estructura terciaria de la prolactina está formada por cuatro largas hélices α que se organizan, de manera antiparalela, de dos en dos (Figura 1). Es una estructura muy similar a la de la hormona de crecimiento (GH) y a la hormona lactógena placentaria, que tienen genes con un origen ancestral común que por duplicación y a lo largo de la evolución animal dio lugar a los hoy presentes en el organismo (Cooke, Coit, Shine, Baxter, & Martial, 1981). El gen de la prolactina humana se localiza en el cromosoma 6 y está compuesto por cinco exones y cuatro intrones (Owerbach, Rutter, Cooke, Martial, & Shows, 1981). La prolactina circula principalmente en la forma monomérica pero existen variantes de la prolactina causadas por modificaciones posttraduccionales como la escisión proteolítica, dimerización, polimerización, fosforilación y glicosilación. En general, estas variantes tienen una actividad biológica reducida. Las isoformas moleculares grandes

(>150 kDa) se denominan macroprolactina, y básicamente son complejos de prolactina y IgG (De Schepper et al., 2003). La macroprolactina tiene una bioactividad reducida, y se considera que no presenta ninguna respuesta sistémica in vivo (Glezer et al., 2006). La macroprolactina se tiene que identificar en un inmunoensayo diferente, por lo que puede dar lugar a una aparente hiperprolactinemia en los análisis convencionales (Gibney, Smith, & McKenna, 2005).

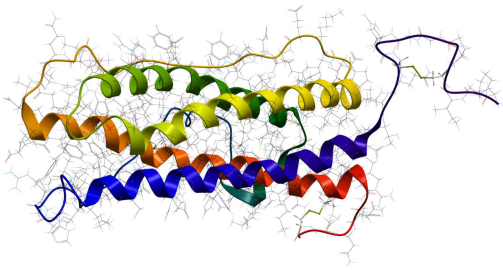


Figura 1. Estructura terciaria de la prolactina humana.

1.1.2. Regulación

La prolactina es una hormona peptídica sintetizada y secretada principalmente por las células lactótropas de la glándula hipofisaria anterior. Estas células presentan una actividad secretora basal elevada, y la secreción de prolactina está regulada principalmente por la inhibición tónica de la dopamina hipotalámica, también conocida por factor inhibitorio de la prolactina (PIF). La dopamina alcanza las células lactótropas de la hipófisis a través del sistema portal hipotalámico-pituitario y, a través de la unión a sus receptores dopaminérgicos D2, suprime rápidamente la liberación de prolactina desde las vesículas secretoras, inhibe la expresión génica de la prolactina e inhibe la proliferación de las células lactótropas (Ben-Jonathan & Hnasko, 2001). Por lo tanto, cualquier mecanismo que interfiera en la liberación o la acción de la dopamina comportará un aumento en los niveles de prolactina por la falta de la acción inhibitoria. Otros factores inhibitorios en la liberación de prolactina son la somatostatina y el γ-ácido aminobutírico (GABA) (Gruszka, Ren, Dong, Culler, & Melmed, 2007). Además, la prolactina ejerce un feedback negativo de su propia secreción, estimulando la síntesis de la dopamina hipotalámica (Ben-Jonathan & Hnasko, 2001). Aunque el control de la secreción de prolactina es principalmente inhibitorio, existen algunos factores liberadores de prolactina, incluyendo la hormona liberadora de tirotropina (TRH), estradiol, oxitocina, endotelina y el péptido vasoactivo intestinal (Chahal & Schlechte, 2008). La regulación de la prolactina esta presentada esquemáticamente en la Figura 2.

La secreción de la prolactina es pulsátil, y sigue un ritmo circadiano con los niveles plasmáticos más elevados durante el sueño y los niveles más bajos tras 2-3 horas después de despertar. El estrés provoca un aumento de la secreción de prolactina, según algunos autores con un efecto protector a través del efecto inmunomodulador, mejorando la respuesta adaptativa al estrés (De Bellis, Bizzarro, & Bellastella, 2008).

Existen también algunas fuentes extrapituitarias de prolactina, incluyendo linfocitos, fibroblastos de la piel, cerebro, glándula mamaria, decidua, próstata y células del tejido adiposo (Capozzi, Scambia, Pontecorvi, & Lello, 2015). La producción de prolactina en estos tejidos no está regulada por la dopamina, y probablemente funciona como un factor autocrino o paracrino (Ben-Jonathan, Mershon, Allen, & Steinmetz, 1996).

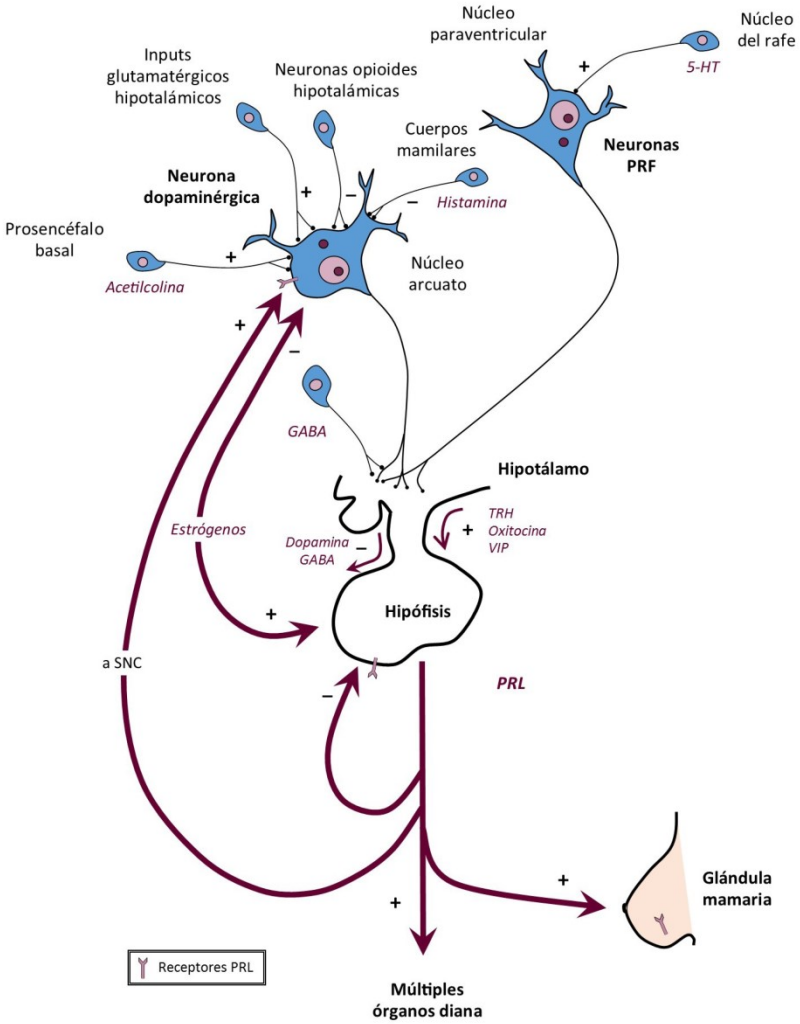


Figura 2. Regulación de la prolactina.

1.1.3. Acción fisiológica

La prolactina actúa a través de la unión al receptor de la prolactina. El receptor de la prolactina es una proteína transmembrana de la superfamilia de receptores de citocina/hematopoyetina, codificado por un gen situado en el cromosoma 5. Este receptor se expresa en diferentes tejidos además de en la glándula mamaria, incluyendo las gónadas, útero, próstata, hígado, riñones, páncreas, glándulas adrenales, cerebro, miocardio, glándula hipofisaria, piel, adipocitos y en las células del sistema inmunológico (Bole-Feysot, Goffin, Edery, Binart, & Kelly, 1998). A la prolactina se le han atribuido múltiples acciones fisiológicas, algunas de las cuales se comentan a continuación:

Desarrollo mamario y acción lactotrófica

El principal papel de la prolactina es el de promover la lactogénesis en el periodo postparto. En el periodo de lactancia, la estimulación del pezón por la succión del bebé produce una elevación de la secreción de la prolactina, basado en el eje neuro-humoral. Durante el embarazo, el aumento de los niveles de estrógenos estimula la proliferación de las células lactótropas, con el consecuente aumento de los niveles de prolactina y su efecto sobre el crecimiento de los alveolos de las glándulas mamarias.

Órganos sexuales masculinos

El receptor de la prolactina está presente en la membrana plasmática de las células intersticiales testiculares incluyendo las células de Leyding, también en las células de Sertoli y en las del epitelio germinal de los testes. En las células de Leyding y de Sertoli, la prolactina aumenta el nivel de expresión de los receptores de LH y FSH respectivamente, con un efecto significativo en la proliferación y metabolismo de estas células (Dombrowicz, Sente, Closset, & Hennen, 1992; Guillaumot, Tabone, & Benahmed, 1996; Scarabelli, Caviglia, Bottazzi, & Palmero, 2003). En general, la prolactina estimula la función testicular en los mamíferos, estimulando la secreción de testosterona y estradiol de las células de Leyding (Maran, Arunakaran, & Aruldhas, 2001) y aumentando el metabolismo energético en las células epididimales y espermatozoides (Pedron & Giner, 1978).

Otro efecto estudiado de la prolactina tanto en roedores como en humanos es sobre la glándula prostática. En 1997 se confirmó la producción local de prolactina en el tejido prostático humano, y también la presencia del receptor de la prolactina en el epitelio secretor de la próstata humana (Nevalainen et al., 1997). Varios estudios apoyan el rol de la prolactina como un factor de crecimiento prostático (Goffin, Hoang, Bogorad, & Nevalainen, 2011).

Efectos en otras hormonas

Se han descrito efectos directos de la prolactina sobre el páncreas y sobre las glándulas adrenales (Glasow et al., 1996; Park, Kim da, Daily, & Kim, 2011). La prolactina regula las células β del páncreas, aumentando la secreción de insulina y disminuyendo el umbral glicémico para la secreción de insulina (Sorenson et al., 1987). Durante el embarazo la prolactina mejora la homeostasis de la glucosa aumentando la masa células β, mientras que en la hiperprolactinemia debida a adenomas hipofisarios exacerba la resistencia insulínica. La prolactina también aumenta los andrógenos, junto con la secreción de cortisol y aldosterona por las células de la corteza adrenal (Glasow et al., 1996).

Efectos en el sistema cardiovascular

La prolactina presenta acciones vasoconstrictoras, ampliamente demostradas en el embarazo pero también en otras situaciones (Molinari et al., 2007). Hay estudios que apoyan la idea de que los niveles de prolactina se relacionan con aumento de la presión arterial y de la rigidez arterial, acelerando la arteriosclerosis en pacientes menopáusicas (Georgiopoulos et al., 2009). También hay evidencia de la influencia de la prolactina sobre el ritmo cardíaco y de su relación con el fallo cardíaco crónico (Carrero et al., 2012). Estos aspectos se pueden explicar por la acción de la prolactina en disminuir la biodisponibilidad del óxido nitroso (NO) y sustrato del óxido nitroso sintasa endotelial (eNOS), y el aumento en la producción de radicales libres derivados del oxígeno (Carrero et al., 2012).

Efectos en el sistema nervioso central

La prolactina contribuye a la neurogénesis, estimulando la proliferación, diferenciación y migración de las células madre neuronales (Pathipati et al., 2011; L. Torner et al., 2009). También se ha observado un efecto proliferativo en progenitores gliales y células precursoras de oligodendrocitos, conllevando la mielinización del sistema nervioso central (Pathipati et al., 2011).

Efectos en el sistema inmunológico

La prolactina es producida también por los linfocitos, y múltiples células del sistema inmune presentan receptores de la prolactina, teniendo un rol importante en la respuesta inmune humana. Los efectos de la prolactina en el sistema inmunológico podrían depender de su concentración, ya que hay estudios en que han demostrado un efecto de inmunoestimulación a niveles modestos y una inhibición a niveles altos (Capozzi et al., 2015).

Otras funciones

La prolactina está involucrada en la osmoregulación, aumentando la absorción de sales y agua en todos los segmentos del intestino y reduciendo la excreción renal de sodio y potasio (Breves, Serizier, Goffin, McCormick, & Karlstrom, 2013). En los últimos años se le han atribuido a la prolactina numerosas acciones biológicas, algunas de ellas continúan estando en investigación.

1.2. HIPERPROLACTINEMIA

El término hiperprolactinemia hace referencia a la elevación de los niveles de prolactina circulantes.

Bajo circunstancias habituales, los niveles normales de prolactina son inferiores a 25 ng/ml (530 miU/l) en mujeres y de 20ng/ml (424 miU/l) en hombres (Schlechte, 2003).

1.2.1. Causas

Existen numerosos factores que pueden causar hiperprolactinemia, y se pueden agrupar en tres categorías etiológicas: fisiológicas, farmacológicas y patológicas (Tabla 1).

Fisiológicas

Existen algunas causas fisiológicas que pueden provocar un aumento de los niveles de prolactina, y tienen que ser descartados antes de plantear la existencia de causas patológicas o farmacológicas. Por una parte, los niveles de prolactina aumentan con el estrés agudo (A.-K. Lennartsson & Jonsdottir, 2011), y pueden llegar a sobrepasar los niveles normales. Por otra parte, el embarazo y la lactancia son la causa más común de hiperprolactinemia fisiológica, por lo que tienen que ser descartados en primer lugar ante el hallazgo de unos niveles elevados de prolactina en mujeres. Por último, la estimulación del pezón (p ej. por la succión del lactante) también aumenta la secreción de prolactina a través de la activación del nervio vago (McNeilly, Robinson, Houston, & Howie, 1983).

Farmacológicas

Los fármacos que repercuten en la dopamina, tanto inhibiendo su síntesis (L-metildopa) o bloqueando su acción (antipsicóticos o antieméticos) pueden causar un aumento de los niveles de prolactina (Ben-Jonathan & Hnasko, 2001). Otros fármacos que pueden causar hiperprolactinemia incluyen antidepresivos y los antagonistas histaminérgicos H2. Los analgésicos opioides también pueden afectar a la secreción de prolactina a través de su interacción con el sistema dopaminérgico hipotalámico (Delitala, Grossman, & Besser, 1983).

Patológicas

Existen múltiples patologías que pueden cursar con un aumento de los niveles de prolactina. Cuando se plantea el diagnóstico diferencial, la cifra de la prolactina sérica puede servir de orientación para decantarnos por una u otra opción. Así, cuando existen niveles muy elevados de prolactina (por encima de 150 ng/ml) se debe considerar la posibilidad de que exista un prolactinoma (adenoma hipofisario productor de prolactina). Los prolactinomas se dividen según el tamaño en microprolactinomas (menores de 1 cm) y macroprolactinomas (tumoraciones mayores de 1 cm), y las cifras de prolactina suelen estar relacionados con el tamaño del adenoma. Otras causas son el hipotiroidismo primario (el aumento de TRH estimula la secreción de prolactina), el síndrome de ovario poliquístico o algunas enfermedades autoinmunes.

En resumen, cuando se detecta una hiperprolactinemia en un paciente, es importante identificar posibles etiologías fisiológicas, como el embarazo, lactancia o el estrés. También hay que interrogar sobre la toma de medicaciones con potencial capacidad para elevar la prolactina, como los fármacos antipsicóticos. Por último, se planteará la posible existencia de un adenoma hipofisario secretor de prolactina u otras patologías que puedan cursar con un aumento de los niveles de prolactina.

Tabla 1. Causas de hiperprolactinemia

Fisiológicas	Patológicas	Farmacológicas
Estrés	**Alteraciones hipotalámicas**	Neurolépticos
	Tumores	
Ejercicio	Craneofaringioma	Antidepresivos tricíclicos,
	Germinoma	IMAO, ISRS, ISRSN
Lactancia	Meningioma	
	Metástasis	Benzodiazepinas
Embarazo	Enfermedades infiltrativas	
	Sarcoidosis	Anticonvulsivantes
Sueño	Tuberculosis	Fenitoína
	Histiocitosis de células de Langerhans	
	Cirugía supraselar	Opiáceos
	Irradiación craneal	
		Antihistamínicos H_2
	Alteraciones pituitarias	
	Prolactinoma	Antihipertensivos
	Acromegalia	Metildopa
	Adenoma plurihormonal	Labetalol
	Macroadenoma compresivo	Reserpina
	Hipofisitis linfocítica	Verapamilo
	Síndrome de silla turca vacía	
	Sección del tallo hipofisario	Antieméticos
		Domperidona
	Otros	Metoclopramida
	Hipotiroidismo primario	
	Insuficiencia renal crónica	Estrógenos
	Cirrosis hepática	Anticonceptivos orales
	Crisis epiléptica	
	Síndrome de ovario poliquístico	
	Traumatismo torácico	
	Idiopático	

1.2.2. Efectos de la hiperprolactinemia

Las consecuencias clínicas de la hiperprolactinemia pueden manifestarse a corto, medio y a largo plazo. Los efectos más inmediatos ocurren sobre la función gonadal y sexual y sobre la glándula mamaria, tanto en mujeres como en hombres. Seguidamente se detallan los principales efectos de la hiperprolactinemia:

Hipogonadismo

Los niveles elevados de prolactina pueden causar hipogonadismo (disminución de estrógenos en las mujeres y de testosterona en hombres) por una inhibición de la hormona liberadora de gonadotropina (GnRH), que a su vez provoca una reducción de los niveles de LH y FSH a nivel hipofisario (Milenković, D'Angelo, Kelly, & Weiner, 1994). Este déficit de gonadotropinas se traducirá en una falta de secreción de hormonas sexuales en pacientes en edad fértil. En mujeres el hipogonadismo puede causar alteraciones menstruales como la oligomenorrea o amenorrea, o infertilidad por una fase lútea corta (Bahamondes et al., 1985). Además también puede presentar disfunción sexual, con problemas de la líbido y anorgasmia. En hombres puede causar disminución de la líbido, disfunción eréctil, impotencia y esterilidad por una oligospermia o azoospermia (Ciccarelli, Daly, & Beckers, 2005).

Si la hiperprolactinemia se mantiene en el tiempo, el déficit de esteroides sexuales puede conllevar una disminución de la densidad mineral ósea, con el consiguiente peligro de desarrollar una osteoporosis futura tanto en hombres como en mujeres. El desarrollo de osteoporosis está mediada por una supresión del eje gonadal, ya que las mujeres con hiperprolactinemia pero sin una repercusión a nivel del ciclo menstrual tienen mayor densidad mineral ósea que aquellas con amenorrea (Biller & Klibanski, 1991). Aunque éste sea el mecanismo mejor descrito, también existen algunos estudios que apuntan a que la prolactina podría tener una acción directa sobre la función osteoblástica (Seriwatanachai, Krishnamra, & Van Leeuwen, 2009).

Sobre las glándulas mamarias

Como ya se ha comentado previamente, la principal función de la prolactina es la de promover la lactogénesis a través de la unión a los receptores presentes en los lactocítos, además de provocar un aumento del volumen mamario. Por lo tanto la hiperprolactinemia puede provocar un aumento del volumen mamario denominado ginecomastia, más evidente en hombres, además de una secreción de leche (galactorrea) fuera del periodo de postparto.

Riesgo de cáncer de mama

El rol de la prolactina en la patogénesis del cáncer de mama en humanos es controvertido. Los datos que empezaron a relacionar prolactina con el cáncer de mama surgieron de un estudio realizado en los años 90 en el que se mostró que la activación del receptor de la prolactina inducía carcinomas mamarios en ratas transgénicas (Wennbo et al., 1997). Otro estudio demostró que en las células cancerígenas mamarias la expresión del receptor de la prolactina era superior que en el tejido mamario normal (Reynolds, Montone, Powell, Tomaszewski, & Clevenger, 1997). A través de estos receptores las células cancerígenas mamarias son sensibles a la estimulación por la prolactina (Touraine et al., 1998). Además, algunos estudios in vitro apuntan que las células mamarias cancerosas producen prolactina, y que esta prolactina ectópica actúa como un factor de crecimiento local por mecanismos paracrinos y autocrinos (Bhatavdekar et al., 2000). Por lo tanto, existe evidencia preclínica que apoyaría el papel de la

prolactina secretada de manera paracrina en el desarrollo del cáncer de mama, especialmente favoreciendo la proliferación celular, la vascularización tumoral, y la movilidad celular, aspectos importantes en la carcinogénesis, y posiblemente en el mecanismo metastásico (Shelley S. Tworoger et al., 2013). Sin embargo, estos hallazgos de los efectos de la prolactina a nivel tisular no son extrapolables a los efectos de la hiperprolactinemia sistémica.

Aunque en modelos animales la prolactina elevada fue reconocida como un factor de riesgo para el cáncer de mama (Wennbo et al., 1997), hasta el momento no existen estudios con niveles de evidencia óptimos que apoyen ésta hipótesis en humanos. Aunque la función fisiológica de la prolactina sobre la glándula mamaria es evidente (estimula la síntesis de DNA, la proliferación celular, la producción de leche), su rol en la patogénesis del cáncer de mama es aún incierto. Estudios realizados con pacientes afectas de cáncer de mama, no han demostrado que la prolactina producida localmente por las células tumorales sea un mecanismo relevante para la tumorogénesis y la progresión de la enfermedad (Nitze et al., 2013). Tampoco han dado resultados positivos los estudios realizados con agentes antagonistas del receptor de la prolactina, fracasando en el intento de parar la progresión del cáncer de mama (Chen, 2015).

En cuanto al riesgo de desarrollo de cáncer de mama en pacientes con hiperprolactinemia, los datos son escasos y controvertidos hasta la actualidad. Algunos estudios prospectivos no encontraron relación entre los niveles de prolactina y el riesgo de cáncer de mama (Berinder, Akre, Granath, & Hulting, 2011; Helzlsouer et al., 1994; Kabuto, Akiba, Stevens, Neriishi, & Land, 2000; Wang et al., 1992). Otros estudios que han reportado asociaciones entre niveles de prolactina y cáncer de mama, como por ejemplo en la cohorte EPIC (Tikk et al., 2014), esta relación se circunscribe a aquellas mujeres que estaban recibiendo tratamiento hormonal sustitutivo en el momento del estudio, siendo este tratamiento un factor de riesgo reconocido para el desarrollo del cáncer de mama (Kerlikowske et al., 2010). Un estudio reciente realizado en más de 30.000 mujeres concluye que los niveles altos de prolactina en los años previos al desarrollo tumoral están asociados con el riesgo de cáncer de mama en pacientes postmenopáusicas, especialmente para tumores con receptor estrogénico positivo y enfermedad metastásica (Shelley S. Tworoger et al., 2013). Sin embargo, en todos estos estudios los niveles de prolactina fueron determinados por inmunoensayo, que es un método que determina múltiples isoformas y puede no reflejar la actividad biológica de la prolactina, que es importante en la carcinogénesis de mama. En otro estudio de casos y controles, se realizó la determinación de prolactina por bioensayo, que refleja la actividad somatolatogénica de la prolactina. En este estudio no se observó una clara asociación entre los niveles de prolactina bioactiva y el riesgo de cáncer de mama, aunque sí hubo relación con otros factores de riesgo de cáncer de mama, como la paridad, historia familiar de cáncer de mama, edad de la menopausia y el índice de masa corporal (S S Tworoger et al., 2015).

Riesgo de cáncer de próstata y otros tipos de cáncer

Algunos datos experimentales apuntan que la prolactina estimula la proliferación de las células prostáticas y que regula el crecimiento prostático, por lo que en un marco teórico podrían afectar a la carcinogénesis en la próstata (Crépin et al., 2007; Negro Vilar, Saad, & McCann, 1977). Sin embargo, el rol de la prolactina en la patología prostática humana no está clarificado y los datos epidemiológicos al respecto son escasos (Hsing & Comstock, 1993; Kindblom et al., 2003).

En cuanto a otros tipos de cáncer, existe escasa evidencia sobre el efecto de la hiperprolactinemia sobre ellos. Hay algunos estudios que han observado aumento de los niveles plasmáticos de prolactina en pacientes que presentan cáncer de ovario y endometrio (Levina et al., 2009; Mor et al., 2005; Yurkovetsky et al., 2007), aunque no existen más datos sobre el papel que juega en la etiopatogenia de la enfermedad. En otro estudio de cohortes se ha observado un riesgo aumentado de cáncer en pacientes con hiperprolactinemia, concretamente de tumores gastrointestinales en ambos sexos y del tejido hematopoyético en mujeres (Berinder et al., 2011).

Efectos metabólicos

Los receptores de la prolactina se expresan en múltiples tejidos involucrados en la regulación metabólica como el hígado, páncreas, tejido adiposo y cerebro. Por otro lado, los ratones modificados que no expresan el gen del receptor de la prolactina no muestran un fenotipo metabólico alterado, indicando que las acciones metabólicas de la prolactina son probablemente redundantes o se solapan con otros efectores fisiológicos (Luque et al., 2016).

En el tejido adiposo, la prolactina es esencial en la adipogénesis y en la diferenciación de los adipocitos, además de para modular el metabolismo lipídico (Fleenor, Arumugam, & Freemark, 2006; Grattan, 2015). También regula la secreción de diversas adipocinas, incluyendo la estimulación de la leptina y la inhibición de la producción de adiponectina (Asai-Sato et al., 2006), además de inhibir la expresión y la actividad de la proteína lipasa (Ling et al., 2003; Millan et al., 2014). Estas acciones metabólicas son adaptativas en el embarazo y lactancia, periodos fisiológicos en que la prolactina promueve que el tejido graso se deposite y se movilice respectivamente, para asegurar una nutrición óptima del recién nacido (Grattan, 2015). En humanos, la hiperprolactinemia patológica o inducida podría conllevar un aumento de peso (Greenman, Tordjman, & Stern, 1998; Pala, Laway, Misgar, & Dar, 2015), aunque este aspecto es aun controvertido ya que algún estudio también apunta a que la prolactina podría inhibir la lipogénesis (Nilsson, Roepstorff, Kiens, Billig, & Ling, 2009).

La prolactina también está involucrada en la biología de las células de los islotes pancreáticos, estimulando la expresión y secreción de insulina y la expansión de las células ß (Brelje, Stout, Bhagroo, & Sorenson, 2004; Grattan, 2015; Sorenson et al., 1987). La hiperPRL tiene un papel importante en la homeostasis glucídica durante el embarazo, promoviendo una mayor transferencia de glucosa al feto gracias al desarrollo de cierta resistencia insulínica por parte de los tejidos maternos (Rieck & Kaestner, 2010). El fallo de esta respuesta adaptativa podría

conllevar el desarrollo de una diabetes gestacional (Ramos-Romn, 2011). Existe cierta evidencia de que los pacientes con hiperprolactinemia presentan una resistencia a la insulina (Serri et al., 2006; Yavuz et al., 2003), aunque otros estudios no han encontrado esta asociación (Balbach et al., 2013; Ernst, Thurnheer, & Schultes, 2009), por lo que es un aspecto aun controvertido.

Además de estas acciones periféricas, la prolactina también actúa en el sistema nervioso central (SNC) aumentando el apetito a través de inducir una resistencia funcional a la leptina (Augustine & Grattan, 2008; Naef & Woodside, 2007), hecho ampliamente demostrado en los estados de gestación (Ladyman, Fieldwick, & Grattan, 2012; Shirley, 1984).

Efectos a nivel cardiovascular

La hiperprolactinemia se ha asociado a efectos negativos a nivel cardiovascular. En pacientes con prolactinomas, la elevación patológica de los niveles séricos de prolactina están asociados a un perfil de riesgo cardiovascular, consistente en mayor resistencia insulínica, un bajo grado de inflamación y una disfunción endotelial (Serri et al., 2006; Yavuz et al., 2003). También se ha relacionado la hiperprolactinemia con un aumento de la agregación paquetaria y con un incremento del grosor de la íntima a nivel carotídeo, compatible con una aterosclerosis preclínica (Arslan et al., 2014; Wallaschofski et al., 2001). En mujeres, niveles séricos más elevados de prolactina están asociados con una mayor presión arterial sistémica y mayor rigidez aórtica (Georgiopoulos et al., 2009; Zhang, Curhan, & Forman, 2010). En un estudio reciente con una muestra de 3929 personas observa un correlación positiva entre los niveles de prolactina y mortalidad cardiovascular en un seguimiento prospectivo a 10 años (Haring et al., 2014).

Estudios in vitro han demostrado que la prolactina puede modular la respuesta inflamatoria y estimular la proliferación celular del músculo liso, además de jugar un papel en la adhesión de las células mononucleares al endotelio, conllevando con todo ello una alteración de la estructura vascular que provoca una disfunción endotelial (Montes de Oca et al., 2005; Sauro, Buckley, Russell, & Fitzpatrick, 1989; Yu-Lee, 2002).

Efectos sobre el sistema inmune

La presencia de hiperprolactinemia es habitual en múltiples enfermedades autoinmunes como el Lupus Eritematoso Sistémico, Artritis reumatoide, esclerosis múltiple o la diabetes mellitus tipo 1, entre otras (De Bellis et al., 2008). En algunas de estas enfermedades los niveles de prolactina se correlacionan con el nivel de actividad de la enfermedad, apoyando la idea de que la prolactina actúa como potenciadora de la respuesta inmune (Fojtikova, Cerna, & Pavelka, 2010). Estudios in vitro sugieren que la prolactina podría tener un efecto inmunomodulador, inhibiéndo la apoptosis, aumentando la presentación de antígenos, aumentando la producción de citoquinas y aumentando la secreción de anticuerpos (Shelly, Boaz, & H, 2012).

Efectos sobre el SNC y cognición

Hay algunos datos que sugieren que la prolactina, además de tener los efectos biológicos mencionados previamente, también presenta un efecto modulador de los procesos cognitivos y conductuales. Uno de los relatos publicados describe a un paciente con un adenoma pituitario secretor de prolactina con sintomatología de demencia, que remitió tras la terapia con bromocriptina (Brisman, Fetell, & Post, 1993). Otro artículo hace referencia a otro caso de prolactinoma que refería dificultades en la memoria a corto plazo (Fleseriu et al., 2006). Un estudio realizado en pacientes varones mostró que los niveles más elevados de prolactina estaban asociados a un peor rendimiento cognitivo (Castanho et al., 2014). Varios estudios recientes realizados en pacientes con hiperprolactinemia han observado un efecto negativo de los niveles de prolactina sobre las habilidades cognitivas. El primer estudio fue realizado por Henry y Sherwin, analizando la capacidad cognitiva de manera prospectiva en mujeres embarazadas con hiperprolactinemia fisiológica, y observaron un efecto negativo de la hiperprolactinemia sobre la memoria y la función ejecutiva (J F Henry & Sherwin, 2012). Otro estudio reciente realizado por Bala y colaboradores evalúa 20 pacientes con prolactinoma y 20 controles sanos, y concluye que la hiperprolactinemia puede tener una influencia negativa en los procesos cognitivos, especialmente en los dominios de atención y memoria (Bala, Lojek, & Marchel, 2016). Hasta el momento no existen estudios que evalúen si la reducción de los niveles de prolactina con agonistas dopaminérgicos en los pacientes con prolactinomas conlleva una mejoría en los dominios cognitivos afectados.

1.3. HIPERPROLACTINEMIA Y TRASTORNOS PSICÓTICOS

1.3.1. Perspectiva histórica

La presencia de anomalías menstruales en mujeres con esquizofrenia fue descrita previamente a la introducción de fármacos antipsicóticos. Schroter (1874) publicó uno de los primeros escritos asociando amenorrea con la psicosis, y otros clínicos del siglo XIX se unieron a estos hallazgos, reforzando la idea de la existencia de una asociación entre la psicosis y la disfunción menstrual.

Allen y Henry (1933) realizaron una descripción detallada de la relación entre menstruación y diferentes enfermedades mentales en mujeres. En su introducción exponen que frecuentemente la enfermedad mental se asociaba a amenorrea, y que habían observado que a menudo las alteraciones mentales coexistían con alteraciones fisiológicas. Concluyen diciendo que observaron problemas reproductivos en una tercera parte de las mujeres con una enfermedad mental crónica, y que las irregularidades menstruales eran frecuentes incluso en las fases previas al inicio de la enfermedad esquizofrénica.

La presencia de las irregularidades menstruales en las mujeres con enfermedades psicóticas, previas a la introducción de los fármacos antipsicóticos, llevó a los investigadores a prestar mayor atención a la posible relación entre los dos fenómenos.

Desde la introducción de los antipsicóticos en 1953, el hallazgo de la disfunción menstrual fue observado de manera más frecuente en los pacientes con esquizofrenia. Winnik y

Tennenbaum (1955) reportaron la aparición de galactorrea en mujeres pocos años después de la introducción de la clorpromazina. Gade y Heinrich en 1955 escribieron sobre la galactorrea como efecto secundario del tratamiento antipsicótico, y Polishuk y Kulcsar en 1956 señalaban que los efectos de la clorpromazina eran sobre la función pituitaria.

1.3.2. Evidencia actual sobre la prolactina en las fases tempranas de las enfermedades psicóticas

En los últimos años ha aumentado la evidencia de la existencia de niveles superiores de prolactina en pacientes con un primer episodio psicótico que aun no ha recibido tratamiento antipsicótico (Garcia-Rizo et al., 2012; Gonzalez-Blanco et al., 2016), y también en pacientes que cumplen criterios de estado mental de alto riesgo (EMAR) (Aston et al., 2010; Riecher-Rossler et al., 2013). Estos hallazgos son importantes ya que ponen en evidencia que en un porcentaje de individuos con trastornos psicóticos en fases tempranas, la elevación de la prolactina no es debida únicamente a un bloqueo dopaminérgico por antipsicóticos. Además, estudios de neuroimagen han demostrado un aumento del volumen de la glándula hipofisaria, tanto en pacientes con un primer episodio psicótico sin haber recibido tratamiento antipsicótico, (Pariante et al., 2005) como en sujetos EMAR que posteriormente desarrollaron un primer episodio psicótico (Büschlen et al., 2011; Garner et al., 2005; Walter et al., 2015). El estudio prospectivo realizado por Labad y colaboradores identificó que los niveles de prolactina podrían ser un biomarcador asociado al riesgo de transición a psicosis en individuos que cumplen criterios de EMAR, junto con otros factores relacionados con el estrés como la respuesta de cortisol al despertar o niveles reducidos de albúmina (Labad et al., 2015). Respecto al mecanismo por el que la prolactina podría jugar un papel en la transición a la psicosis, algunos autores han hipotetizado que el estrés conllevaría un aumento de los niveles de prolactina, y que este aumento de la prolactina sería el responsable de desencadenar un aumento de la liberación de dopamina por el mecanismo de feed-back, mediando la relación entre el estrés y el inicio de la psicosis (Riecher-Rossler et al., 2013). No obstante, este posicionamiento es muy especulativo porque el estado hiperdopaminérgico como desencadenante de psicosis estaría vinculado a la vía mesolímbica, y la regulación de la secreción de prolactina está vinculada a la vía tuberoinfundibular, que es una vía independiente a la vía mesolímbica.

1.3.3. Hiperprolactinemia causada por antipsicóticos

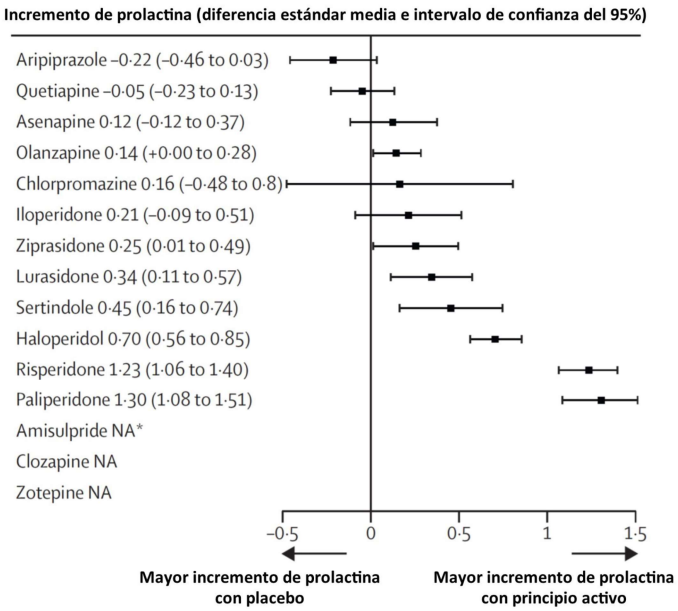
La hiperprolactinemia es un hallazgo frecuente en pacientes con esquizofrenia, presente en más de un 65% de mujeres en edad reproductiva y entre un 40-70% de los hombres que reciben tratamiento antipsicótico (Kinon, Gilmore, Liu, & Halbreich, 2003; Montgomery et al., 2004).

El mecanismo por el que los antipsicóticos pueden producir hiperprolactinemia se basa en el antagonismo dopaminérgico que ejercen en los receptores del sistema tuberoinfundibular y en las células lactótropas. Bloqueando la interacción de entre la dopamina y los receptores dopaminérgicos D2 se impide la inhibición tónica de la secreción de prolactina, con la consecuente elevación de la misma (Cookson, Hodgson, & Wildgust, 2012; Horseman & Gregerson, 2013).

Las variables más importantes a tener en cuenta en cuanto a la capacidad de producir una elevación de la prolactina son el tipo de antipsicótico y la dosis empleada (mayores elevaciones con mayores dosis) (Montgomery et al., 2004). Los antipsicóticos con un mayor índice de ocupación D2 son los que producen mayores elevaciones de la prolactina. Los antipsicóticos típicos incluyen tres amplios grupos: las fenotiazinas (clorpormazina, flufenazina, tioridazina, trifluoperazina y perfenazina), las tioxantenos (tiotixeno, zuclopentixol) y butirofenonas (haloperidol). La capacidad de elevar los niveles de prolactina es equivalente a la potencia antipsicótica del fármaco, siendo el haloperidol el más potente en ambos sentidos. Los antipsicóticos atípicos son un grupo heterogéneo de fármacos con perfiles farmacológicos variados, y es por ello que encontramos amplia variabilidad respecto a la capacidad de elevar la prolactina. Existen marcadas diferencias entre estos fármacos en la afinidad a los receptores dopamiérgicos D2 y de la duración de la unión con el receptor. Otra variable a tener en cuenta es la capacidad del fármaco de atravesar la barrera hematoencefálica (BHE) ya que la hipófisis se sitúa fuera de ésta, y dependiendo de la liposolubilidad de la molécula se alcanzan mayores concentraciones fuera de la BHE, donde ejerce el bloqueo dopaminérgico D2 en la glándula hipofisaria. La relación entre la concentración del antipsicótico en cerebro y plasma (B/P ratio) medida mediante PET se considera que puede ser útil para medir esta variable de riesgo de hiperprolactinemia de diferentes fármacos. Así, los ratios más bajos (risperidona y amisulpiride) predicen un mayor riesgo de producir hiperprolactinemia (Arakawa et al., 2010), que son los antipsicóticos atípicos que se asocian a unas tasas más elevadas de hiperprolactinemia (70-90%), igualando e incluso excediendo las de los antipsicóticos típicos (Bushe, Shaw, & Peveler, 2008). Olanzapina y quetiapina se asocian con menor frecuencia a hiperprolactinemia (10-40%), mientras que la clozapina tiene una pobre afinidad por los receptores dopaminérgicos D2 y raramente eleva la prolactina (<5%) (Melkersson, 2005). Por último el aripiprazol presenta una actividad agonista parcial de los receptores dopaminérgicos D2, por lo que incluso se ha demostrado su capacidad para disminuir los niveles de prolactina (Raghuthaman, Venkateswaran, & Krishnadas, 2015).

En un reciente metaanálisis sobre la eficacia y tolerabilidad de 15 antipsicóticos, los fármacos que se relacionan con mayores tasas de hiperprolactinemia son la risperidona y la paliperidona (Figura 3). Al contrario, aripiprazol y quetiapina son los que muestran menor asociación con la elevación de la prolactina (Leucht et al., 2013).

Figura 3. Diagrama de efectos de diferentes antipsicóticos comparados con placebo sobre el aumento de prolactina (figura modificada de Leucht et al., 2013).



Dado el interés que genera este aspecto de los antipsicóticos, en la literatura se ha establecido una clasificación de los antipsicóticos dependiendo de su capacidad para elevar los niveles de prolactina: por una parte los antipsicóticos hiperprolactinémicos (o "prolactin-raising APS" en inglés), que incluye la risperidona, paliperidona, amisulpiride y la mayoría de los antipsicóticos típicos; y por otra parte los denominados "prolactin-sparing APS", como el aripiprazol, asenapina, clozapina, quetiapina y ziprasidona (Leucht et al., 2013).

1.3.4. Consecuencias de la hiperprolactinemia secundaria a antipsicóticos

Las consecuencias clínicas de los efectos de la hiperprolactinemia asociada al tratamiento antipsicótico no difieren de las descritas en la hiperprolactinemia por otras causas. Estas consecuencias ya se han comentado ampliamente en el apartado 1.2.2. y pueden observarse a corto, medio o largo plazo.

A continuación comentaremos las consecuencias más frecuentemente reportadas en la práctica clínica habitual:

A corto plazo es frecuente que los pacientes presenten una disfunción gonadal, con alteraciones menstruales e incluso amenorrea en mujeres e infertilidad tanto en mujeres como hombres (Montejo et al., 2010).

La prevalencia de disfunción sexual en pacientes que reciben tratamiento antipsicótico es alta (de hasta un 40% en mujeres y un 60% en hombres (Hellewell & Gerlach, 2000)), aunque es un problema que esta infradiagnosticado ya que frecuentemente los pacientes no lo comunican espontáneamente y no se realiza una exploración sistemática de este aspecto (Cutler, 2003). Se considera que este efecto adverso es un factor importante en la adherencia al tratamiento pautado, ya que las tasas de discontinuación por iniciativa de los pacientes es alta cuando existe este efecto secundario (Cutler, 2003).

Otro de los efectos de la hiperprolactinemia en varones puede ser la ginecomastia, presente hasta en un 20% de los pacientes tratados con antipsicóticos (Luciano, 1999). También por su efecto en la glándula mamaria, puede aparecer la galactorrea, con una prevalencia de entre un 10 y un 50% de los pacientes con esquizofrenia en tratamiento con antipsicóticos (Windgassen, Wesselmann, & Schulze Mönking, 1996).

Existen estudios que apuntan a que los pacientes con esquizofrenia tratados con antipsicóticos y niveles elevados de prolactina presentan una reducción de la densidad mineral ósea, con el consiguiente aumento de riesgo de fracturas tanto en mujeres como en hombres (van der Leeuw et al., 2013).

Respecto al riesgo de cáncer de mama en pacientes con esquizofrenia tratados con antipsicóticos, estudios recientes sugieren que no existe una relación entre la hiperprolactinemia y el riesgo de cáncer de mama en esta población (De Hert et al., 2016).

Como se ha comentado en la sección anterior, hay cierta evidencia de las consecuencias negativas de la hiperprolactinemia a nivel cognitivo en población no psiquiátrica. Hasta el momento no existen estudios que evalúen este aspecto en población psiquiátrica, a pesar de que el hallazgo de hiperprolactinemia es frecuente en pacientes tratados con antipsicóticos. En este sentido, dado que el deterioro cognitivo en pacientes con trastorno del espectro psicótico se considera un factor importante en la funcionalidad de los pacientes, creemos necesario investigar si los niveles elevados de prolactina en pacientes con un trastorno psicótico podrían conllevar un deterioro en las habilidades cognitivas que puedan interferir en la funcionalidad y calidad de vida de estos pacientes.

1.4. COGNICIÓN Y PSICOSIS

1.4.1. Generalidades

Las alteraciones cognitivas son una característica nuclear de la esquizofrenia y de otros trastornos psicóticos. Estas alteraciones incluyen dificultades atencionales, de memoria, de velocidad de procesamiento, de funciones ejecutivas y de cognición social. Estas alteraciones cognitivas están presentes en las fases iniciales de la enfermedad, incluso antes del primer episodio psicótico franco (Davidson et al., 1999; Reichenberg et al., 2005) y son un factor determinante de la funcionalidad de los pacientes (Green, 1996; Schmidt, Mueller, & Roder, 2011). Los esfuerzos dedicados a encontrar nuevos agentes procognitivos para la esquizofrenia no han tenido los resultados esperados, en parte por el desconocimiento de las bases neurobiológicas de la dimensión cognitiva de las enfermedades psicóticas. Dado que la discapacidad producida por esta enfermedad es muy elevada y el impacto a nivel socio-económico es muy alto, se ha considerado importante conocer las bases neurobiológicas de las alteraciones cognitivas en los trastornos psicóticos, y así conocer nuevas dianas terapéuticas y desarrollar fármacos procognitivos para la esquizofrenia hasta ahora no aprobados (R. S. E. Keefe et al., 2013; Yang, Marder, & Green, 2017).

Tanto es el interés es este aspecto, que el National Institute of Mental Health (NIMH) de los EEUU creó una iniciativa llamada Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS), en el que un grupo de expertos desarrolló una batería cognitiva llamada MATRICS Consensus Cognitive Battery (MCCB) con los dominios que consideraron relevantes para los estudios de potenciales tratamientos procognitivos en la esquizofrenia, incluyendo los siguientes: velocidad de procesamiento, atención/vigilancia, memoria de trabajo, aprendizaje verbal, aprendizaje visual, razonamiento y resolución de problemas, y la cognición social (Keith H. Nuechterlein et al., 2004). Junto con el NIMH y la FDA, también facilitaron una guía de recomendaciones para el diseño de ensayos clínicos que evaluasen la eficacia de nuevos agentes para el deterioro cognitivo en la esquizofrenia (Buchanan et al., 2005).

1.4.2. Hormonas implicadas en los procesos cognitivos de los pacientes con psicosis

Diversas hormonas pueden estar implicadas en los procesos cognitivos de los pacientes, y las más estudiadas hasta el momento han sido las hormonas sexuales y el cortisol.

Hormonas sexuales

El papel de las hormonas sexuales en el curso de la esquizofrenia se ha estudiado ampliamente. En primer lugar, la edad de presentación, el curso de la enfermedad, la presentación clínica y la respuesta al tratamiento en pacientes con esquizofrenia es diferente en hombres que en mujeres (Abel, Drake, & Goldstein, 2010). Las mujeres tienen mayor probabilidad de presentar un primer episodio psicótico o una reagudización de la enfermedad en los periodos en que los estrógenos están en los niveles más bajos, como en el postparto o

en la perimenopausia (Riecher-Rössler, Häfner, Stumbaum, Maurer, & Schmidt, 1994). El periodo en el que los estrógenos y la progesterona están en niveles más elevados como en el embarazo suele ser de menor riesgo para presentar este tipo de síntomas (Häfner, Behrens, De Vry, & Gattaz, 1991; Riecher-Rössler et al., 1994). Estas observaciones han conllevado a la hipótesis de que los estrógenos tendrían un papel protector sobre la esquizofrenia. En hombres con esquizofrenia los niveles de testosterona son más bajos que en hombres sanos, y los niveles más bajos de testosterona se han asociado a sintomatología negativa y cognitiva más severa (Bratek, Koźmin-Burzyńska, Krysta, Cierpka-Wiszniewska, & Krupka-Matuszczyk, 2015). Con todo ello, tanto los estrógenos como la progesterona podrían modular ciertos aspectos de la esquizofrenia en ambos sexos.

Los esteroides sexuales son importantes para los procesos cognitivos (Wolf & Kirschbaum, 2002). Existe evidencia científica sobre algunos efectos beneficiosos de los estrógenos a nivel cognitivo, sobre la memoria y la capacidad atencional (Sherwin & McGill, 2003). En estudios animales, el aumento de los niveles de estrógenos endógenos promueve el crecimiento neuronal, mejora la plasticidad neuronal, aumenta la densidad sináptica y aumenta la neurogénesis en la corteza cerebral e hipocampo (Montague et al., 2008; Perlman et al., 2005). En pacientes con esquizofrenia, se sabe que los esteroides sexuales pueden modular la capacidad cognitiva tanto en mujeres (Huerta-Ramos et al., 2014) como en hombres (Moore et al., 2013). En los últimos años se ha hipotetizado que la disfunción cognitiva de los pacientes con esquizofrenia se podría paliar con una estimulación estrogénica en el cerebro (Weickert et al., 2015). Algunos estudios realizados en pacientes con esquizofrenia con terapia estrogénica han observado una reducción sintomática a nivel cognitivo tanto en mujeres como en hombres (Begemann, Dekker, van Lunenburg, & Sommer, 2012; J Kulkarni et al., 2015; Jayashri Kulkarni et al., 1996, 2008, 2011). Dado que el tratamiento con estrógenos puede conllevar riesgos y efectos adversos a largo plazo (Barrett-Connor, 2001; Chlebowski et al., 2009), se ha sugerido que el raloxifeno podría tener los efectos procognitivos deseados sin un perfil de efectos indeseados asociados. El raloxifeno es un modulador del receptor estrogénico, con actividad agonista del receptor estrogénico en el cerebro y hueso, y antagonista en otros tejidos (Landry, Lévesque, & Di Paolo, 2002). Es un fármaco aprobado para el tratamiento de la osteoporosis en mujeres postmenopáusicas y para el cáncer de mama en mujeres. Estudios recientes han demostrado que el tratamiento coadyuvante con raloxifeno en mujeres postmenopáusicas con esquizofrenia conlleva una mejoría a nivel psicopatológico, incluyendo sintomatología positiva (Kianimehr et al., 2014; Usall et al., 2011), sintomatología negativa (Usall et al., 2011, 2015), psicopatología general (Jayashri Kulkarni et al., 2010; Usall et al., 2011) y rendimiento cognitivo (Huerta-Ramos et al., 2014). Hasta hace poco no existían estudios realizados en hombres, y un estudio reciente ha demostrado que la mejoría cognitiva con raloxifeno también se observa en hombres, además de en mujeres con esquizofrenia (Weickert et al., 2015).

Eje hipotálamo-pituitario-adrenal

Hay diversos estudios que relacionan el hipercorticismo con la disfunción cognitiva en población no psiquiátrica (B. K. Lee et al., 2007; Lupien et al., 1994; Wolkowitz et al., 1990), principalmente en los dominios de funciones ejecutivas, memoria verbal, lenguaje y la velocidad de procesamiento (B. K. Lee et al., 2007). Varios estudios realizados en población afecta por un trastorno psicótico observaron una relación negativa entre el rendimiento cognitivo (sobre todo en el dominio de memoria de trabajo) y los niveles de cortisol (Newcomer, Faustman, Whiteford, Moses, & Csernansky, 1991; Walder, Walker, & Lewine, 2000). Estudios posteriores han sugerido que esta relación entre los niveles plasmáticos elevados de cortisol y un peor rendimiento cognitivo se da sobre todo en hombres con esquizofrenia y no en mujeres (R Halari et al., 2004). Ya que los niveles de cortisol siguen un ritmo circadiano, también se han realizado estudios con determinaciones de cortisol en saliva que han permitido realizar tests dinámicos determinando la respuesta del cortisol al despertar y a lo largo del día. En un estudio realizado por nuestro grupo en pacientes con un primer episodio psicótico (Labad et al., 2016) se encontraron diferencias de género en la relación entre las medidas del eje HPA y las tareas cognitivas. Se relacionó una mayor respuesta del cortisol al despertar con peor velocidad de procesamiento y memoria verbal sólo en el grupo de mujeres. Otros grupos han observado que los niveles más elevados de cortisol durante las pruebas neuropsicológicas se asocian a un peor rendimiento en velocidad de procesamiento en pacientes varones con esquizofrenia (Rozmin Halari, Mehrotra, Sharma, Ng, & Kumari, 2006). Otro estudio realizado en pacientes con un primer episodio psicótico observó una relación entre la respuesta aplanada del cortisol al despertar con peor rendimiento en memoria verbal (Aas et al., 2011).

Prolactina

Durante muchos años las consecuencias más estudiadas de la hiperprolactinemia en pacientes psicóticos han sido la amenorrea, galactorrea, la disfunción sexual y la infertilidad (Horseman & Gregerson, 2013). Sin embargo, la prolactina juega un papel importante como neuropéptido y regula la neurogénesis (Luz Torner, 2016), sugiriendo un posible papel en las habilidades cognitivas. Algunos estudios en humanos han demostrado una relación negativa entre los niveles elevados de prolactina y la velocidad de procesamiento y funciones ejecutivas en diferentes poblaciones, incluyendo mujeres embarazadas (Jessica F Henry & Sherwin, 2011) y pacientes con prolactinoma (Bala et al., 2016). En estudios animales la hiperprolactinemia crónica se ha asociado a un peor reconocimiento de objetos (L Torner, Tinajero, Lajud, Quintanar-Stephano, & Olvera-Cortes, 2013).

Sin embargo, se desconocen los mecanismos por los que la hiperprolactinemia se asocia a disfunción cognitiva. Una hipótesis es que el hipogonadismo resultante de la hiperprolactinemia sea el que induce la sintomatología cognitiva (Castanho et al., 2014). Por un lado, los niveles de testosterona pueden modular el rendimiento cognitivo en varones con esquizofrenia (Moore et al., 2013) y por otro lado, hay estudios que apoyan la idea de que los estrógenos también juegan un papel en los procesos cognitivos en la esquizofrenia. Se ha visto que el tratamiento con moduladores selectivos de los receptores estrogénicos mejora el

rendimiento en varios dominios cognitivos en pacientes postmenopáusicas con esquizofrenia (Huerta-Ramos et al., 2014). Por otro lado, la prolactina es una hormona que se eleva en situaciones de estrés (Armario, Marti, Molina, De Pablo, & Valdes, 1996; A. K. Lennartsson & Jonsdottir, 2011), como también lo hace el cortisol por una activación del eje hipotálamo-pituitario-adrenal. Por lo tanto, la asociación entre los niveles de prolactina y rendimiento cognitivo podría estar mediados por las hormonas del eje HPA. Como se ha mencionado en el apartado anterior, hay múltiples estudios que han demostrado una relación entre los niveles de cortisol y el rendimiento cognitivo en los pacientes con esquizofrenia.

En esta tesis doctoral se plantea la hipótesis de que los niveles elevados de prolactina puedan afectar al rendimiento cognitivo de los pacientes con esquizofrenia, afectando así a la funcionalidad y calidad de vida de los pacientes. Como se ha comentado con anterioridad, la elevación de los niveles séricos de la prolactina puede deberse tanto a la propia enfermedad como a un efecto secundario de los fármacos empleados para el tratamiento de los trastornos psicóticos. Así mismo, los fármacos antipsicóticos también pueden tener un efecto negativo sobre la capacidad cognitiva de los pacientes por su efecto anticolinérgico. Por ello se ha planteado evaluar el efecto de la prolactina sobre la capacidad cognitiva en la población afecta de un trastorno psicótico, pero también en pacientes con hiperprolactinemia debida a un prolactinoma que no están bajo tratamiento antipsicótico y su efecto tras la reducción de los niveles de prolactina con agonistas dopaminérgicos en esta misma población. He considerado que es una población de estudio muy interesante para poder demostrar la implicación de la hiperprolactinemia en el rendimiento cognitivo, por no tener variables confusoras que puedan afectar a la cognición, como la propia enfermedad mental o el tratamiento con fármacos antipsicóticos. Un estudio reciente ha observado que los pacientes con prolactinoma presentan un peor rendimiento cognitivo (Bala et al., 2016), pero no existen estudios hasta la actualidad que analicen si la reducción de los niveles de prolactina comportan una mejoría de las capacidades cognitivas en los distintos dominios afectados. En caso de que se confirmen las hipótesis mencionadas, los agentes agonistas dopaminérgicos como la cabergolina podrían ejercer una función procognitiva en los pacientes con esquizofrenia que presenten hiperprolactinemia.

Aunque hay estudios que sugieren la implicación de otras hormonas como las tiroideas (Barbero et al., 2015) o la oxitocina (Quintana, Dieset, Elvsåshagen, Westlye, & Andreassen, 2017) en funciones cognitivas, la presente tesis se centra en el estudio de la prolactina así como otras hormonas relacionadas como son las hormonas sexuales y el cortisol.

OBJETIVOS E HIPÓTESIS

2. OBJETIVOS E HIPÓTESIS

El objetivo principal de este trabajo es esclarecer la influencia de los niveles de prolactina a nivel cognitivo y funcional de los pacientes con una psicosis temprana. Nos hemos marcado los siguientes objetivos concretos:

2.1. OBJETIVOS

2.1.1. Objetivo 1

Estudiar si el cambio de risperidona inyectable de larga duración a Paliperidona Palmitato en pacientes con una psicosis e hiperprolactinemia comporta una reducción de los niveles de prolactina, mejoría en la funcionalidad sexual, psicopatología y en la funcionalidad global.

2.1.2. Objetivo 2

Estudiar si los niveles plasmáticos elevados de prolactina se asocian a un peor rendimiento cognitivo en pacientes con una psicosis temprana.

2.1.3. Objetivo 3

Explorar si existen diferencias de género en la asociación entre los niveles plasmáticos de prolactina y rendimiento cognitivo en pacientes con una psicosis temprana, y si estas diferencias pueden estar moderadas por cambios en hormonas sexuales o en cortisol.

2.1.4. Objetivo 4

Estudiar si la reducción de los niveles de prolactina en pacientes endocrinológicos con un prolactinoma conlleva una mejoría en el rendimiento cognitivo.

2.2. HIPÓTESIS DE TRABAJO

2.2.1. Hipótesis 1

El cambio de risperidona inyectable de larga duración a Paliperidona Palmitato en pacientes con una psicosis e hiperprolactinemia no comporta una reducción de los niveles de prolactina, ni cambios en la funcionalidad sexual, psicopatología o en la funcionalidad global.

2.2.2. Hipótesis 2

Los niveles plasmáticos elevados de prolactina se relacionan con un peor rendimiento cognitivo en pacientes con una psicosis temprana.

2.2.3. Hipótesis 3

Existe una asociación entre los niveles de prolactina y rendimiento cognitivo en pacientes con una psicosis, que es independiente del género y de los niveles de hormonas sexuales y de cortisol.

2.2.4. Hipótesis 4

La reducción de los niveles de prolactina con cabergolina en pacientes con un prolactinoma conlleva una mejoría del rendimiento cognitivo.

Tabla 2. Resumen de los estudios realizados para contrastar las hipótesis de trabajo.

HIPÓTESIS	ESTUDIO	PUBLICACIÓN
1	**Estudio 1** Variación de los niveles de prolactina, funcionalidad sexual y funcionalidad global tras el cambio de risperidona inyectable de larga duración a paliperidona palmitato.	"Changes in prolactin levels and sexual function in young psychotic patients after switching from long-actin injectable risperidone to paliperidone palmitate" Montalvo I, Ortega L, López X, Solé M, Monseny R, Franch J, Vilella E, Labad J. Int Clin Psychopharmacol. 2013; 28:46-9
2	**Estudio 2** Relación entre los niveles de prolactina y el rendimiento cognitivo en pacientes con una psicosis temprana.	"Increased prolactin levels are associated with impaired processing speed in subjects with early psychosis" Montalvo I, Gutiérrez-Zotes A, Creus M, Monseny R, Ortega L, Franch J, Lawrie SM, Reynolds RM, Vilella E, Labad J. PLoS One 2014; 9:e89428
3	**Estudio 3** Diferencias de género en la afectación cognitiva por los niveles de prolactina en pacientes con una psicosis temprana.	"Sex differences in the relationship between prolactin levels and impaired processing speed in early psychosis" Montalvo I, Nadal R, Armario A, Gutiérrez-Zotes A, Creus M, Cabezas A, Solé M, Algora MJ, Sánchez-Gistau V, Vilella E, Labad J. Aceptado por la revista Australian & New Zealand Journal of Psychiatry
4	**Estudio 4** Cambios en el rendimiento cognitivo tras la reducción de los niveles de prolactina en pacientes con prolactinoma.	"Improvement in cognitive abilities following cabergoline treatment in patients with a prolactin-secreting pituitary adenoma" Montalvo I, Llorens M, Caparrós L, Pamias M, Torralbas J, Giménez O, Caixàs A, Palao DJ, Labad J. Aceptado por Int Clin Psychopharmacol.

MÉTODOS

3. MÉTODOS

3.1. Poblaciones de estudio

Los pacientes de los estudios 1, 2 y 3 se han reclutado en la Unidad de Psicosis Incipiente de Reus del Hospital Universitari Institut Pere Mata (HUIPM). Además de los pacientes afectos de una psicosis, en el estudio 2 también se reclutaron pacientes que cumplían criterios de EMAR.

Los criterios de exclusión en los tres estudios fueron: Embarazo, retraso mental, enfermedades neurológicas, tratamiento con glucocorticoides, barrera idiomática, deficiencia visual o dependencia a alcohol, cocaína o heroína.

Los pacientes del estudio 4 se han reclutado en la unidad de Endocrinología de la Corporació Sanitària Parc Taulí de Sabadell, todos ellos afectos de hiperprolactinemia secundaria a un prolactinoma y con indicación de iniciar tratamiento con un agonista dopaminérgico (cabergolina). Los criterios de exclusión fueron padecer otra enfermedad endocrinológica, el retraso mental, enfermedades autoinmunes, embarazo, antecedentes personales de enfermedades psiquiátricas, abuso o dependencia a tóxicos y toma de fármacos que potencialmente pudieran aumentar la prolactina.

Los estudios 1 y 3 son estudios prospectivos, que evalúan cambios tras una intervención concreta. Tabla 3. Resumen de las características de los estudios realizados.

ESTUDIO	MUESTRA	DISEÑO	LUGAR DE RECLUTAMIENTO
1	11 pacientes con psicosis en tratamiento con Risperdal CONSTA® e hiperprolactinemia	PROSPECTIVO 3 meses	Unidad Psicosis Incipiente Reus HUIPM*
2	55 pacientes con psicosis incipiente 23 E.M.A.R. 29 Controles sanos	TRANSVERSAL	Unidad Psicosis Incipiente Reus HUIPM*
3	60 pacientes con psicosis incipiente 50 controles sanos	TRANSVERSAL	Unidad Psicosis Incipiente Reus HUIPM*
4	10 pacientes con prolactinoma	PROSPECTIVO 12 meses	CCS Parc Taulí**

* Hospital Universitari Institut Pere Mata

** Consorci Corporació Sanitària Parc Taulí

3.2. Evaluación clínica

Todos los paciente de los estudios 1, 2 y 3 fueron entrevistados por un psiquiatra, realizándose una entrevista semiestructurada con Schedules for Clinical Assessment in Neuropsychiatry (SCAN) (Wing et al., 1990). Se utilizó la OPCRIT checklist v4.0 (Craddock et al., 1996) para generar diagnósticos DSM-IV. La gravedad de los síntomas psicóticos se evaluó con la escala PANSS (Kay, Fiszbein, Vital-Herne, & Fuentes, 1990), y para los síntomas depresivos se utilizó la escala Calgary de depresión (Addington, Addington, & Schissel, 1990). En el estudio 1 se utilizó la versión española de la escala Personal and Social Performance Scale (PSP) (Apiquian et al., 2009) para medir la funcionalidad de los pacientes, y la escala Arizona Sexual Experiences Scale (ASEX) (McGahuey et al.) para evaluar la funcionalidad sexual. La ASEX es una escala autoadministrada y consta de 5 ítems, cada una con puntuaciones entre 1 y 6. Una mayor puntuación indica mayor disfunción sexual.

En el estudio 2, para los pacientes EMAR se utilizó la Comprehensive Assessment of At Risk Mental States (CAARMS) (Yung et al., 1998) para asegurar que cumpliesen criterios de EMAR.

Las evaluaciones cognitivas se realizaron en los estudios 2, 3 y 4 con la versión española de la batería MATRICS Consensus Cognitive Battery (MCCB) (K H Nuechterlein et al., 2008). En la tabla 4 se resumen los test empleados y los dominios estudiados en la MCCB. En el estudio 4 se realizaron evaluaciones cognitivas repetidas, por lo que se cambiaron las versiones de los test que podían tener un efecto memoria, tal y como recomiendan los autores de la batería cognitiva.

Tabla 4. Dominios cognitivos evaluados con los 10 test neuropsicológicos de la batería MCCB.

Dominios cognitivos	Test
Velocidad de procesamiento	Brief Assessment of Cognition in Schizophrenia (BACS): Symbol Coding Category Fluency-Animal naming Trail Making Test (TMT): Part A
Atención y vigilancia	Continuous Performance Test-Identical Pairs (CPT-IP)
Memoria de trabajo	Wechsler Memory Scale-3rd edition (WMS-III): Spatial Span Letter-Number Span
Aprendizaje verbal	Hopkins Verbal Learning Test-Revised (HVLT-R)
Aprendizaje visual	Brief Visuospatial Memory Test-Revised (BVMT-R)
Razonamiento y resolución de problemas	Neuropsychological Assessment Battery (NAB): Mazes
Cognición social	Mayer-Salovey-Caruso Emotional Intelligence Test: Managing Emotions

En todos los estudios se recogieron por entrevista datos sobre el consumo de alcohol, tabaco y otras drogas, así como el uso de fármacos.

En el estudio 4 se evaluó a los pacientes con un cuestionario de salud general de 12 ítems (GHQ-12) (Sánchez-López & Dresch, 2008), para asegurar el bienestar psicológico de los pacientes.

Tabla 5. Resumen de las evaluaciones clínicas realizadas en los cuatro estudios.

ESTUDIO	SCAN	OPCRIT	CAARMS	PANSS	CDS	PSP	ASEX	MCCB	GHQ-12
1	X	X		X	X	X	X		
2	X	X	X	X	X			X	
3	X	X		X	X			X	
4						X		X	X

3.3. Medidas hormonales

Las muestras de sangre para determinar los niveles plasmáticos de prolactina (estudios 1,2,3,4), cortisol (estudios 2 y 3) y hormonas sexuales (estudio 3) se obtuvieron mediante punción venosa por la mañana entre las 8:30 y 9:30 en condiciones de reposo. Las concentraciones plasmáticas de prolactina, cortisol, estradiol, progesterona y testosterona se midieron con un sistema de inmunoensayo de quimioluminiscencia en todos los estudios.

Los niveles de cortisol en saliva se determinaron en el estudio 3, obteniendo la muestra con los tubos de Salivette ® (Sarstedt AG & Co, Nümbrecht, Germany) y analizándolo con un sistema de inmunoensayo de quimioluminiscencia comercial (IBL, Hamburgo, Alemania).

Tabla 6. Resumen de las medidas hormonales analizadas en los cuatro estudios.

ESTUDIO	Prolactina plasmática	Cortisol plasmático	Cortisol saliva	Hormonas sexuales
1	X			
2	X	X		
3	X	X	X	X
4	X			

3.4. Análisis estadístico

Los análisis estadísticos se realizaron mediante el programa estadístico SPSS (SPSS Inc, Chicago, IL, USA), con un nivel de significación (p) menor de 0,05. Dado que los análisis estadísticos realizados difieren entre los 4 estudios, los detalles concretos se especifican en el apartado de métodos de cada artículo.

3.5. Aspectos éticos

Los estudios presentados en este trabajo fueron aprobados por los comités de ética de los respectivos hospitales, y respetan los principios éticos de la Declaración de Helsinki del 2013.

Todos los participantes de los estudios recibieron la información de las características del estudio y firmaron el consentimiento informado antes de su inclusión al estudio.

RESULTADOS

4. RESULTADOS

A continuación se detallan los principales resultados de los cuatro estudios. Los resultados más detallados se exponen en los artículos adjuntados en el último apartado de este trabajo.

4.1. Resultados del estudio 1

Efectos del cambio de risperidona ILD a PP en los niveles de prolactina y otras variables clínicas en pacientes con un trastorno psicótico:

Se estudió el cambio en los niveles séricos de prolactina y cambios en las escalas de funcionalidad sexual (ASEX) y funcionalidad global (PSP) a nivel basal y tras 3 meses del cambio de risperidona ILD a PP en una serie de casos (11 pacientes) afectos de una psicosis que presentaban hiperprolactinemia previa (Montalvo et al., 2013). En el análisis prospectivo se observó una reducción significativa de los niveles de prolactina tras tres meses del cambio de risperidona ILD a PP, siendo los cambios más pronunciados en los pacientes con niveles basales más elevados de prolactina. No hubo cambios significativos en la funcionalidad sexual medida con la escala ASEX ni en las escalas de psicopatología PANSS y CDS. Se muestran los resultados detallados en la tabla 7.

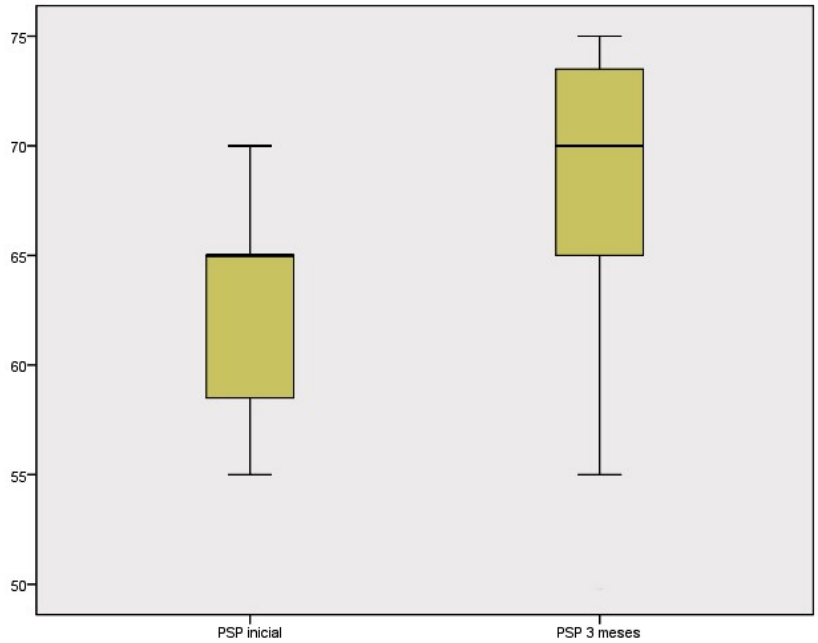
Tabla 7. Datos de la muestra en la evaluación basal y 3 meses después del cambio de risperidona ILD a PP.

Casos	Edad (años)	Evaluación	Dosis LAI [a]	Prolactina (mIU/l)	ASEX	PANSS-P	PANSS-N	PANSS-G	CDS	PSP
1	29	Basal 3 meses	37.5 75	655 930	29 30	8 8	18 15	29 26	3 3	60 65
2	30	Basal 3 meses	37.5 75	4042 3018	16 16	11 11	15 16	25 28	3 1	65 71
3	23	Basal 3 meses	50 100	943 282	19 14	7 7	19 19	22 24	0 0	55 50
4	39	Basal 3 meses	75 150	738 590	23 15	9 7	15 11	23 19	6 0	65 70
5	27	Basal 3 meses	75 150	952 599	15 14	16 13	11 11	29 24	0 0	70 75
6	22	Basal 3 meses	37.5 75	1861 731	15 15	17 8	13 12	29 23	0 0	58 72
7	28	Basal 3 meses	50 100	758 880	15 15	9 8	11 12	22 20	0 0	65 75
8	25	Basal 3 meses	75 150	502 301	10 13	10 11	17 16	27 30	0 1	55 55
9	19	Basal 3 meses	50 100	901 830	14 12	7 9	7 7	23 19	0 0	59 65
10	19	Basal 3 meses	75 150	1201 1138	15 13	11 9	21 15	34 24	4 0	65 70
11	31	Basal 3 meses	37.5 75	1080 868	16 14	7 7	9 8	18 17	0 0	70 75
Total										
Basal Media DE	26.6 5.9		54.5 17.0	1239.3* 996.1	17.0 5.1	10.2 3.5	14.2 4.4	25.5 4.5	1.5 2.2	62.4* 5.4
3 meses Media DE	— —		109.1 34.0	924.3* 741.5	15.5 4.9	8.9 2.0	12.9 3.6	23.1 4.0	0.5 0.9	67.5* 8.3

* $p<0.05$ (Test Wilcoxon); [a] Risperidona inyectable (mg) en basal y a PP (mg eq) a los 3 meses.

Aunque en el artículo no se publicaron los resultados sobre los cambios en la funcionalidad global medida con la PSP, a los tres meses de seguimiento tras el cambio de risperidona ILD a PP se observó una mejoría significativa en este aspecto (ver tabla 7 y figura 4).

Figura 4. Cambios en la funcionalidad medida con la PSP tras 3 meses del cambio de risperidona ILD a PP.



4.2. Resultados del estudio 2

Efectos de la prolactina sobre la cognición en pacientes con una psicosis incipiente:

En este estudio se evaluaron 55 pacientes con un trastorno psicótico de menos de 3 años de evolución, 23 pacientes que cumplían criterios de EMAR y 29 sujetos sanos (Montalvo et al., 2014). Se exploró de manera transversal si los niveles de prolactina se relacionaban con el rendimiento cognitivo de los sujetos, observándose que los niveles elevados de prolactina están asociados a un peor rendimiento cognitivo, en concreto en el dominio de velocidad de procesamiento, tanto en pacientes con una psicosis establecida como en el grupo que cumplía criterios de EMAR. Este efecto, tal y como se muestra en la tabla 8, se mantiene tras ajustar por variables potencialmente confusoras como el tratamiento farmacológico, psicopatología, consumo de sustancias y los niveles plasmáticos de cortisol. Tanto los niveles de prolactina como la dosis de risperidona/paliperidona se asociaron a una peor velocidad de procesamiento en el grupo de pacientes.

Tabla 8. Resultados de la regresión linear múltiple mostrando la relación entre los niveles de prolactina y velocidad de procesamiento en pacientes con una psicosis temprana.

	Modelo 1 No ajustado		**Modelo 2 + antipsicóticos**		**Modelo 3 + otros tratamientos**		**Modelo 4 + síntomas psicóticos, uso sustancias y cortisol**	
R^2 de cada modelo	*0.140*		*0.214*		*0.300*		*0.434*	
	β	*P*	*β*	*P*	*β*	*P*	*β*	*P*
Prolactina (ln)	-0.374	0.001	-0.256	0.044	-0.245	0.046	-0.283	0.022
Dosis Risperidona/Paliperidona*			-0.243	0.042	-0.139	0.311	-0.003	0.986
Dosis Olanzapina/Quetiapina/Clozapina*			-0.140	0.210	0.037	0.769	0.131	0.297
Dosis Aripiprazol*			-0.152	0.176	-0.146	0.168	-0.072	0.497
Dosis Benzodiazepinas‡					-0.353	0.006	-0.324	0.015
Dosis Biperideno (mg/día)					-0.045	0.699	-0.034	0.773
Dosis antidepresivos†					0.066	0.547	0.067	0.537
PANSS – P (ln)							-0.192	0.143
PANSS – N (ln)							-0.283	0.035
PANSS – G (ln)							0.103	0.434
Tabaco (cigarros/día)							-0.129	0.316
Cannabis (porros/día)							0.060	0.610
Alcohol (unidades estándar/día)							0.042	0.727
Cortisol (nmol/L)							0.029	0.794

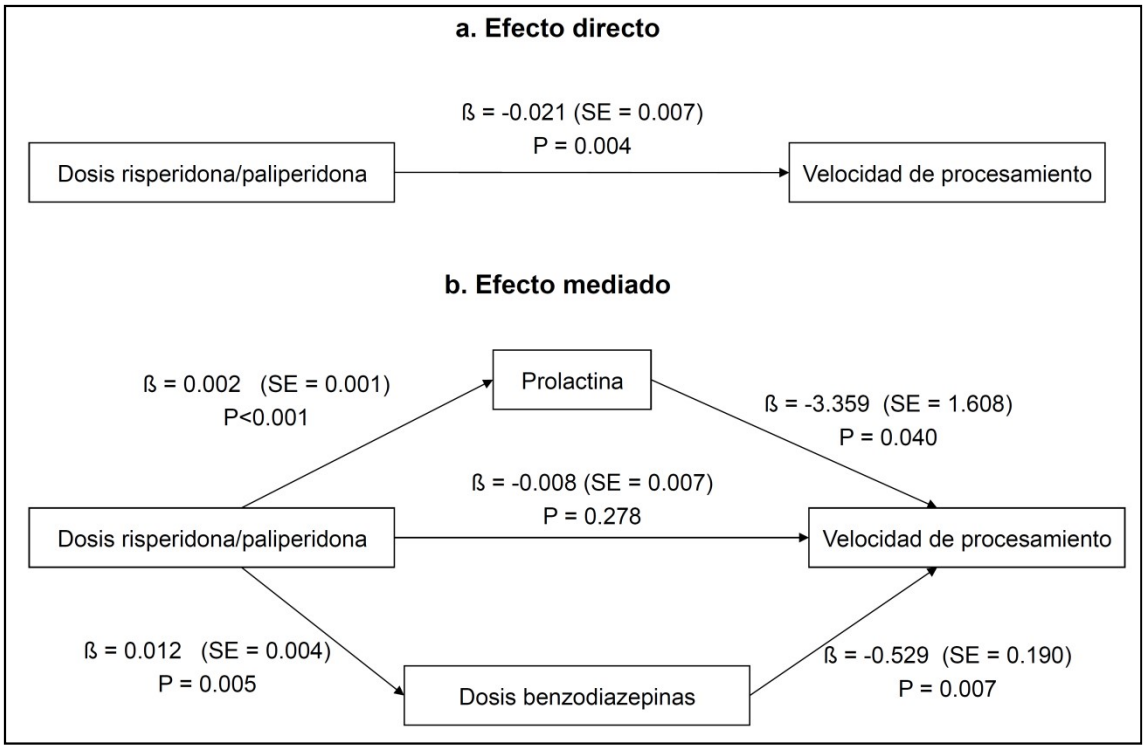
* En equivalentes de clorpromacina, mg/día

‡ En equivalentes de diazepam, mg/día

† En equivalentes de fluoxetina, mg/día

Por otro lado, se realizó un análisis de mediación para testar 2 potenciales mediadores (niveles de prolactina y el tratamiento con benzodiazepinas) en la relación entre la dosis de risperidona/paliperidona y la velocidad de procesamiento. En este análisis observamos que los niveles de prolactina y la dosis de benzodiazepinas son variables mediadoras que explican por completo la relación negativa entre el tratamiento antipsicótico (dosis de risperidona o paliperidona) y la velocidad de procesamiento, ya que la relación entre ambos pierde su significación tras incluir los mediadores en la ecuación (Figura 5).

Figura 5. Análisis de mediación



4.3. Resultados del estudio 3

Diferencias de género en la relación entre los niveles plasmáticos de prolactina y el rendimiento cognitivo en pacientes con una psicosis incipiente:

En este estudio se evaluaron 60 pacientes (39 hombres y 21 mujeres) afectos de un trastorno psicótico incipiente y 50 controles sanos (Montalvo et al. 2017, en prensa. Ver artículo adjunto en la última sección de este trabajo). Se observaron diferencias de género en la correlación de los niveles plasmáticos de prolactina y el rendimiento cognitivo, ya que en los hombres los niveles más elevados de prolactina se asociaron a un peor rendimiento en la mayoría de los dominios cognitivos, mientras que en mujeres sólo se vio afectado un test de la velocidad de procesamiento (BACS-SC).

En el análisis de la regresión lineal, las medidas de la respuesta del cortisol al despertar, niveles de cortisol durante el día o los niveles de esteroides sexuales no modificaron la relación entre

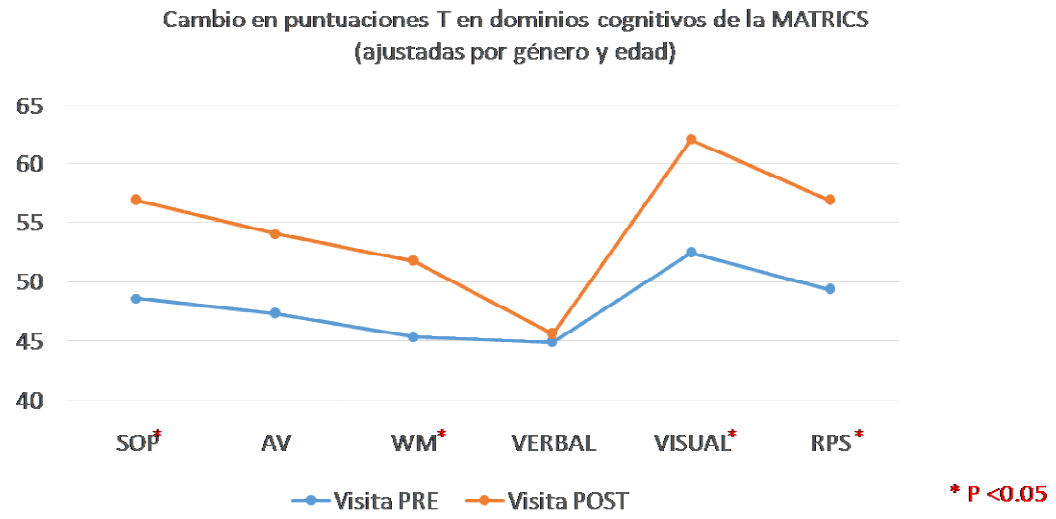
los niveles de prolactina y la funcionalidad cognitiva, sugiriendo que la prolactina podría tener un efecto directo sobre los procesos cognitivos que no está influenciada por el eje HPA ni hipotálamo-pituitario-gonadal.

4.4. Resultados del estudio 4

Efectos cognitivos tras la reducción de los niveles plasmáticos de prolactina en pacientes con un prolactinoma:

La reducción de los niveles de prolactina con un agonista dopaminérgico (cabergolina) en pacientes con hiperprolactinemia debida a un prolactinoma comportó una mejoría en las habilidades cognitivas en diversos dominios cognitivos (Figura 6) (Montalvo et al. 2017, en prensa. Ver artículo adjunto en la última sección de este trabajo).

Figura 6.



SOP: Speed of Processing (Velocidad de procesamiento); AV: Atención y vigilancia; WM: Working Memory (memoria de trabajo); Verbal: Aprendizaje verbal; Visual: Aprendizaje visual; RPS: Reasoning and problem solving (razonamiento y resolución de problemas).

DISCUSIÓN

5. DISCUSIÓN

En este trabajo de tesis se han realizado estudios con el objetivo de explorar las consecuencias clínicas de los niveles elevados de prolactina.

Las principales hipótesis de este trabajo surgieron tras el primer estudio en el que se exploró si el cambio de risperidona ILD a PP en pacientes con psicosis e hiperprolactinemia comportaba cambios en los niveles de prolactina, la funcionalidad sexual y funcionalidad global en una serie de casos. A pesar de que en la literatura previa no se apuntaba a que existieran diferencias respecto al perfil de ambas moléculas en cuanto a la capacidad de elevar los niveles de prolactina (Nussbaum & Stroup, 2012), nuestro estudio observó un descenso significativo de los niveles de prolactina a los 3 meses del cambio de risperidona ILD a PP. Este hallazgo no fue acompañado por una mejoría significativa en la funcionalidad sexual de los pacientes, teniendo que tener en cuenta las limitaciones del tamaño de la muestra y el tiempo de seguimiento relativamente corto. Es posible que tras la reducción de los niveles de prolactina la mejoría de la funcionalidad sexual sea más lenta y que también interfieran otros factores tanto biológicos, psicológicos y sociales que en el estudio no se controlaron (Waldinger, 2015). Otro hallazgo del estudio fue que observamos una mejoría en la funcionalidad global de los pacientes medida con la escala PSP, y los pacientes verbalizaban sentirse con más habilidad mental que previamente. En la literatura se ha explorado ampliamente la relación entre la funcionalidad de los pacientes psicóticos y su asociación con el rendimiento cognitivo (Green, 1996), por lo que a pesar de las limitaciones que tenía el estudio, de estas observaciones surgió la segunda hipótesis de trabajo: la posible asociación de los niveles de prolactina con el rendimiento cognitivo de los pacientes con una enfermedad psicótica.

Durante muchos años las consecuencias más estudiadas de la hiperprolactinemia en la población psicótica han sido la amenorrea, galactorrea, disfunción sexual y la infertilidad (Horseman & Gregerson, 2013). Sin embargo, la prolactina juega un papel importante como neuropéptido y regula la neurogénesis (Luz Torner, 2016), sugiriendo un potencial papel de la prolactina en los procesos cognitivos. Estudios en humanos han demostrado la relación negativa entre los niveles elevados de prolactina y la velocidad de procesamiento y funciones ejecutivas en diferentes poblaciones clínicas incluyendo mujeres embarazadas (Jessica F Henry & Sherwin, 2011) y pacientes con prolactinomas (Bala et al., 2016). Otro estudio realizado en animales también apoya la idea de que niveles elevados de prolactina podrían perjudicar ciertas tareas cognitivas como el reconocimiento de objetos (L Torner et al., 2013). Aunque es un aspecto que genera un creciente interés, aún no existían estudios que evaluasen el posible papel de la hiperprolactinemia en el rendimiento cognitivo de los pacientes con una psicosis, a pesar de que la hiperprolactinemia es una condición muy frecuente en esta población.

Nuestro segundo estudio aporta información relevante sobre las posibles implicaciones de la hiperprolactinemia en las funciones cognitivas de los pacientes con una psicosis incipiente, mostrando una asociación entre los niveles elevados de prolactina y un peor rendimiento cognitivo, concretamente en el dominio de velocidad de procesamiento, en pacientes con psicosis en las fases tempranas. En este sentido, nuestros resultados fueron consistentes con estudios previos que demostraban que la velocidad de procesamiento es el primer dominio cognitivo afectado en los trastornos psicóticos en fases precoces (Dickinson, Ramsey, & Gold,

2007; Riecher-Rossler et al., 2009). Algunos autores han sugerido que este dominio cognitivo, que se ha llegado a considerar un aspecto nuclear del deterioro cognitivo de la esquizofrenia, podría mediar en la relación entre los síntomas cognitivos y la funcionalidad en la esquizofrenia (Ojeda, Pena, Sanchez, Elizagarate, & Ezcurra, 2008).

El aumento de los niveles de prolactina en la población psiquiátrica es un hallazgo frecuente, con una prevalencia de hasta un 70% en pacientes con una psicosis (Montgomery et al., 2004). Por un lado, los antipsicóticos empleados para el tratamiento de los trastornos psicóticos tienen la capacidad de elevar los niveles de prolactina por el bloqueo de los receptores dopaminérgicos D2 en la vía dopaminérgica tuberoinfundibular, aunque esta característica no es igual para todos los antipsicóticos. Hay variables como el grado de bloqueo de los receptores D2 o la capacidad de atravesar la BHE que juegan un papel importante en la capacidad de provocar una hiperprolactinemia. Aunque la relación entre los niveles de prolactina y la capacidad cognitiva es un área poco explorada hasta el momento, sí hay estudios previos que han intentado mirar el perfil cognitivo de diferentes antipsicóticos. Aunque es un tema aun controvertido, la literatura apunta a que existen diferencias en este sentido entre los diferentes antipsicóticos. Hay numerosos ensayos clínicos aleatorizados realizados a doble ciego que demuestran que los antipsicóticos atípicos tiene un mejor perfil cognitivo que los antipsicóticos típicos (haloperidol) en pacientes con esquizofrenia (Bilder et al., 2002; Harvey et al., 2004; R. S. Keefe et al., 2004; M. A. Lee, Jayathilake, & Meltzer, 1999; S E Purdon, Malla, Labelle, & Lit, 2001; Scot E. Purdon, 2000). Además, también se sabe que los efectos negativos del haloperidol a nivel cognitivo son dosis-dependientes, siendo peor el rendimiento cognitivo a dosis más altas (R. S. Keefe et al., 2004; Woodward, Purdon, Meltzer, & Zald, 2007). Dentro del grupo de los AP atípicos, los fármacos con peor perfil cognitivo son la risperidona y la paliperidona, que son a su vez los que más elevan los niveles de prolactina (Leucht et al., 2013). Todos estos hallazgos son compatibles con la idea de que el aumento de los niveles de prolactina podrían contribuir al efecto negativo a nivel cognitivo, ya que los factores que contribuyen a elevar la prolactina se han demostrado perjudiciales para la cognición. Sin embargo es importante apuntar que el uso de AP típicos (especialmente el haloperidol) está asociado a un mayor uso coadyuvante de fármacos anticolinérgicos y benzodiazepinas para controlar los posibles efectos extrapiramidales, que también pueden afectar negativamente a los procesos cognitivos (Woodward et al., 2007), por lo que es una variable a controlar tal y como se realizó en nuestro segundo estudio.

La relación que se observó entre los niveles de prolactina y la velocidad de procesamiento fue tanto en la población con un primer episodio psicótico como en la población EMAR, que la mayoría no tomaban psicofármacos. En este sentido, este hallazgo esta en concordancia con la evidencia de que pacientes con una psicosis, incluso en las fases previas al primer episodio psicótico (población EMAR), presentan niveles más elevados de prolactina que la población sana, a pesar de nunca haber recibido ningún tratamiento antipsicótico (Aston et al., 2010; Garcia-Rizo et al., 2012; Riecher-Rossler et al., 2013).

De hecho, estudios recientes apuntan a que los pacientes EMAR con niveles más elevados de prolactina son los que tiene más riesgo de transitar a una psicosis franca (Labad et al., 2015).

Lo que no se sabe hasta el momento es si este aumento de la prolactina refleja una condición premórbida de estrés (ya que la prolactina es una hormona que se eleva en condiciones de estrés (A. K. Lennartsson & Jonsdottir, 2011)), o una disregulación de la secreción de prolactina en diferentes niveles de la vía tuberoinfundibular causada por un desequilibrio entre los factores secretores e inhibidores de la secreción de la prolactina.

Los resultados de nuestro estudio apoyan los datos previos de que de todos los dominios cognitivos, la velocidad de procesamiento es el primer dominio afectado en las fases tempranas de los trastornos psicóticos (Dickinson et al., 2007) y se cree que media entre los síntomas cognitivos y la funcionalidad en la esquizofrenia (Ojeda et al., 2008). Además, la disfunción cognitiva es uno de los factores clínicos más asociados a la transición a la psicosis en los individuos EMAR (Riecher-Rossler et al., 2009). Aunque tanto la disfunción de la velocidad de procesamiento como la hiperprolactinemia son factores de riesgo conocidos para desarrollar un trastorno psicótico en pacientes EMAR, aun no se ha estudiado si estos factores son independientes o no en la relación con el riesgo de psicosis.

Los mecanismos por el que la hiperprolactinemia podría repercutir en el rendimiento cognitivo son aun desconocidos. Por un lado, existe la posibilidad de que la prolactina actúe directamente sobre el SNC provocando alteraciones en los procesos cognitivos. En modelos animales hay evidencia de que la prolactina potencia la liberación de dopamina en el estriado tanto in vitro como in vivo (Jin-Chung Chen & Ramirez, 1988; Laping & Ramirez, 1988; Perkins & Westfall, 1978). Los receptores D2 del estriado son importantes en la expresión de los receptores D1 y modulan procesos cognitivos y motores (Stelzel, Fiebach, Cools, Tafazoli, & D'Esposito, 2013; van Holstein et al., 2011) junto con los receptores D1 y D2 de la corteza prefrontal (Durstewitz & Seamans, 2008; Takahashi, 2013). Por otro lado, la relación entre los niveles de prolactina y la afectación cognitiva podría explicarse por un mecanismo indirecto a través del hipogonadismo provocado por la hiperprolactinemia (Castanho et al., 2014). La prolactina inhibe la secreción de GnHR hipotalámica, provocando una disminución de la secreción de LH y FSH por la glándula hipofisaria, que a su vez reduce la secreción de esteroides sexuales por parte de las gónadas. Existe evidencia de que los esteroides sexuales son hormonas importantes para los procesos cognitivos (Wolf & Kirschbaum, 2002) y modulan la cognición en los pacientes con esquizofrenia, tanto en hombres (Moore et al., 2013) como en mujeres (Huerta-Ramos et al., 2014). Además de por este posible mecanismo, es importante estudiar si existen diferencias de género entre la relación de los niveles de prolactina y rendimiento cognitivo, ya que la prolactina y el cortisol son ambas hormonas que aumentan con el estrés (Armario et al., 1996; A. K. Lennartsson & Jonsdottir, 2011), y también se han documentado diferencias de género en la asociación entre la respuesta del cortisol al despertar (CAR) y tareas cognitivas en individuos con una psicosis incipiente (Labad et al., 2016). Por todo ello, en el siguiente trabajo se estudiaron las diferencias de género en la relación de los niveles de prolactina y rendimiento cognitivo controlando variables hormonales como el cortisol y las hormonas sexuales.

En el tercer estudio que presentamos en este trabajo, se observaron diferencias de género en la relación entre los niveles de prolactina y la afectación cognitiva: en hombres los niveles de prolactina se asociaron a un peor rendimiento cognitivo en la mayoría de dominios cognitivos, mientras que en mujeres sólo se observó un peor rendimiento en uno de los 10 tests de la

batería cognitiva MCCB. Se estudió la posible contribución del cortisol y hormonas sexuales en esta relación, pero en nuestra muestra no observamos que la relación entre los niveles de prolactina y rendimiento cognitivo se expliquen por las hormonas sexuales ni por hormonas del eje HPA.

Los estudios previos analizando la relación entre los niveles de prolactina y rendimiento cognitivo en pacientes con psicosis presentan unas limitaciones metodológicas, ya que los pacientes requieren estar bajo tratamiento antipsicótico debido a la enfermedad mental, que además de poder aumentar los niveles de prolactina a través del bloqueo D2 en la vía tuberoinfundibular también pueden tener un efecto negativo sobre la capacidad cognitiva de los pacientes por el bloqueo D2 en otras áreas cerebrales como el estriado y córtex prefrontal (Sakurai et al., 2013). Para resolver este problema metodológico, una aproximación alternativa es demostrar la relación entre los niveles de prolactina y el rendimiento cognitivo en personas con hiperprolactinemia por un prolactinoma, que no tengan ninguna enfermedad mental y no estan recibiendo fármacos que puedan aumentar los niveles de prolactina, tal y como se realizó en un trabajo de Bala et al. publicado recientemente (Bala et al., 2016). Una vía indirecta de explorar el potencial rol de la prolactina en los procesos cognitivos es demostrar que la reducción de los niveles de prolactina con agonistas dopaminérgicos comporta una mejoría de la funcionalidad cognitiva. En el cuarto trabajo de esta tesis se explora el rendimiento cognitivo de pacientes afectos de un prolactinoma antes y después de recibir tratamiento con agonistas dopaminérgicos (cabergolina), tratamiento que habitualmente se da en estos casos para reducir los niveles de prolactina. Se trata de una serie de casos, en la que observamos que la reducción de los niveles de prolactina comportó una mejoría del rendimiento cognitivo en diversos dominios cognitivos.

Como la dopamina inhibe la secreción de prolactina, los agonistas dopaminérgicos son fármacos candidatos que podría disminuir los niveles de prolactina y mejorar las funciones cognitivas de los pacientes afectos de trastornos psicóticos. La cabergolina es un potente agonista dopaminérgico D2 y débil agonista D1 que atraviesa la barrera hemato-encefálica y que es efectivo para disminuir los niveles de prolactina, tratamiento de elección para los prolactinomas (Melmed et al., 2011). Es un fármaco que podría mejorar el rendimiento cognitivo por varios mecanismos. El primero por su efecto agonista D2 en los receptores del estriado, que modulan los procesos cognitivos y aumentan la expresión de receptores D1 (Stelzel et al., 2013). Segundo, el agonismo D1 y D2 en la corteza prefrontal podría contribuir a mejorar el rendimiento cognitivo en los dominios asociados a la actividad de la corteza prefrontal (funciones ejecutivas y memoria de trabajo) (Puig & Miller, 2012). Por último, por la reducción de los niveles de prolactina por su agonismo D2 en la via tuberoinfundibular. Creemos que este último mecanismo es el responsable de explicar la mejoría cognitiva observada en nuestro estudio con la cabergolina, ya que los pacientes con niveles basales más elevados de prolactina fueron los que más mejoraron el rendimiento cognitivo en los dominios cognitivos que implican el córtex prefrontal (la velocidad de procesamiento y el razonamiento y resolución de problemas). Si estos resultados se replican en estudios futuros, los agonistas dopaminérgicos podrían ser considerados fármacos candidatos para mejorar la cognición por sus acciones en los niveles de prolactina. Esta estrategia farmacológica para mejorar la cognición en pacientes con una psicosis sería muy novedosa, ya que a pesar de los múltiples

esfuerzos realizados hasta el momento las estrategias farmacológicas procognitivas en pacientes con enfermedades psicóticas son muy escasas.

Un potencial problema en tratar con cabergolina los pacientes afectos de un trastorno psicótico es el riesgo de empeorar la sintomatología psicótica o de desencadenar una recaída debido al agonismo D2 en la vía mesolímbica (Chang, Chen, & Lu, 2008). Sin embargo, ensayos clínicos llevados a cabo en pacientes con psicosis han demostrado reducciones de los niveles de prolactina sin un empeoramiento de los síntomas psicóticos (Cavallaro, Cocchi, Angelone, Lattuada, & Smeraldi, 2004; Coronas, Cobo, Gimenez-Palop, Ortega, & Marquez, 2012; Kalkavoura et al., 2013). Estos estudios coinciden que es una estrategia segura con menor riesgo de descompensación psicótica del que se podría esperar según los estudios iniciales, y que es efectivo para reducir los niveles de prolactina usando a dosis bajas de cabergolina (0.25-0.5mg/semana).

Los estudios que conforman esta tesis doctoral tienen limitaciones que hay que mencionar. Hay dos series de casos prospectivos (trabajos 1 y 4) en que el tamaño de la muestra es pequeño y se han realizado en condiciones pragmáticas, por lo que el ciego no era posible. El periodo de seguimiento fue relativamente corto sobre todo en el primer estudio (3 meses), aspecto que podría ser relevante a la hora de detectar diferencias en la funcionalidad sexual. En el cuarto estudio, las pruebas neuropsicológicas se realizaron 2 veces a cada paciente, pudiendo haber un efecto retest. Sin embargo, para minimizar esta limitación las evaluaciones se espaciaron más de 6 meses y se cambiaron las versiones de aquellas pruebas que podrían tener un efecto aprendizaje. Los estudios 2 y 3 son transversales, por lo que no permiten inferir causalidad. En el segundo trabajo se observó la relación entre los niveles de prolactina y cognición controlando por variables confusoras como el tratamiento con psicofármacos, psicopatología, uso de sustancias y niveles de cortisol, pero no se controlaron las hormonas sexuales, ya que el tamaño de la muestra no permitía el análisis estratificado por sexo. Este aspecto se solucionó en el tercer trabajo, ya que la muestra era más amplia y permitía analizar los dos grupos por separado.

En conclusión, los datos aportados por esta tesis doctoral apuntan a que los niveles elevados de prolactina en pacientes con una psicosis deberían de ser considerados como un potencial factor perjudicial para las capacidades cognitivas, pudiendo contribuir negativamente a la calidad de vida de estos pacientes. Son necesarios futuros estudios que investiguen las bases neurobiológicas de dicha asociación y que aporten un mayor conocimiento sobre la reversibilidad estas alteraciones cognitivas. Una línea de investigación interesante podría evaluar los cambios cognitivos en casos de hiperprolactinemias de corta duración y compararlos con hiperprolactinemias de larga evolución, intentando esclarecer si los efectos perjudiciales se podrían minimizar con una detección y un tratamiento precoz de la hiperprolactinemia en pacientes con una psicosis.

CONCLUSIONES

6. CONCLUSIONES

6.1. El cambio de risperidona inyectable de larga duración a paliperidona palmitato comporta una reducción de los niveles de prolactina y una mejoría en la funcionalidad de los pacientes con un trastorno psicótico.

6.2. Los niveles de prolactina se asocian negativamente al rendimiento cognitivo de los pacientes con una psicosis, concretamente en el dominio de velocidad de procesamiento. Los niveles de prolactina y las dosis de benzodiazepinas actúan como mediadores en la relación entre el tratamiento antipsicótico con risperidona o paliperidona y la velocidad de procesamiento.

6.3. Existen diferencias de género en la afectación de los niveles de prolactina en el rendimiento cognitivo, siendo mayor la afectación en hombres que en mujeres. Esta afectación es independiente de los niveles de hormonas sexuales o de los niveles de cortisol.

6.4. La reducción de los niveles de prolactina con agonistas dopaminérgicos (cabergolina) en pacientes con hiperprolactinemia secundaria un prolactinoma comporta una mejoría en el rendimiento cognitivo en diferentes dominios cognitivos.

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7. REFERENCIAS

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ARTÍCULOS

Changes in prolactin levels and sexual function in young psychotic patients after switching from long-acting injectable risperidone to paliperidone palmitate

Itziar Montalvo, Laura Ortega, Xavi López, Montse Solé, Rosa Monseny, Joan Franch, Elisabet Vilella and Javier Labad

Hyperprolactinaemia is a significant side effect of antipsychotic medications and may cause sexual dysfunction. The aim of our study was to assess the effect of switching from long-acting injectable (LAI) risperidone to paliperidone palmitate (PP) on sexual function and prolactin levels in patients with psychosis. We carried out a prospective observational study during a 3-month period that involved 11 patients with psychosis treated with risperidone-LAI who suffered from hyperprolactinaemia and who were then switched to PP. Two assessments were completed: the first one before the switch and the second one 3 months after the switch. These assessments measured sexual function using the Arizona Sexual Experience Scale and assessed prolactin levels. Our results showed a significant decrease in serum prolactin levels ($P=0.041$). We observed a four-fold reduction in clinically significant sexual dysfunction that is suggestive of benefit, although the sample size is too small to be sure. Our study suggests that prolactin levels seem to decrease after switching from risperidone-LAI to PP in patients with a psychotic disorder. *Int Clin Psychopharmacol* **28:46–49**

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Keywords: long-acting injectable risperidone, paliperidone palmitate, prolactin, psychotic disorder, sexual function

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Introduction

Schizophrenia is a chronic psychiatric disorder associated with high noncompliance and discontinuation rates. Poor adherence to treatment guidelines increases the risk for relapse and both clinical and functional deterioration. Long-acting injectable (LAI) formulations of antipsychotics have been developed to increase compliance and to simplify the medication regimen. Risperidone-LAI was the first atypical antipsychotic drug with an LAI formulation used as a biweekly injection for the treatment of schizophrenia. Paliperidone palmitate (PP) is a recently developed LAI atypical antipsychotic that is hydrolysed to paliperidone (9-hydroxyrisperidone), the primary active metabolite of risperidone. It is administered once a month. There is no consensus on whether both LAI formulations differ in terms of efficacy, functionality or side effects (Nussbaum and Stroup, 2012).

A significant side effect of risperidone-LAI and PP is hyperprolactinaemia, which may cause sexual dysfunction. This side effect is an important cause of drug discontinuation, mainly in young patients (Yuan *et al.*, 2008). There is limited information on whether these two LAI formulations differ in terms of hyperprolactinaemia or sexual dysfunction. A few studies have compared the rates of hyperprolactinaemia between these two compounds, with contradictory findings, as some trials favour risperidone-LAI, whereas others favour PP (Nussbaum and Stroup, 2012). There are no studies addressing whether the switch from risperidone-LAI to PP leads to an improvement in prolactin levels or sexual function. In clinical practices, some patients are switched from risperidone-LAI to PP because of the benefits of a once-monthly administration (instead of a biweekly administration for risperidone-LAI), which results in increased convenience for the patient and improved quality of life (Pandina *et al.*, 2011). The main aim of our study was to assess whether the switch from risperidone-LAI to PP was followed by an improvement in prolactin levels or sexual function. Because there are no previous studies exploring this subject, we have designed a prospective, observational and pragmatic case series study.

Materials and methods

Participants

We studied 11 patients with a psychotic disorder ($n=9$ schizophrenia, one schizoaffective, one psychosis not otherwise specified) who attended the Early Psychosis Programme from Reus (HPU Institut Pere Mata, Spain) and who were switched from risperidone-LAI to PP. The 11 patients fulfilled the following inclusion criteria: (a) hyperprolactinaemia (defined as prolactin levels greater than 375 mIU/l for men and 632 mIU/l for women), (b) being treated with risperidone-LAI for at least the previous 6 months and (c) not having changed antipsychotic treatment (neither

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changes in antipsychotic doses nor the introduction of another oral antipsychotic) during the last 3 months. The dose conversion when switching from risperidone-LAI to PP was determined according to the technical specifications of the product, with the monthly paliperidone dose being double the fortnightly risperidone dose.

Our study was based on routine clinical practice and did not receive any industry support. Ethical approval was obtained from the institutional review board and all participants provided written informed consent.

Clinical assessment

A clinical assessment of psychopathological status was carried out at baseline and 3 months after the switch. The Positive and Negative Syndrome Scale (Kay *et al.*, 1990) was used to assess positive, negative and general psychotic symptoms. The Calgary Depression Scale (Addington, 1990) was administered to rate depressive symptoms. The Arizona Sexual Experiences Scale (ASEX) (Mcgahuey *et al.*, 2000) was used to assess sexual function. This scale is a five-item (scored from 1 to 6), self-administered scale that yields a total score ranging from 5 to 30, with higher scores indicating increased sexual dysfunction. A total score greater than 18, a score of at least 5 on any single item or any three items with individual scores of at least 4 is indicative of clinically significant sexual dysfunction.

Psychopharmacological treatment at baseline and at 3 months was assessed by a semistructured interview. There were no changes in antipsychotic treatment during the follow-up.

Prolactin and obesity measures

Two fasting blood samples (baseline and 3 months after switch) were obtained to determine the plasma prolactin levels. Prolactin concentrations were determined using a chemiluminescence immunoassay. We also obtained anthropometric data at both visits. BMI was calculated

Table 1 Demographic and clinical characteristics of the sample at baseline and 3 months after the switch from risperidone long-acting injectable to paliperidone palmitate

Case number	Sex	Age (years)	Other treatments	Assessment time	LAI dose[a]	Prolactin (mIU/l)	ASEX	CSSD	PANSS-P	PANSS-N	PANSS-G	CDS
1	M	29	Aripiprazole, clonazepam	Baseline	37.5	655	29	Yes	8	18	29	3
				3 months	75	930	30	Yes	8	15	26	3
2	F	30	Valproate, biperden	Baseline	37.5	4042	16	No	11	15	25	3
				3 months	75	3018	16	No	11	16	28	1
3	M	23	Lithium, olanzapine	Baseline	50	943	19	Yes	7	19	22	0
				3 months	100	282	14	No	7	19	24	0
4	M	39	Biperden	Baseline	75	738	23	Yes	9	15	23	6
				3 months	150	590	15	No	7	11	19	0
5	M	27	None	Baseline	75	952	15	Yes	16	11	29	0
				3 months	150	599	14	No	13	11	24	0
6	F	22	Clozapine, biperden	Baseline	37.5	1861	15	No	17	13	29	0
				3 months	75	731	15	No	8	12	23	0
7	M	28	None	Baseline	50	758	15	No	9	11	22	0
				3 months	100	880	15	No	8	12	20	0
8	M	25	Biperden, lorazepam	Baseline	75	502	10	No	10	17	27	0
				3 months	150	301	13	No	11	16	30	1
9	M	19	Oxcarbazepine, quetiapine	Baseline	50	901	14	No	7	7	23	0
				3 months	100	830	12	No	9	7	19	0
10	M	19	Topiramate, sertraline, biperden	Baseline	75	1201	15	No	11	21	34	4
				3 months	150	1138	13	No	9	15	24	0
11	F	31	None	Baseline	37.5	1080	16	No	7	9	18	0
				3 months	75	868	14	No	7	8	17	0
Total												
Baseline												
Mean		26.6			54.5	1239.3*	17.0		10.2	14.2	25.5	1.5
SD		5.9			17.0	996.1	5.1		3.5	4.4	4.5	2.2
3 months												
Mean		–			109.1	924.3*	15.5		8.9	12.9	23.1	0.5
SD		–			34.0	741.5	4.9		2.0	3.6	4.0	0.9

ASEX, Arizona Sexual Experience Scale; CDS, Calgary Depression Scale; CSSD, clinically significant sexual dysfunction; F, female; LAI, long-acting injectable; M, male; PANSS-G, Positive and Negative Syndrome Scale – general score; PANSS-N, Positive and Negative Syndrome Scale – negative score; PANSS-P, Positive and Negative Syndrome Scale – positive score; PP, paliperidone palmitate.
[a]LAI dose refers to risperidone-LAI (mg) at the baseline visit and refers to PP (mg eq) at 3 months.
*$P<0.05$ (Wilcoxon's signed-rank test).

using the following formula: weight (kg) divided by height (m^2).

Statistical analysis

The SPSS version 17.0 software (SPSS Inc., Chicago, Illinois, USA) was used to carry out statistical analyses. The Wilcoxon signed-rank test was used to explore the changes in continuous variables during the study period. The McNemar test was used to explore the changes in clinically significant sexual dysfunction after the switch. A P value less than 0.05 was considered to be significant. R and a ggplot2 package (*http://www.r-project.org/*) were used to plot changes in prolactin from the baseline to the end of the treatment period.

Results

Of all 11 participants, eight (72%) were men. They had a mean age (SD) of 26.6 (5.9) years. The mean (SD) duration of illness was 56.6 (30.1) months, and they were treated with risperidone-LAI for 21.45 (12.5) months. The mean BMI value was 26.5 (4.4) at baseline and 26.2 (4.7) 3 months after the switch. This difference was not significant. The demographic and clinical characteristics for each participant are shown in Table 1.

There was a significant reduction (25.5%) in prolactin levels from baseline over the 3-month assessment period ($P = 0.041$). Those patients with higher prolactin levels at baseline seemed to show a greater reduction (Fig. 1). All three women from our sample (cases #2, #6 and #11 from Table 1) showed a decrease (35.2%) in serum prolactin levels during the follow-up period. None of them had amenorrhoea, and only one participant reported galactorrhoea (case #2 from Table 1) at baseline, which did not disappear 3 months after the switch. In terms of sexual dysfunction, although some cases showed a notable improvement in their ASEX scores (e.g. case #4 from Table 1), the average reduction for all patients was not statistically significant. We found that four out of the 11 cases (36.4%) fulfilled the criteria for clinically significant sexual dysfunction at baseline, and only one (9.1%) fulfilled the criteria after the switch. Although this reduction is suggestive of benefit, with these small numbers, significance testing was uninformative. Interestingly, the patient who continued to fulfil the criteria for clinically significant sexual dysfunction 3 months after the switch (case #1 from Table 1) was the only one who did not show a decrease in serum prolactin levels. In terms of changes in psychopathological status, none of the patients reported worsening of psychotic symptoms or depressive symptoms.

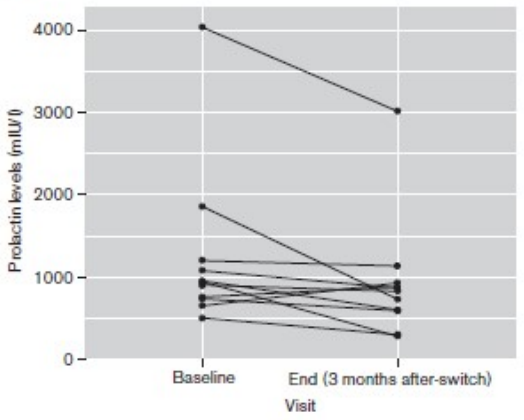
Discussion

In a sample of 11 patients who were switched from risperidone-LAI to PP, we observed an improvement in prolactin levels. To our knowledge, this is the first study to find a reduction in prolactin levels after switching from risperidone-LAI to PP. Several participants reported clinical improvement in sexual function, which can be related to a reduction in prolactin levels as well as improvement in depressive or psychotic symptoms. The majority of cases did not report significant changes in ASEX scores. These findings could be explained by several factors: (a) the duration of the follow-up period (3 months), as it may not be long enough to detect clinical changes after the decrease in prolactin levels; (b) although prolactin levels decreased in most cases, a significant proportion of patients did not have fully normalized prolactin levels at the end of the study; and (c) most patients were taking other psychopharmacological drugs, including oral antipsychotics, antidepressants and/or mood stabilizers, which may have also affected sexual function. None of the patients experienced an increase in psychotic symptoms after the switch, nor did they report severe side effects that required changes in psychopharmacological treatment.

Our results are in contrast with other double-blind studies that have not reported differences in prolactin levels between risperidone-LAI and PP (Pandina *et al.*, 2011). However, these studies are methodologically different because they compare two long-acting formulations but do not assess the switch from risperidone-LAI to PP.

Risperidone-LAI and PP differ in their pharmacokinetics, as PP is excreted renally, with limited hepatic metabolism. We wonder whether this pharmacokinetic difference may explain the greater reduction in prolactin levels after the switch. As we did not determine 9-hydroxyrisperidone levels before and after the switch, we do not know whether changes in prolactin levels could be explained

Fig. 1



Prolactin levels at baseline and 3 months after the switch from risperidone-LAI to paliperidone palmitate in 11 patients with a psychotic disorder. LAI, long-acting injectable.

by changes in 9-hydroxyrisperidone levels because of a different metabolism of risperidone-LAI and PP. It has been suggested that hyperprolactinaemia in patients treated with risperidone-LAI or PP is driven by 9-hydroxyrisperidone and the higher occupancy of D2 at the pituitary level compared with the striatum (Madaan *et al.*, 2011).

Several limitations of our study need to be addressed. We have designed an open-label study under pragmatic conditions; therefore, blinding was not available. Patients received other psychopharmacological treatments, which could limit the potential benefits on sexual function after the switch to PP. Generalization of the results to paliperidone alone is difficult, as only three out of 11 patients were on monotherapy. The follow-up period of 3 months may be insufficient to detect changes in sexual function over time. The sample size is also small, which limits the possibility of comparing prolactin changes in subgroups (e.g. sex differences).

The main strength of our study is that it is the first to assess the potential changes in prolactin levels and sexual function after switching from risperidone-LAI to PP. Our results should be considered preliminary. Further prospective studies that extend the duration of the follow-up period are required to confirm whether the reduction in prolactin levels is followed by an improvement in sexual function.

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Conflicts of interest

There are no conflicts of interest.

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PLOS | ONE

Increased Prolactin Levels Are Associated with Impaired Processing Speed in Subjects with Early Psychosis

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Abstract

Hyperprolactinaemia, a common side effect of some antipsychotic drugs, is also present in drug-naïve psychotic patients and subjects at risk for psychosis. Recent studies in non-psychiatric populations suggest that increased prolactin may have negative effects on cognition. The aim of our study was to explore whether high plasma prolactin levels are associated with poorer cognitive functioning in subjects with early psychoses. We studied 107 participants: 29 healthy subjects and 78 subjects with an early psychosis (55 psychotic disorders with <3 years of illness, 23 high-risk subjects). Cognitive assessment was performed with the MATRICS Cognitive Consensus Cognitive Battery, and prolactin levels were determined as well as total cortisol levels in plasma. Psychopathological status was assessed and the use of psychopharmacological treatments (antipsychotics, antidepressants, benzodiazepines) recorded. Prolactin levels were negatively associated with cognitive performance in processing speed, in patients with a psychotic disorder and high-risk subjects. In the latter group, increased prolactin levels were also associated with impaired reasoning and problem solving and poorer general cognition. In a multiple linear regression analysis conducted in both high-risk and psychotic patients, controlling for potential confounders, prolactin and benzodiazepines were independently related to poorer cognitive performance in the speed of processing domain. A mediation analysis showed that both prolactin and benzodiazepine treatment act as mediators of the relationship between risperidone/paliperidone treatment and speed of processing. These results suggest that increased prolactin levels are associated with impaired processing speed in early psychosis. If these results are confirmed in future studies, strategies targeting reduction of prolactin levels may improve cognition in this population.

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Introduction

Hyperprolactinaemia is a common condition in subjects with a psychotic disorder. As dopamine is the main prolactin inhibiting factor, hyperprolactinaemia is a common consequence of D2 receptor blockade in the tuberoinfundibular dopaminergic pathway [1,2] by antipsychotic drugs. However, increased prolactin levels have also been reported in drug-naïve patients with a first psychotic episode or at risk mental states [3–5]. The mechanisms that mediate the increase of prolactin levels in psychotic subjects not receiving antipsychotic drugs are poorly understood. Moreover, prolactin levels may be increased by stress [6], which may in turn contribute to the increased prolactin levels in drug-naïve psychotic populations.

The most studied consequences of hyperprolactinaemia in psychotic subjects are amenorrhoea, galactorrhoea, sexual impairment and infertility [7,8]. A recent study conducted in non-psychiatric population suggests that increased prolactin may have negative effects on cognition [9]. This prospective study examined the cognitive changes during late pregnancy and the early postpartum period, and their possible association with fluctuating hormone levels (estradiol, progesterone, testosterone, prolactin and cortisol). A total of 55 pregnant women and 21 controls were studied, with a neuropsychological assessment during the third trimester of pregnancy and retest during the early postpartum period. They concluded that very high and very low levels of cortisol were associated with poorer performance in certain cognitive domains, but the most novel finding was that they found a negative linear association between prolactin levels and executive function scores, suggesting that higher levels of prolactin are detrimental to executive function abilities. Animal studies also support a role for prolactin in the modulation of non-spatial cognitive tasks [10]. In this recent study, the induction of hyperprolactinaemia in male rats receiving pituitary grafts was associated with impaired object recognition. Other studies have

Table 1. Clinical and cognitive variables by diagnostic groups.

	Healthy subjects (HS) N = 29	High-Risk (HR) N = 23	Psychotic disorder (PD) N = 55	P value[†]
Age (years)	26.4 (4.3)	22.5 (4.3)	24.5 (5.3)	0.019[b]
Female gender	14 (48.3)	5 (21.7)	25 (45.5)	0.100
PANSS positive	–	9.9 (2.8)	10.3 (3.6)	0.094
PANSS negative	–	13.2 (6.2)	14.4 (5.5)	0.870
PANSS general	–	28 (7.4)	25.6 (7.4)	0.180
Calgary Depression Scale	–	3.8 (0.8)	3.3 (0.4)	0.555
Plasma prolactin (µg/L)	15.5 (6.3)	27.5 (29.0)	44.4 (40.7)	<0.001[a]
Plasma total cortisol (µg/dL)	17.7 (6.1)	19.8 (1.5)	18.8 (5.5)	0.468
MCCB cognitive domains (T-scores)				
Speed of processing	50.8 (9.9)	41.4 (11.4)	34.5 (12.6)	<0.001[a,b]
Attention and vigilance	44.9 (9.4)	37.0 (10.1)	36.8 (9.5)	0.001[a,b]
Working memory	44.6 (9.6)	37.0 (8.2)	36.7 (9.1)	0.002[a,b]
Verbal learning	48.9 (9.8)	43.9 (7.7)	41.9 (7.9)	<0.001[a]
Visual learning	50.5 (6.2)	44.9 (9.3)	37.3 (12.3)	<0.001[a,b]
Reasoning and problem solving	49.0 (8.5)	44.5 (10.2)	41.8 (9.7)	0.006[a]
Social cognition	52.1 (10.6)	47.4 (11.4)	39.5 (11.1)	<0.001[a,b]
Composite factor (global)	47.6 (8.6)	37.3 (7.5)	32.0 (9.4)	<0.001[a,b]
Psychopharmacological treatment[‡]				
Antipsychotic treatment				
None	29 (100)	17 (73.9)	10 (18.2)	<0.001
Risperidone/Paliperidone in monotherapy	0 (0)	3 (13.0)	17 (30.9)	
Olanzapine/Quetiapine in monotherapy	0(0)	0 (0)	14 (25.5)	
Aripiprazole in monotherapy	0 (0)	2 (8.7)	6 (10.9)	
Polytherapy	0 (0)	1 (4.3)	8 (14.5)	
Benzodiazepine treatment	0 (0)	3 (13.0)	12 (21.8)	0.370
Biperiden treatment	0 (0)	1 (4.3)	7 (12.7)	0.266
Antidepressant treatment	0 (0)	14 (60.9)	8 (14.5)	<0.001
Substance use				
Tobacco (cigarettes/day)	1.8 (4.6)	3.3 (6.1)	9.4 (9.9)	<0.001[a,c]
Cannabis (joint/day)	0 (0)	0.4 (1.5)	1.9 (4.6)	0.035
Alcohol (standard units/day)	0.1 (0.4)	0 (0)	0.8 (2.4)	0.097

Data are mean (SD) or N (%). Four participants (3 PD, 1 HR) had missing data for prolactin analyses.
Abbreviation: PANSS = Positive and Negative Syndrome Scale; MCCB = MATRICS Consensus Cognitive Battery.
[†]One-way ANOVA was used to compare continuous data among groups. Chi-square test was used to compare categorical data among groups.
[‡]Psychopharmacologic treatment was compared between PD and HR groups (HS were excluded in the comparison).
Significant ANOVA post-hoc analyses (with Bonferroni adjustment) are highlighted: [a] HS vs PD, [b]HS vs HR, [c]PD vs HR.
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reported an association between low gonadal steroid levels and poorer cognitive abilities [11,12]. To our knowledge, there are no studies addressing whether high prolactin levels often found in psychotic patients can contribute to the cognitive impairment of patients with a psychotic disorder.

Subjects with schizophrenia show mild to moderate cognitive impairment, and perform an average of 1.5 to 2 standard deviations below population norms [13,14]. These cognitive alterations appear before the onset of the first psychotic episode [15,16] and are an important determinant of functional outcome [17]. Early intervention in psychosis is a novel approach to mental health care that includes treatment of both psychotic disorders at first years after the onset (defined as a critical period in the first 3 to 5 years after the onset) as well as subjects with prodromal symptoms who are at risk for psychosis (high-risk, HR). Early intervention services have been developed to reduce the duration of untreated psychosis, a variable that has been associated with a poorer prognosis of the illness and poorer cognitive performance [18].

Some studies have shown that atypical antipsychotic drugs have a better cognitive profile than typicals [19–22], but this remains controversial. Antipsychotic drugs differ in their affinity at muscarinic receptors, with detrimental effects on cognitive abilities in those antipsychotics with higher anticholinergic activity [23]. However, whether different antipsychotic medications exert any benefits on cognitive performance remains questionable [24,25]. Based on the degree of blockade of D2 receptors at this pathway, the risk of hyperprolactinaemia differs among different antipsychotics, being greater for typical antipsychotics and some atypicals including risperidone and paliperidone [26,27]. Also, concomitant

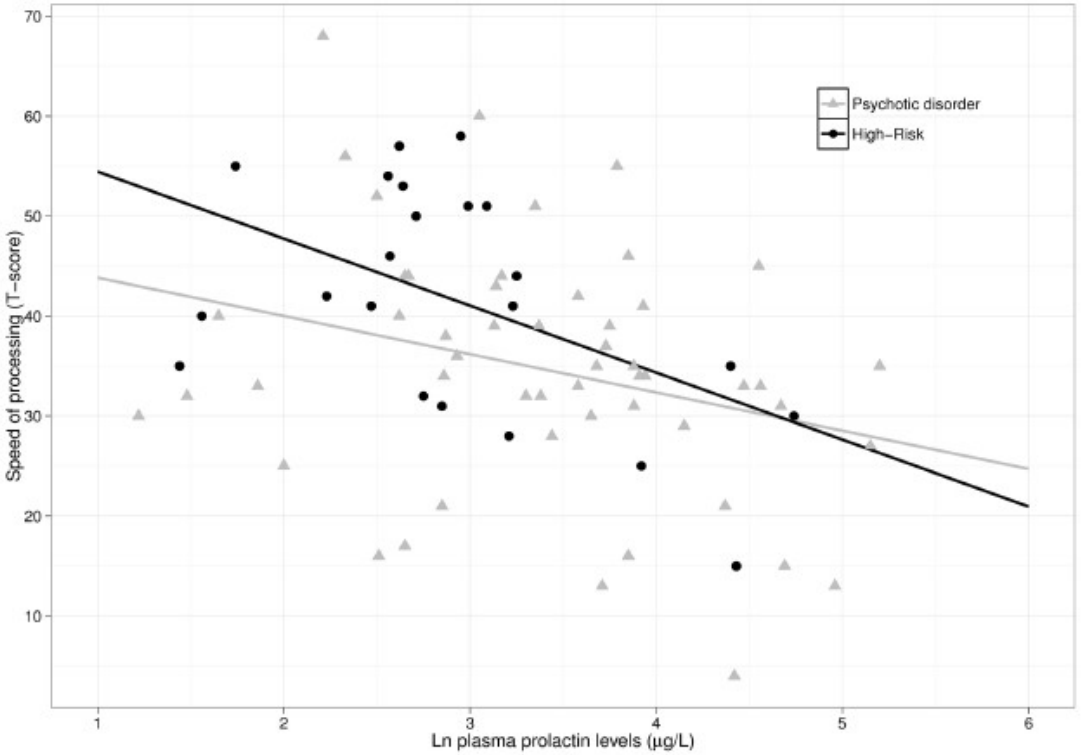

Figure 1. Scatter plot of the relationship between prolactin levels and speed of processing T-scores between diagnostic groups (psychotic disorder vs high-risk).
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treatment with anticholinergics or benzodiazepines can also have deleterious effects on cognition [28–30].

The main aim of our study was to explore whether prolactin levels are associated with poorer cognitive functioning in subjects with early psychoses, including both first episode of psychosis and high-risk subjects. We hypothesized that increased prolactin is associated with poorer cognitive performance in subjects with early psychoses. We also aimed to determine whether prolactin may mediate the relationship between antipsychotic drugs and cognition while adjusting for other potential contributors (e.g. adjunctive treatment with benzodiazepines or anticholinergic drugs).

Materials and Methods

Ethics Statement

All procedures are in accordance with the Declaration of Helsinki. Ethical approval was obtained from the Committee for Ethical Clinical Investigation of the *Hospital Sant Joan de Reus*. The capacity of the patients to provide informed consent was evaluated and confirmed by a psychiatrist. After complete description of the study to the subjects, written informed consent was obtained from all participants (or their guardians if the patients had a compromised capacity). All potential participants who declined to participate or otherwise did not participate were not disadvantaged in any way by not participating in the study.

Participants

We studied 78 outpatients with an early psychosis, aged between 18 and 35 years old, attending the Early Psychosis Program from Reus (HPU Institut Pere Mata, Spain). We included a control group of 29 healthy subjects (HS) that were recruited among patients' friends and non-genetic relatives, and screened to rule out past or current history of psychiatric disorder.

Early psychosis patients were divided into two different clinical populations: 1) High risk for psychosis (HR, subjects with prodromal psychotic symptoms fulfilling set criteria for At Risk Mental State [31], N = 23); 2) Psychotic Disorder with less than 3 years from the onset of the illness (PD, N = 55). DSM-IV diagnoses for the PD group were: schizophreniform disorder (N = 11), schizophrenia (N = 10), schizoaffective disorder (N = 3), psychotic disorder not otherwise specified (N = 31). Exclusion criteria were: pregnancy, mental retardation, severe head injury or neurological disease, active glucocorticoid treatment, language difficulties, visual impairment and alcohol, cocaine or heroin dependence.

Characteristics of Patients

All subjects were assessed with the Schedules for Clinical Assessment in Neuropsychiatry [32]. OPCRIT checklist v.4.0. (available at http://sgdp.iop.kcl.ac.uk/opcrit/) was used to generate DSM-IV diagnoses for psychotic disorders. HR subjects were also assessed with the Comprehensive Assessment of At Risk

Table 2. Correlation between prolactin levels and MCCB cognitive domains (T-scores) and psychopharmacological treatments.

	Healthy subjects (N = 29) Prolactin*		High-Risk (N = 23) Prolactin*		Psychotic disorder (N = 55) Prolactin*	
	r	P	r	P	r	P
Speed of processing	−0.023	0.906	−0.498	0.018	−0.286	0.040
Attention and vigilance	0.040	0.838	−0.128	0.569	−0.070	0.625
Working memory	−0.043	0.826	−0.150	0.504	0.119	0.400
Verbal learning	−0.302	0.111	−0.236	0.290	−0.037	0.795
Visual learning	−0.159	0.411	−0.303	0.181	0.016	0.910
Reasoning and problem solving	0.083	0.670	−0.449	0.036	0.001	0.992
Social cognition	0.191	0.321	0.212	0.370	0.119	0.420
Composite (global)	−0.042	0.830	−0.458	0.049	0.137	0.369
Risperidone/Paliperidone dose†			0.372	0.088	0.479	<0.001
Olanzapine/Clozapine/Quetiapine dose†			0.074	0.744	0.131	0.355
Aripiprazole dose†			−0.263	0.237	−0.203	0.149
Benzodiazepine dose‡			−0.049	0.828	0.270	0.053
Biperiden dose (mg/day)			0.389	0.074	0.122	0.389
Antidepressant dose§			0.135	0.549	−0.030	0.831

Stratified analysis by diagnostic group.
* Log transformed (ln) values of prolactin.
†In equivalents of chlorpromazine (mg/day).
‡In equivalents of diazepam (mg/day).
§In equivalents of fluoxetine (mg/day).
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Mental States, to ensure that subjects met criteria for any of the three HR groups defined by At Risk Mental State criteria [31].

Socio-demographic and clinical variables related to psychosis (age at onset, antipsychotic treatment, substance use) were assessed by semistructured interview. Tobacco, cannabis and alcohol consumption were registered in cigarettes/day, joints/day and standard units/day respectively. Positive and Negative Symptom Scale [33] was administered to explore positive, negative and overall psychotic symptoms. Calgary Depression Scale [34] was administered to explore depressive symptoms. These scales were administered the same day of the cognitive assessment.

Psychopharmacological treatment at neuropsychological assessment was registered. Of all 78 patients, 27 (34.6%) were not taking antipsychotics, 42 (53.8%) were on antipsychotic monotherapy (risperidone [n = 20], paliperidone [n = 5], olanzapine [n = 13], quetiapine [n = 1], aripiprazole [n = 8]) and 9 (11.5%) were on polytherapy.

Each antipsychotic dose was transformed into chlorpromazine equivalents in mg/day [35]. We recoded chlorpromazine equivalent doses into three different variables taking into account the mechanism of action of each antipsychotic and its effects on prolactin and anticholinergic activity: 1) risperidone/paliperidone (prolactin elevating without anticholinergic activity), 2) olanzapine/quetiapine/clozapine (prolactin sparing with anticholinergic activity) and 3) aripiprazole (prolactin sparing without anticholinergic activity). Benzodiazepine treatment was registered in diazepam equivalent doses. Biperiden dose was registered in mg/day. Antidepressant treatment was registered as fluoxetine equivalents in mg/day.

Cognitive Assessment

The MATRICS Consensus Cognitive Battery (MCCB) was administered to explore neuropsychological functioning [36]. This cognitive battery has demonstrated practicality of administration, high test-retest reliability, small practice effects, small ceiling effects and relationship to functional outcome. The MCCB contains 10 tests to measure cognitive performance in 7 cognitive domains: speed processing, attention/vigilance, working memory, verbal learning, visual learning, reasoning and problem solving, and social cognition (Table S1). A composite Score is obtained, which combines the individual scores of the 10 tests and scores them on a normative scale to derive a T-score, where the mean is 50 and a standard deviation is 10 for the composite. Normative data for the MCCB has been obtained in Spain [37], suggesting that significant age, gender, and education effects are comparable to those effects described for the original standardized English version in the U.S. All neuropsychological assessments were performed in the morning, with starting times between 9 h and 12 h. Cognitive testing in PD was assessed when they were clinically stable.

Hormonal Measures

A fasting blood sample was obtained in the morning between 8:30 h and 9:30 h in resting conditions, to determine unstimulated plasma prolactin and total cortisol levels. Participants were told to avoid stressful activities (sports, physical exercise) or breast stimulation in the 12 hours prior to blood sampling. Prolactin and cortisol concentrations were measured using the Maglumi 2000 Analyzer chemiluminescence immunoassay system (SNIBE Co, Ltd, Guandong, China). The sensitivity of the prolactin assay was 1.77 μg/L.

Statistical Analysis

The SPSS version 19.0 software (SPSS Inc., Chicago, Illinois, USA) was used to carry out the statistical analyses. As prolactin levels, PANSS and CDS scores were skewed, we log transformed (ln) these variables to reduce skewness. Chi-square tests and one-way ANOVA were used to compare categorical and continuous

Table 3. Results of the multiple linear regression analysis exploring the relationship between prolactin levels and speed of processing in subjects with early psychoses.

	Model 1 unadjusted		Model 2+ antipsychotics		Model 3+ other treatments		Model 4+ psychotic symptoms, substance use and cortisol	
R^2 of each model	**0.140**		**0.214**		**0.300**		**0.434**	
	β	P	β	P	β	P	β	P
Prolactin (ln)	−0.374	0.001	−0.256	0.044	−0.245	0.046	−0.283	0.022
Risperidone/Paliperidone dose*			−0.243	0.042	−0.139	0.311	−0.003	0.986
Olanzapine/Quetiapine/Clozapine dose*			−0.140	0.210	0.037	0.769	0.131	0.297
Aripiprazole dose*			−0.152	0.176	−0.146	0.168	−0.072	0.497
Benzodiazepine treatment‡					−0.353	0.006	−0.324	0.015
Biperiden (mg/day)					−0.045	0.699	−0.034	0.773
Antidepressant treatment†					0.066	0.547	0.067	0.537
PANSS - positive subscore (ln)							−0.192	0.143
PANSS – negative subscore (ln)							−0.283	0.035
PANSS – general subscore (ln)							0.103	0.434
Tobacco (cigarettes/day)							−0.129	0.316
Cannabis (joints/day)							0.060	0.610
Alcohol (standard units/day)							0.042	0.727
Cortisol (μg/dL)							0.029	0.794

T-score (adjusted for age, gender and education level) in the speed of processing MCCB domain was considered the dependent variable.
Abbreviations: PANSS = Positive and Negative Syndrome Scale; β = Standardized beta coefficient; MCCB = MATRICS Consensus Cognitive Battery.
* ln chlorpromazine equivalents, mg/day.
‡ln diazepam equivalents, mg/day.
†ln fluoxetine equivalents, mg/day.
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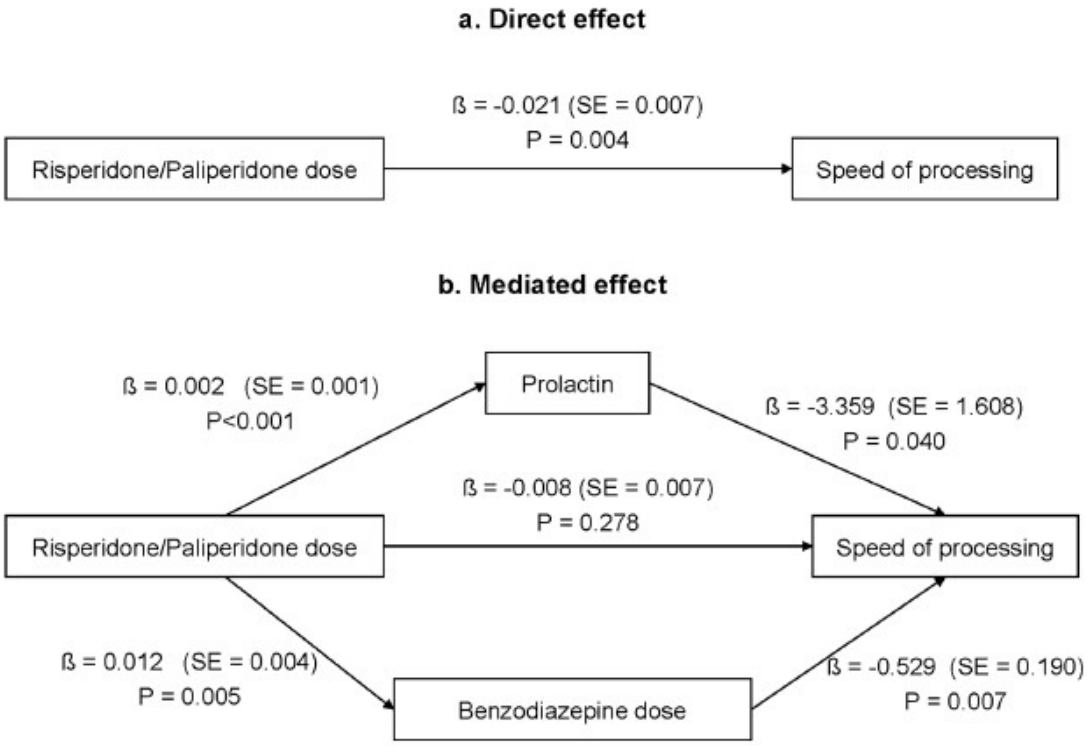

Figure 2. Results of the mediation analysis exploring the relationship between risperidone/paliperidone dose and processing speed in subjects with early psychoses. Log transformed (ln) levels of prolactin were used in the mediation analysis. The mediated effect (b) was adjusted for the following covariates: olanzapine/clozapine/quetiapine dose (β = 0.002, SE = 0.008, P = 0.848), aripiprazole dose (β = −0.016, SE = 0.011, P = 0.151), biperiden dose (β = −0.567, SE = 1.486, P = 0.704) and antidepressant dose (β = 0.048, SE = 0.101, P = 0.638). Abbreviations: β = unstandardized regression coefficient; SE = standard error.
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data between groups. Post-hoc ANOVA analyses were adjusted with a Bonferroni correction. Spearman correlation was used to explore the association between continuous or ordinal variables. Significance was set at $p<0.05$ (two-tailed). For all statistical analyses we used MCCB T-scores corrected for age, gender and education level.

We first divided the sample by diagnostic group (HS, PD and HR). A stratified analysis by diagnostic group was conducted to explore the association between prolactin levels and cognitive measures in each subgroup of participants.

A multiple linear regression analysis was performed in all patients (including both PD and HR subjects) to explore the relationship between plasma prolactin levels (main independent variable) and MCCB cognitive domains (dependent variable) while controlling for covariables such as other psychopharmacological treatments, psychopathological status, smoking and other substance use (cannabis and alcohol) and cortisol.

Furthermore, those MCCB domains that showed a significant association with prolactin in the multivariate analyses were also tested with a mediation analysis to explore whether the effect of antipsychotic treatment on cognition could be mediated by prolactin levels and benzodiazepine treatment. We conducted a mediation analysis according to Baron and Kenny [38] and used bootstrapping to test the indirect effect of mediation [39]. A description of mediation analysis is shown in Box S1.

We used a SPSS macro [40] that allows the inclusion of multiple mediators and covariates. In this mediation analysis, we decided to include risperidone/paliperidone dose as the main independent variable because its elevating effect on prolactin levels. MCCB cognitive T-score (e.g. Speed of Processing) was used as the dependent variable. Two potential mediators were considered: prolactin and benzodiazepine treatment. We included as covariates other antipsychotic drugs, biperiden and antidepressant treatments. Significance of the indirect effects in this model was tested by bootstrapping.

R and ggplot2 package (http://www.r-project.org/) were used to draw scatterplot figures exploring the association between prolactin and MCCB cognitive domains.

Results

Univariate Analyses

Clinical characteristics of the sample by diagnostic group are described in Table 1. As expected, we found that HS performed significantly better than PD in all cognitive domains, and better than HR in most domains (Table 1). There were no significant differences in psychopathological scales between PD and HR. PD

subjects were more frequently treated with antipsychotics, when compared to HR. However, the latter group was more frequently treated with antidepressants.

In the stratified analysis by diagnostic group, prolactin levels were significantly associated with processing speed in both PD and HR subjects (Table 2). In HR subjects, prolactin levels were also related with poorer cognitive performance in reasoning and problem solving, and global cognition. A scatter plot by diagnostic group (PD vs HR) is shown in Figure 1. We also performed another analysis including both HR and PD together (Table S2). In this analysis, prolactin was positively associated with risperidone/paliperidone and benzodiazepine doses and negatively associated with speed of processing.

Multivariate Analyses

In the multivariate analysis conducted in both HR and PD groups, the significant negative association between prolactin and speed of processing was maintained after adjusting for psychopharmacological treatments, smoking and substance use (cannabis and alcohol consumption), severity of psychotic symptoms and cortisol levels (Table 3). As shown in this table, both prolactin and risperidone/paliperidone treatment were related to a poorer processing speed (Model 2). However, when other drugs were included in the equation (Model 3), impaired processing speed was associated with benzodiazepine treatment but not antipsychotic doses. Other MCCB cognitive domains were not associated with prolactin levels in the multiple linear regression analyses (Table S3).

In the mediation analysis, we tested two potential mediators (prolactin and benzodiazepine treatment) in the relationship between risperidone/paliperidone doses and processing speed (Figure 2). In the unadjusted model (a), risperidone/paliperidone treatment was negatively associated with speed of processing. This effect was fully mediated by both prolactin and benzodiazepine treatment (b), as the relationship between antipsychotic treatment and speed of processing lost its significance when these two mediators were included in the equation. In this mediated analysis, other antipsychotics, antidepressants and biperiden were included as covariates, thus the results are adjusted for these psychopharmacological drugs. As a multiple mediation model is analogous to conducting a regression analysis with several predictors testing the total indirect effect of the independent variable (risperidone/paliperidone treatment) on the dependent variable (speed of processing), both prolactin and benzodiazepines are independently associated with speed of processing. The indirect effects of both variables account for all the observed relationship between risperidone/paliperidone treatment and speed of processing. Bootstrap results for indirect effects were significant for both prolactin (95% CI: −0.165 to −0.001) and benzodiazepine treatment (95% CI: −0.167 to −0.002).

Discussion

Our study suggests that increased prolactin levels are associated with impaired processing speed independent of antipsychotic drugs in subjects with early psychosis. In HR subjects only, increased prolactin was also associated with impaired reasoning and problem solving and poorer general cognition. The results of the mediation analysis also showed that the effect of risperidone/paliperidone treatment on speed of processing is mediated by both prolactin levels and benzodiazepine treatment. To our knowledge, this is the first study to highlight prolactin as an important contributor to cognitive impairment in subjects with psychosis.

Regarding speed of processing, our results are consistent with previous studies reporting that processing speed is the first cognitive domain to be affected in psychotic disorders at early stages [41] and in at risk mental states subjects [42]. This cognitive domain, that may be considered a core feature of schizophrenia neurocognitive impairment, is thought to mediate the relationship between cognitive symptoms and functional outcome in schizophrenia [43]. In contrast to other cognitive domains, speed of processing is considered a "system based" domain, reflecting a process of integration and coordination between distributed brain networks [44]. This is in line with the disconnection hypothesis of schizophrenia, which asserts that impaired communication within the brains of schizophrenia patients occurs when there is focal disruption that adversely affects the entire network. Speed of processing deficits may point to aberrant functional connectivity within and between whole brain neural systems, rather than indexing impairment in discrete neural networks [45].

Although antipsychotic drugs are a common cause of hyperprolactinaemia, other studies in drug-naïve patients have also shown increased prolactin levels in PD and HR subjects [3–5]. Interestingly, in our study the relationship between prolactin and processing speed was also found in HR subjects, most of whom were not receiving antipsychotic treatment. Moreover, in the multivariate analyses, the association between prolactin levels and impaired processing speed remained significant after adjusting for psychopharmacological treatments. Prolactin is a hormone that may be raised in stressful situations. We accounted for this by controlling for cortisol levels in the multivariate analysis, and the effect of prolactin on cognition was independent of hypothalamic-pituitary-adrenal axis activity.

Antipsychotic-induced hyperprolactinaemia, which is caused by tuberoinfundibular blockade of D2 receptors, may be reflecting the blockade of D2 receptors in other dopaminergic pathways including the striatum, which causes extrapyramidal symptoms, or the mesocortical pathway, that may be related to worsening in cognitive and negative symptoms. The mediated analysis suggests that the negative effect of risperidone/paliperidone on processing speed is mediated by both prolactin and benzodiazepines. This could be explained by the prolactin-elevating profile of these antipsychotics as well as the induction of extrapyramidal symptoms (e.g. akathysia) that are often treated with benzodiazepines.

Our study suggests that prolactin may be considered as a biomarker that is associated with impaired processing speed in subjects with early psychoses. This finding may have important clinical implications. Further studies are needed to explore whether a reduction in prolactin levels by optimizing psychopharmacological treatment leads to an improvement in processing speed.

The main limitation of our study is the cross-sectional design that does not allow us to infer causality. Further prospective studies may overcome this limitation by repeatedly assessing prolactin levels and cognitive performance over time to explore whether persistent hyperprolactinaemia is a risk factor for cognitive decline in subjects with psychoses. We did not control for other hormones that may affect cognition such as sex steroids. Hyperprolactinaemia inhibits the hypothalamic-pituitary-gonadal axis [7], and hypogonadism secondary to hyperprolactinaemia may contribute to the negative effects of prolactin on cognition. However, in order to control for these variables, larger samples are required because a sex-stratified analysis is necessary (controlling for estradiol in women and testosterone in men).

We designed a pragmatic study with consecutive sampling in an Early Intervention Service. For this reason, the sample of our

study included both HR subjects and psychotic disorders at early stages, and patients were treated with different antipsychotics that were chosen by clinicians based on the clinical routine practice. HR subjects and PD patients exhibited similar PANSS scores. As our Early Intervention Service is an outpatient service, some patients who have been previously admitted to the referral Acute Psychiatric Unit are stabilized before attending our service. Moreover, patients need to be informed of the research project and must sign the informed consent; thus in most cases, PD patients are clinically stable at recruitment. As most PD patients have been treated before entering the study, the PANSS scores reflect the psychopathological state at the neuropsychological assessment (not at the acute phase of the illness). These characteristics could explain why both groups (HR and PD) exhibited similar PANSS scores. Although HR group shares some characteristics with PD group at early stages such as cognitive impairment, only 30% develop psychosis at one year [46]. From our cross-sectional design we do not know whether prolactin could be a biomarker related to the risk of transition to psychosis. Future prospective studies are needed to clarify this question. Finally, the sample of our study was composed by outpatients, and none of whom were receiving first-generation antipsychotics. Thus, our results may not be generalizable to other populations including inpatients, psychotic patients with a longer duration of illness or patients taking typical antipsychotics. In fact, a recent study conducted in patients with chronic schizophrenia showed that switching to aripiprazole led to a decrease in prolactin levels but was not associated with cognitive improvement [47]. Our results should be replicated in other samples to draw definite conclusions.

However, several strengths of our study need to be highlighted: 1) our study is the first to describe the potential role of prolactin on cognition in subjects with psychoses, 2) we have used a standardized neurocognitive battery (MCCB) to assess cognition, 3) the sample included subjects with a short duration of the illness, and 4) we controlled for potential confounders such as concomitant antipsychotic medication (chlorpromazine equivalents) by differentiating antipsychotics depending upon their mechanism of action, as well as controlling for benzodiazepines that have been suggested as moderating factors of processing speed [48], and 5) we also controlled for smoking status, which has been describe to modify prolactin levels [49] and to interfere with cognition in early psychosis patients [50].

Conclusions

In summary, our study suggests that increased prolactin levels are associated with impaired processing speed in early psychosis and that also mediate the negative effects of prolactin elevating antipsychotics on processing speed. If these results are replicated in further studies, hyperprolactinaemia may be considered as a potential contributor to cognitive deterioration in psychotic subjects and strategies targeting reduction of prolactin levels may improve cognition in this population.

Supporting Information

Table S1 MATRICS Consensus Cognitive Battery tests and cognitive domains.
(DOC)

Table S2 Correlations between prolactin levels, psychopharmacological treatment, psychopathological status and MCCB cognitive domains in subjects with early psychosis.
(DOC)

Table S3 Multiple regression analyses exploring the relationship between prolactin levels in plasma and MCCB Cognitive domains in subjects with early psychosis.
(DOC)

Box S1 Explanation of the mediation analysis.
(DOC)

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Author Contributions

Conceived and designed the experiments: JL AGZ RMR SML. Performed the experiments: IM MC JF LO RM. Analyzed the data: JL IM. Contributed reagents/materials/analysis tools: RMR EV. Wrote the paper: IM RMR EV JL.

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Sex differences in the relationship between prolactin levels and impaired processing speed in early psychosis

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ABSTRACT

INTRODUCTION: Hyperprolactinaemia is commonly observed in people with psychotic disorders due to D2 receptor blockade by antipsychotic drugs, although it may also exist in drug-naïve patients with first-episode psychosis. Recent studies suggest that hyperprolactinaemia may have a negative impact on cognitive function in people with early psychosis (EP). We aimed to explore whether there are sex differences in the association between prolactin levels and cognitive performance in EP patients.

METHODS: We studied 60 young patients with EP (aged 18-35 years, 35% females) and a sex- and age-matched control group of 50 healthy subjects (HS). Cognitive assessment was performed with the MATRICS Consensus Cognitive Battery. Prolactin, total cortisol, follicular-stimulating hormone (FSH), luteal hormone (LH), and sex steroids (testosterone in men, oestradiol and progesterone in women) were measured in plasma. Salivary cortisol was measured at different sampling times (awakening response, 10:00 and 23:00) was measured. Psychopathological status was assessed, and antipsychotic treatment was registered. Multiple linear regression analyses were used to explore the relationship between prolactin and cognitive tasks while adjusting for covariates.

RESULTS: Prolactin levels were associated with impaired processing speed in men, and this association was independent of cortisol and testosterone. In women, prolactin levels were not associated with processing speed tasks, although we observed a negative effect of prolactin on verbal learning and spatial working memory in female HS. The male-dependent effect maintained its significance after adjusting for education status, antipsychotic treatment and negative symptoms.

CONCLUSIONS: Our study demonstrates that the previously reported association between high prolactin levels and impaired cognitive processes in EP is restricted to men.

Keywords: prolactin; cortisol; psychosis; cognition; sex differences

1. INTRODUCTION

Hyperprolactinaemia is a common condition in subjects with psychotic disorders. As dopamine released by the tuberoinfundibular dopaminergic pathway into the pituitary portal blood is the main prolactin-inhibiting factor, hyperprolactinaemia is a common consequence of D2 receptor blockade by antipsychotic drugs (Cookson et al. 2012; Horseman and Gregerson, 2013). However, increased prolactin levels have also been reported in drug-naïve patients with first-episode psychosis (FEP) (Aston et al., 2010; Garcia-Rizo et al., 2012; Riecher-Rössler et al., 2013).

Although the most studied consequences of hyperprolactinaemia in psychotic subjects are amenorrhoea, galactorrhoea, sexual impairment and infertility, previous studies conducted in non-psychiatric populations (Henry and Sherwin, 2011) and animal models (Torner et al., 2013) suggest that hyperprolactinaemia may also have negative effects on cognition. In this regard, our group has demonstrated (Montalvo et al., 2014) that increased prolactin levels are associated with impaired processing speed in subjects with early psychosis (EP) and mediate the negative effects of antipsychotic-induced prolactin increase on processing speed.

In the study of the relation between prolactin levels and cognition, it is also important to explore whether there are sex differences because prolactin levels are higher in women (Horseman and Gregerson, 2013) and because cognitive effects may be modulated by specific sex steroids (e.g., 17-β-oestradiol or progesterone in women, testosterone in men) (Castanho et al., 2014). It is also important to know whether the effects of prolactin on cognition are moderated by other hormones that might affect cognitive processes in patients with psychotic disorders, including sex steroids (Huerta-Ramos et al., 2014; Moore et al., 2013) and hypothalamic-pituitary-adrenal (HPA) axis hormones (Aas et al., 2011; Halari et al., 2004). In previous studies by our group, we have reported a sex difference in the association between cortisol awakening response (CAR) and cognitive tasks in individuals with EP (Labad et al., 2016): An increased CAR was associated with poorer processing speed and verbal memory in female

patients only. However, another study reported that a blunted CAR, but not cortisol levels during the day, was associated with poorer verbal memory and processing speed in individuals with FEP (Aas et al., 2011).

In sum, several studies have addressed the relationship among prolactin, HPA axis measures or sex steroids and cognition in subjects with psychotic disorders; however, there are no studies that have considered all these hormones together with a particular focus on prolactin levels and sex differences. Thus, we conducted an exploratory analysis that might generate hypotheses for future studies on the topic. The main aim of our work was to explore whether there are sex differences in the association between prolactin levels and cognitive performance in people with EP. We also wanted to determine whether prolactin's effects on cognition are direct or are explained by HPA axis measures or plasma concentrations of follicular-stimulating hormone (FSH), luteal hormone (LH), or sex steroids (oestradiol and progesterone in women; testosterone in men).

2. METHODS

2.1 Participants

We studied 60 outpatients (39 men, 21 women) with EP, aged between 18 and 35 years, from the Early Intervention Service of the Hospital Universitari Institut Pere Mata (Reus, Spain). Each patient had a psychotic disorder (fulfilling DSM-IV criteria for a schizophreniform disorder [N=14], schizophrenia [N=10], schizoaffective disorder [N=8] or psychotic disorder not otherwise specified [N=28]) with a duration of illness of <3 years (65% had FEP). We used a control population of 50 healthy subjects (HS), matched by sex and age, who were recruited from the community using advertisements. The exclusion criteria were severe neurological disease or mental

retardation; pregnancy; language difficulties; visual impairment; alcohol, heroin or cocaine dependence; and treatment with glucocorticoids or oral contraceptive pill use.

2.2 Clinical and cognitive assessment

All the patients were interviewed by a psychiatrist using the Schedules for Clinical Assessment in Neuropsychiatry (Wing et al., 1990). The "Operational Criteria" (OPCRIT) checklist version 4.0 (available at http://sgdp.iop.kcl.ac.uk/opcrit/) was used to obtain DSM-IV diagnoses. The Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1990) was used to assess the severity of psychotic symptoms. We considered the 5 dimensions suggested by a consensus (Wallwork et al., 2012): positive, negative, disorganized, cognitive and depressive. The Calgary Depression Scale for Schizophrenia (CDSS) (Addington et al., 1990) was administered to assess depressive symptoms.

The Spanish version of the MATRICS Consensus Cognitive Battery (MCCB) was used to assess neurocognitive functioning (Nuechterlein et al., 2008). The MCCB contains 10 tests within 7 domains to measure cognitive functioning (Table 1S).

Sociodemographic and clinical variables were obtained in a semi-structured interview. Consumption of alcohol was measured in standard units/day, tobacco in cigarettes/day and cannabis in joints/day. Psychopharmacological treatment was recorded during the neuropsychological assessment. Each antipsychotic dosage was transformed into chlorpromazine equivalents in mg/day (Gardner et al., 2010). However, for descriptive information in tables, antipsychotic doses will be represented in risperidone equivalents taking into account the clinically equivalent doses suggested by Gardner et al. (2010). Of all 60 patients, 11 (18.3%) did not receive antipsychotic treatment, 41 (68.3%) received antipsychotic monotherapy (risperidone [n=15], paliperidone [n=5], olanzapine [n=14], aripiprazole [n=5], quetiapine [n=1], perphenazine [n=1]), and 8 (13.3%) received polytherapy. There were no sex differences regarding antipsychotic treatment.

2.3. Hormonal measures

2.3.1. Plasma

A fasting blood sample was obtained in the morning between 8:30 h and 9:30 h in resting conditions to measure unstimulated plasma prolactin, total cortisol levels and sex hormones. The participants were told to avoid stressful and physical activities or breast stimulation in the 12 hours prior to blood sampling. Prolactin, cortisol, FSH, LH, oestradiol, progesterone and testosterone concentrations were measured using the Maglumi 2000 Analyser chemiluminescence immunoassay system (SNIBE Co, Ltd, Guandong, China). The sensitivity for each assay was as follows: prolactin 77 pmol/L, cortisol 69 nmol/L, testosterone 0.5 nmol/L, oestradiol 29.7 pmol/L, progesterone 0.4 nmol/L, FSH 0.5 UI/L and LH 0.5 UI/L. The intra-assay and inter-assay coefficients of variation for all the serum assays were under 9%.

2.3.2. Saliva

We also obtained saliva samples with Salivette® tubes (Sarstedt AG & Co, Nümbrecht, Germany) at different times for cortisol determination: 1) one sample before the fasting blood sample, 2) one sample during the neuropsychological assessment (before and after the MCCB administration, which was conducted in the morning, with initial assessment times ranging between 9:00 h and 12:00 h), and 3) 5 home-collected saliva samples (another day of the fasting blood analysis and cognitive assessment) for calculating the CAR and cortisol levels over the day, using the following sampling times: awakening (T1), 30' post-awakening (T2), 60' post-awakening (T3), 10:00 h (T4), and 23:00 h (T5).

The saliva samples were processed at the Biobank at the Institut d'Investigació Sanitària Pere Virgili (IISPV). After centrifugation of the Salivette tubes at 3000 rpm for 5 min, the saliva was aliquoted and frozen at –20 °C until the assay. Salivary cortisol was determined by a commercial chemiluminescence immunoassay (IBL, Hamburg,

Germany). The sensitivity of the salivary cortisol assay was 0.08 nmol/L. The intra-assay and inter-assay coefficients of variation for this assay were under 8%.

2.4 Statistical analysis

SPSS version 19.0 (SPSS Inc., Chicago, Illinois, USA) was used for the statistical analyses.

2.4.1. Transformation of variables

We explored the distribution of plasma hormone concentrations and performed a log transformation (ln) for those hormones that had a skewed distribution. For salivary cortisol values, as suggested by recent expert consensus guidelines (Stalder et al., 2016), we transformed all the values using the following power transformation: $X'=(X^{.26}-1)/.26$ (Miller and Plessow, 2013). The CAR was calculated using the area under the curve with respect to the increase (Pruessner et al., 2003), and the cortisol levels over the day using the area under the curve with respect to the ground (AUCg). Cortisol levels during the neuropsychological assessment were calculated as the mean value of the pre-MCCB and post-MCCB samples.

Although we transformed the cortisol values with a power transformation, we did not use transformed values in the calculation of cortisol levels throughout the day. This approach was preferred because the cited power transformation sometimes yields negative values for very low cortisol values (that would be the case for most evening cortisol levels), which could affect the interpretation of cortisol levels using the trapezoid formula.

2.4.2. Univariate and general lineal model (GLM)

Pearson's correlation was used to analyse the association between continuous variables. Partial correlation analyses were used when needed to adjust for potential confounders. A GLM was performed to study the effect of sex and diagnostic groups (HS vs. EP) on continuous data and the possible interaction of those factors. To

compare female and male EP patients, a t-test was performed. Significance was set at $p<0.05$ (two-tailed).

2.4.3. Multiple linear regression analyses

To explore the association between prolactin and cognitive tasks, testing interactions among prolactin, sex and diagnosis as well as adjusting for potential confounders, we conducted a series of multiple linear regression analyses. Cognitive performance was considered the dependent variable, and an independent equation was conducted for each cognitive task. Prolactin was considered an independent variable, and we included sex, diagnosis, education level and antipsychotic treatment as the other independent variables. Three-way and two-way interactions among prolactin levels, sex and diagnosis were tested. Following hierarchical modelling, both significant interactions and lower-level non-significant interactions were included in the final model.

2.4.4. Multiple testing

Many exploratory analyses were addressed in our study. We did not correct for multiple testing because the correction for multiple testing is not strictly necessary in analyses that are exploratory in nature (Bender and Lange, 2001).

3. RESULTS

3.1. Univariate analysis and GLM

Clinically relevant variables of the two populations (HS and EP) and statistics corresponding to these variables can be seen in Table 1. As shown, EP patients had lower education, smoked more cigarettes and showed poorer cognitive performance in all tasks. No sex differences on the psychometric PANSS or CDSS scales were found

among the EP subjects. Sex differences in the cognitive MCCB tests were small, with males performing worse than females in managing emotions and better in Neuropsychological Assessment Battery (NAB) mazes, regardless of diagnosis. The only significant interaction between sex and diagnosis was found in CPT-IP: Healthy men outscored healthy women in this attention and vigilance task, whereas female patients outperformed male patients. We repeated the sex comparison on cognitive performance in the subgroup of patients receiving risperidone or paliperidone in monotherapy (Table 3S). Female patients receiving these prolactin-elevating antipsychotics showed better social cognition.

Endocrine variables in plasma and saliva are indicated in Table 2. Early morning fasting plasma levels of prolactin were higher in females than in males and higher in EP than in HS, with no interaction between the two factors. Prolactin levels by antipsychotic treatment group are presented in Table 2S. No significant influence of either sex or diagnosis was found for plasma cortisol, and female sex hormones (17-β-oestradiol and progesterone) were not affected by diagnosis. Regarding saliva, cortisol concentration in samples taken at the same time as plasma in the early morning was affected by sex (higher levels in females) and diagnosis (lower levels in EP), with no interaction. Neither CAR nor AUCg was significantly affected by sex or diagnosis.

3.2. Correlation of prolactin and sex hormones with cognitive tasks

When all the subjects were studied together (HS and EP, Table 3), the correlational analyses indicated that in men prolactin levels correlated negatively with testosterone, whereas in women prolactin correlated negatively with plasma and saliva cortisol, and progesterone correlated positively with oestradiol.

Regarding cognitive tasks, no statistically significant correlations were found with sex steroids. In women, FSH and LH levels did not correlate with cognitive functioning (data not shown). In men, LH levels were not associated with cognitive performance in any task; however, FSH levels were positively associated with CPT-IP

scores (r=0.329, p=0.007). Prolactin levels correlated with poorer cognitive performance in most cognitive tasks in men and only one cognitive task in women (BACS-SC).

As correlation analyses included both HS and EP patients, we conducted an additional partial correlation analysis adjusting for education status and antipsychotic treatment. In these adjusted correlations, in men prolactin was significantly associated with TMT (r=0.41, p=0.001), BACS-SC (r=-0.35, p=0.005) and CPT-IP (-r=-0.30, p=0.020). In women, prolactin was not associated with any cognitive measure when adjusting for education and antipsychotic treatment. FSH was associated with improved cognition in CPT-IP (r=0.25, p=0.050) in men only.

3.3. Multiple linear regression analyses

3.3.1. Multiple linear regression analyses in all participants

Multiple linear regression analyses of the association between prolactin and cognitive tasks are presented in Table 4.

Processing speed, as measured by the TMT (higher scores reflected lower cognitive performance), was associated positively with prolactin levels and negatively with EP diagnosis, although the sex x prolactin interaction was also statistically significant, indicating that the effects of prolactin on this cognitive task differed between men and women. Another measure of processing speed (BACS-SC) was also affected by prolactin and EP diagnosis: A poorer processing speed was associated with increased levels of prolactin and an EP diagnosis, with no statistical interactions.

For working memory, as measured by the WMS-III spatial span task, there were two significant interaction terms in the final equation (a negative female sex x EP diagnosis interaction and a positive female sex x EP diagnosis x prolactin three-way interaction). These two interaction terms mean that female EP patients showed poorer performance in this cognitive task but that this subgroup (female EP) performed better

as prolactin levels increased. To better understand these interaction terms, we have included a scatterplot figure as supplementary material (Figure 1S). As shown in the figure, female EP patients scored lower on the WMS-III spatial span task. However, female EP patients with higher prolactin levels showed better performance on this task.

Prolactin levels were not associated with other cognitive tasks, including attention and vigilance, working memory, verbal learning, visual learning, reasoning and problem solving and social cognition.

3.3.2. Multiple linear regression analyses in EP patients: adjusting for negative symptoms

Additional regression analyses were performed to further characterize the relation between prolactin and cognitive impairment in EP patients while adjusting for education status, negative symptoms and antipsychotic treatment. As shown in Table 5, negative symptoms were associated with impaired cognition in all domains but working memory. A negative relationship between prolactin and cognitive performance was observed in all the tasks measuring processing speed. In two of these three tasks (TMT and fluency), a sex by prolactin interaction was observed (the relation was found only in males), whereas on the BACS-SC no sex-specific effects were found.

3.3.3. Multiple linear regression analyses by sex: adjusting for cortisol and sex steroids

We conducted additional multiple linear regression analyses in men and women separately, including sex steroids and cortisol measures (CAR, cortisol levels over the day) as covariates. All these analyses were also adjusted for education level. In men, prolactin levels were negatively associated with impaired performance in all three tasks measuring processing speed: TMT (β=0.364, p 0.002), BACS (β=-0.313, p=0.006) and fluency (β=-0.279, p=0.027). These significant associations were independent of testosterone levels and cortisol measures. Testosterone levels or HPA axis measures were not related to cognitive performance in any cognitive task.

In women, prolactin levels were associated with poorer performance in two cognitive tasks, along with prolactin by diagnosis interactions: 1) WMS-III spatial span (prolactin effect: β=-1.132, p=0.009; prolactin x early psychosis interaction: β=3.406, p=0.006); and 2) BVMT-R (prolactin effect: β=-1.065, p=0.024; prolactin x early psychosis interaction: β=2.776, p=0.016). These findings suggest that the pattern in the relationship between prolactin and these two cognitive tasks differs in EP and HS (interactions suggest that higher prolactin levels are associated with poorer performance in HS and better performance in EP; Figures 1S and 2S). These results complement the results of the analyses including all the participants (section 3.3.1) once they are adjusted for HPA axis measures and sex hormones. Regarding HPA axis measures, cortisol levels during the day were associated with poorer performance in two cognitive tasks: TMT (β=0.412, p=0.022) and HVLT-R (β=-0.345, p=0.030). Neither oestradiol nor progesterone was associated with cognitive performance in any task.

4. DISCUSSION

The present work demonstrates that the previously reported association between high prolactin levels and impaired cognitive processes in EP is restricted to men. These sex differences were not driven by a better cognitive profile or lower prolactin levels in women. In men, neither testosterone levels nor cortisol levels moderated the relationship between prolactin and cognitive performance in processing speed tasks. In women, prolactin levels were not associated with processing speed tasks, although we observed a negative effect of prolactin on verbal learning and spatial working memory in female HS.

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Given our previous results showing an association of high prolactin levels with impaired cognition in men and women with EP (Montalvo et al. 2014), we explored whether sex can affect such a relationship. As expected (Cookson et al. 2012; Horseman and Gregerson, 2013), we observed higher levels of prolactin in EP. Although prolactin levels in the controls were higher in women than in men, the specific effect of the diagnosis of a psychotic disorder was similar in both sexes. However, when the correlation between plasma prolactin and cognitive performance was studied in all the subjects, marked sex differences were observed: In men, prolactin was associated with an impairment in most cognitive domains, whereas in women only a component of processing speed (BACS-SC) was negatively affected. The reason for the observed sex differences in the relationship between prolactin and cognition is not clear. Although EP men showed lower levels of testosterone than HS, testosterone levels were not associated with cognitive performance in any cognitive task. Some studies in the literature have reported that testosterone levels may modulate cognitive functioning in people with schizophrenia (Moore et al., 2013), although other studies have not reported such an association (Halari et al., 2004). In relation to female sex steroids, we did not find an association between oestradiol or progesterone and cognitive performance in women. These results are in accordance with previous studies of female patients with schizophrenia (Rubin et al., 2015), although other studies have reported that higher progesterone levels are associated with poorer performance in spatial memory tasks (Halari et al., 2004). We would like to clarify that markers of hypothalamic-pituitary-gonadal axis function in our study are peripheral and that central nervous system markers were not assessed. The reproductive age of women in our sample could bring some neuroprotection from oestradiol at the central nervous system that could partially explain some of the sex differences reported in our study.

In a previous study by our group of HPA axis measures of cognition in EP patients (Labad et al., 2016), we did report sex differences in the relationship between

HPA axis measures and cognitive tasks. In our current study, the addition of two cortisol measures (CAR and cortisol levels over the day) or sex steroids in the linear regression analyses did not modify the relationship between prolactin and cognitive functioning in men or women, suggesting that prolactin may have a direct effect on cognition that is not moderated by the HPA or hypothalamic-pituitary-gonadal axes. However, in women we found that higher cortisol levels during the day were associated with poorer processing speed and verbal learning, pointing to the sex-specific relationship between HPA axis measures and cognitive abilities that was found in our previous study (Labad et al., 2016).

Sex differences in the relationship between prolactin and cognition may be explained by sex-specific effects at the brain level. A sexual dimorphism has been described in patients with schizophrenia, particularly in the cortex, with men showing smaller cortex volumes, relative to cerebrum size, compared to women (Goldstein et al., 2002). Another study reporting reduced grey matter volume in the prefrontal cortex of patients with schizophrenia has shown similar reductions in dorsolateral prefrontal regions in men and women but larger reductions in men, compared to women, in the dorsomedial cortex (Gur et al., 2000). Prefrontal cortex volumes correlate with executive function tasks in patients with schizophrenia (Antonova et al., 2004). Although speculative, it is plausible that the sex-specific negative association of prolactin with the speed of processing tasks might rely on sex-specific volumetric brain abnormalities in the prefrontal cortex.

When adjusting for covariates including antipsychotic treatment and negative symptoms—two known variables that affect cognition (Bora et al., 2009; Sakurai et al., 2013)—out of all cognitive tasks, poorer performance in those tasks related to processing speed was significantly associated with prolactin levels. These results are consistent with previous reports that have found an association between prolactin levels and cognitive tasks involving processing speed (Bratek et al., 2015; Montalvo et al., 2014). Antipsychotic-induced hyperprolactinaemia, which is caused by

tuberoinfundibular blockade of D2 receptors (Horseman and Gregerson, 2013), may reflect the blockade of D2 receptors in other dopaminergic pathways including the striatum, which causes extrapyramidal symptoms, or the mesocortical pathway and may be related to worsening of cognitive and negative symptoms. The multivariate analyses suggest that there is an independent effect of prolactin, as all the analyses were adjusted for sex, education level, antipsychotic treatment and negative symptoms.

The possible mechanisms linking higher levels of prolactin to impaired cognitive function are not known; however, a direct action on the brain is quite possible. Only one study has investigated the influence of prolactin on cognitive functions in rats (Torner et al. 2013), showing impaired object recognition but not spatial memory deficit in hyperprolactinaemic rats; nonetheless, a wider effect of prolactin on brain function is plausible. It is well known that prolactin has access to the brain, although the precise mechanisms are still unclear. Whereas the hypothesis has been accepted for years that the hormone accesses the brain though prolactin receptors located in the choroid plexus, recent evidence in mice with deletion of the receptor has demonstrated that it is not necessary to the mechanism and that endothelial cells of brain capillaries, rather than the choroid plexus, might be the route of transport (Brown et al., 2016). Regardless of the mechanisms, prolactin accesses the brain, where it can exert important behavioural effects, most of them related to reproductive and maternal behaviour. Importantly for the relationship between prolactin and EP, there is evidence in animals that prolactin might potentiate striatal DA release in vitro and in vivo (Chen and Ramirez, 1988; Perkins and Westfall, 1978; Ramirez, 1983), suggesting a direct effect on the striatum. In fact, the presence of the receptor has been detected by immunohistochemistry in the cortex and striatum of the rat (Roky et al., 1996). However, in the mouse there is no evidence of the expression of the prolactin receptor in either the prefrontal cortex or the dorsal or ventral striatum (Brown et al., 2010), suggesting that the possible influence of prolactin on cortical or striatal function might

involve terminals arising from other brain areas where the receptor is expressed. Nothing is known in humans about the possible influence of hyperprolactinaemia on brain function.

The main limitation of our study is the cross-sectional design, which does not allow us to infer causality. Further prospective studies may overcome this limitation by repeatedly assessing prolactin levels and cognitive performance over time to explore whether persistent hyperprolactinaemia is a risk factor for cognitive decline in subjects with psychoses, particularly in men. Most of the patients in our study were receiving antipsychotic drugs, which may affect both prolactin and cognitive performance. Antipsychotic-induced extrapyramidal symptoms, that could affect processing speed, were not assessed. As our Early Intervention Service is an outpatient service, some patients who have previously been admitted to the referral Acute Psychiatric Unit are stabilized before attending our service. Moreover, patients must be informed of the research project and must sign the informed consent form; thus, in most cases, EP patients are clinically stable at recruitment. For all these reasons, most of the patients were taking antipsychotic drugs. We tried to address this limitation by adjusting most of the multivariate analyses for antipsychotic treatment. The fasting morning samples in plasma and saliva were obtained in a clinical setting, which may be considered a stressful environment for some participants. However, as EP patients had frequent appointments in this clinical unit, it is plausible that environmental novelty was lower for EP than for HS, which could partially explain the increased fasting morning salivary cortisol levels in this latter group. Finally, menstrual cycle status was not ascertained clinically because we preferred to adjust for sex steroids (oestradiol and progesterone) in the multivariate analyses. Up to 45% of women with psychotic disorders receiving antipsychotic treatment have irregular menses (Gleeson, PC, Worsley, R, Gavrilidis, E, Nathoo, S, Ng, E, Lee, S, Kulkarni, 2016), which makes assessment of female psychotic patients with the same menstrual status difficult. Prolactin concentrations are influenced by oestradiol levels, with significantly higher levels during the ovulatory and

luteal phases than during the follicular phase (Franchimont et al., 1976). For this reason, the multiple linear regression analyses were also adjusted for oestradiol concentrations.

If our findings are replicated in further studies, they may have potential clinical implications. Currently, the monitoring of hyperprolactinaemia side effects is focused on sexual and reproductive functions. However, our study suggests that prolactin may also have brain effects that could influence cognitive processes, which needs to be considered when treating patients with psychotic disorders and antipsychotic-induced hyperprolactinaemia.

In conclusion, our study suggests that there are sex differences in the relationship between prolactin levels and impairment of cognitive tasks involving processing speed in the early stages of a psychotic disorder. The detrimental effects of prolactin on cognition are not moderated by the HPA or hypothalamic-pituitary-gonadal axes.

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Table 1. Clinical variables of the sample.

	Healthy subjects		Early psychosis (EP)		P values*		
	Male (N= 28)	Female (N= 22)	Male (N= 39)	Female (N= 21)	Sex	EP	Sex x EP
Age	24.1 (5.3)	23.4 (4.0)	23.5 (4.5)	26.5 (6.4)	0.261	0.222	0.058
Education level (years of study)	13.0 (2.9)	13.8 (2.6)	11.0 (2.9)	11.8 (2.6)	0.146	<0.001	0.978
Smoking (cigarettes/day)	2.2 (5.1)	0.8 (3.2)	10.7 (10.2)	5.8 (7.8)	0.036	<0.001	0.240
Cannabis (joints/day)	0.2 (0.7)	0 (0)	0.6 (1.8)	0.2 (0.9)	0.369	0.085	0.867
Alcohol (standard units/day)	0.1 (0.4)	0 (0)	0.3 (1.0)	0.1 (0.2)	0.212	0.291	0.505
Antipsychotic treatment (N, %)	0 (0)	0 (0)	32 (82.1)	17 (81.0)	0.916		
Risperidone equivalents (mg/day)	0 (0)	0 (0)	4.2 (3.5)	2.8 (2.8)	0.125		
Psychometric scales							
PANSS positive factor	-	-	5.7 (2.3)	5.0 (1.6)	0.160		
PANSS negative factor	-	-	13.5 (5.1)	13.3 (5.6)	0.897		
PANSS disorganized factor	-	-	5.0 (2.2)	5.0 (1.8)	0.963		
PANSS excited factor	-	-	4.9 (1.6)	4.5 (0.8)	0.166		
PANSS depressed factor	-	-	5.3 (2.5)	4.7 (2.2)	0.297		
Calgary-Depression scale	-	-	2.6 (3.5)	1.9 (2.6)	0.413		
Cognitive testing (MCCB)							
Speed of processing							
Trail making test, part A (seconds)†	23.5 (6.9)	26.1 (10.2)	39.5 (15.6)	35.7 (7.5)	0.778	<0.001	0.153
BACS-SC	61.4 (11.1)	62.5 (7.3)	45.6 (13.5)	46.5 (10.1)	0.661	<0.001	0.951
Category fluency: animal naming	24.9 (5.4)	23.1 (4.5)	18.7 (4.9)	17.5 (5.9)	0.147	<0.001	0.790
Attention and vigilance							
CPT-IP	2.9 (0.6)	2.4 (0.5)	1.9 (0.7)	2.1 (0.6)	0.185	<0.001	0.020
Working memory							
WMS-III spatial span	16.5 (2.6)	15.9 (3.3)	14.2 (3.9)	14.2 (3.3)	0.609	0.003	0.624
Letter-number span	14.1 (2.5)	14.2 (3.4)	12.1 (2.5)	11.9 (2.1)	0.916	<0.001	0.739
Verbal learning							
HVLT-R	27.6 (4.1)	27.3 (3.5)	22.1 (4.7)	24.1 (5.1)	0.322	<0.001	0.201
Visual learning							
BVMT-R	27.6 (6.0)	26.1 (5.9)	20.0 (7.9)	18.9 (5.8)	0.320	<0.001	0.884
Reasoning and problem solving							
NAB mazes	22.5 (3.7)	21.2 (3.4)	19.3 (5.0)	16.3 (6.0)	0.017	<0.001	0.353
Social Cognition							
MSCEIT: managing emotions	92.8 (9.4)	96.5 (8.7)	84.3 (8.9)	90.8 (9.9)	0.007	<0.001	0.438

*An ANCOVA analysis was conducted for all variables that were obtained from all participants. P values for the effects of sex, EP and the interaction of sex and EP are shown. As the PANSS and Calgary-Depression scales were only administered to EP patients, sex differences in these variables were compared using a T-test. P values for antipsychotic treatment were applied only to patients.

†For all cognitive tests, higher scores reflect a better cognitive performance, with the exception of the Trail Making Test. As this test is measured in seconds, lower scores reflect a better cognitive performance.

Abbreviation: PANSS= Positive and Negative Syndrome Scale; BACS-SC= Brief Assessment of Cognition in Schizophrenia-Symbol Coding; CPT-IP= Continuous Performance Test-Identical Pairs; WMS-III= Wechsler Memory Scale – 3rd Edition; HVLT-R= Hopkins Verbal Learning Test-Revised; BVMT-R= Brief Visuospatial Memory Test-Revised; NAB= Neuropsychological Assessment Battery; MSCEIT= Mayer-Salovey-Caruso Emotional Intelligence Test.

Table 2. Hormonal measures of the sample.

	Healthy subjects		Early psychosis (EP)		P values*		
	Male (N= 28)	Female (N= 22)	Male (N= 39)	Female (N= 21)	Sex	EP	Female sex x EP
Hormonal measures							
Fasting morning hormones in plasma							
Prolactin (pmol/L)	578.6 (212.6)	874.9 (284.0)	1799.5 (1317.5)	2548.5 (2361.5)	0.039	<0.001	0.380
Cortisol (nmol/L)	500.8 (113.3)	543.0 (151.5)	539.0 (164.4)	536.5 (171.5)	0.509	0.597	0.456
FSH (UI/L)	4.6 (2.8)	5.3 (2.6)	3.1 (1.9)	5.2 (2.4)	0.005	0.085	0.191
LH (UI/L)	3.5 (1.4)	6.9 (5.1)	3.7 (1.5)	10.9 (16.7)	0.001	0.172	0.214
17-β-oestradiol (nmol/L)		227.7 (138.3)		231.2 (203.5)		0.952	
Progesterone (nmol/L)		16.8 (20.8)		14.6 (13.1)		0.708	
Testosterone (nmol/L)	20.8 (6.1)		16.5 (7.5)			0.015	
Salivary cortisol							
Fasting morning cortisol (nmol/L)	24.2 (8.7)	30.3 (10.2)	20.7 (11.2)	23.2 (10.8)	0.046	0.005	0.616
Mean cortisol levels during MCCB, nmol/L	13.3 (6.6)	15.7 (9.3)	14.9 (8.8)	14.6 (7.0)	0.305	0.523	0.390
Cortisol at awakening (T1), nmol/L	12.7 (7.7)	17.2 (10.0)	11.3 (8.1)	16.3 (8.8)	0.015	0.575	0.672
Cortisol 30' post-awakening (T2), nmol/L	23.8 (12.8)	24.0 (12.8)	18.4 (9.5)	23.8 (11.9)	0.324	0.566	0.177
Cortisol 60' post-awakening (T3), nmol/L	21.8 (13.2)	20.1 (12.6)	15.6 (7.4)	17.6 (7.6)	0.927	0.316	0.300
Cortisol at 10 h (T4), nmol/L	12.5 (8.4)	12.4 (6.0)	11.0 (5.6)	14.0 (7.4)	0.166	0.713	0.342
Cortisol at 23 h (T5), nmol/L	2.3 (1.7)	3.3 (2.6)	3.0 (2.6)	2.9 (3.8)	0.775	0.927	0.275
Cortisol at 10 h after DXM (T6), nmol/L	8.5 (10.1)	9.2 (5.6)	8.5 (8.1)	10.9 (9.8)	0.275	0.944	0.654
CAR	52.3 (55.1)	23.4 (71.2)	45.4 (56.5)	31.6 (48.2)	0.067	0.956	0.516
Cortisol levels during the day (AUCg)	2001.4 (823.2)	2009.3 (699.2)	2122.0 (876.8)	2217.3 (793.4)	0.312	0.750	0.787

Cortisol raw scores are shown. P values calculated upon transformed cortisol values (with the exception of AUCg, that was calculated with untransformed values).

*An ANCOVA analysis was conducted for all variables that were obtained from all participants. P values for the effects of sex, EP and the interaction of sex and EP are shown. As the PANSS and Calgary-Depression scales were only administered to EP patients, sex differences in these variables were compared using a T-test.

†For all cognitive tests, higher scores reflect a better cognitive performance, with the exception of the Trail Making Test. As this test is measured in seconds, lower scores reflect a better cognitive performance.

Abbreviation: EP= Early psychosis; CAR= Cortisol awakening response.

Table 3. Correlation analysis between hormones and cognitive tasks. Sex-stratified analysis.

	All men (N= 67)		All women (N= 43)		
	Prolactin	Testosterone	Prolactin	17-B-Estradiol	Progesterone
Hormones					
Prolactin	-	-0.25 (p=0.042)	-	-0.09	-0.19
Testosterone	-0.25 (p=0.042)	-			
Oestradiol			-0.09	-	0.46 (p= 0.005)
Progesterone			-0.19	0.46 (p= 0.005)	-
Cortisol (plasma)	0.05	0.05	-0.30 (p=0.05)	-0.07	-0.12
Cortisol (saliva)	-0.22	0.20	-0.38 (p=0.011)	-0.015	-0.14
Cortisol (NPS)	0.18	-0.05	0.07	-0.27	-0.31
CAR	-0.19	-0.05	0.10	0.01	0.20
AUCg (all day)	-0.05	0.02	-0.15	0.05	0.17
Cognitive tests					
TMT	0.50 (p<0.001)	-0.09	0.25	0.02	0.09
BACS SC	-0.49 (p<0.001)	0.17	-0.32 (p=0.03)	-0.12	0.02
HVLT-R	-0.37 (p=0.003)	0.23	-0.07	0.06	-0.06
WMS-III SS	-0.23	0.13	0.00	-0.06	-0.28
LNS	-0.25	0.20	-0.06	-0.07	-0.15
NAB Mazes	-0.30 (p= 0.015)	0.04	-0.17	0.11	0.02
BVMT-R	-0.32 (p= 0.009)	0.24	-0.15	-0.03	-0.01
Fluency	-0.47 (p<0.001)	0.18	-0.12	-0.06	0.10
MSCEIT ME	-0.11	0.05	-0.01	0.10	-0.03
CPT-IP	-0.44 (p<0.001)	0.13	-0.01	0.18	0.06

Correlation coefficients (r) are shown. P values for significant associations are also shown.

Abbreviations: CAR= Cortisol awakening response; AUCg= Area under the curve (calculated with respect to the ground); BACS-SC= Brief Assessment of Cognition in Schizophrenia-Symbol Coding; CPT-IP= Continuous Performance Test-Identical Pairs; WMS-III= Wechsler Memory

Scale – 3rd Edition; LNS= Letter-Number Sequencing; HVLT-R= Hopkins Verbal Learning Test-Revised; BVMT-R= Brief Visuospatial Memory Test-Revised; NAB= Neuropsychological Assessment Battery; MSCEIT= Mayer-Salovey-Caruso Emotional Intelligence Test.

Table 4. The results of the multiple linear regression analyses exploring the association between prolactin and cognitive tasks in all participants.

	R^2	Prolactin	Female sex	EP diagnosis	Significant interactions
Speed of processing					
Trail making test, part A (seconds)	0.41	0.421 (p= 0.001)	0.591 (p= 0.061)	0.284 (p= 0.006)	female sex x prolactin (-0.678, p= 0.044)
BACS-SC	0.54	-0.179 (p= 0.044)	-0.004 (p= 0.957)	-0.285 (p= 0.002)	NSI
Category fluency: animal naming	0.34	-0.074 (p= 0.488)	-0.157 (p= 0.069)	-0.286 (p= 0.008)	NSI
Attention and vigilance					
CPT-IP	0.45	-0.025 (p= 0.796)	-0.349 (p= 0.002)	-0.434 (p<0.001)	female sex x EP diagnosis (0.314, p= 0.012)
Working memory					
WMS-III spatial span	0.37	-0.091 (p=0.824)	1.483 (p= 0.120)	-0.075 (p= 0.916)	female sex x EP diagnosis (-1.799, p= 0.035) female sex x prolactin (-1,899, p= 0.111) EP diagnosis x prolactin (0.012, p= 0.991) female sex x EP diagnosis x prolactin (2.251, p= 0.046)
Letter-number span	0.26	-0.012 (p= 0.914)	-0.048 (p= 0.606)	-0.270 (p= 0.021)	NSI
Verbal learning					
HVLT-R	0.37	0.040 (p= 0.695)	0.014 (p= 0.867)	-0.236 (p= 0.024)	NSI
Visual learning					
BVMT-R	0.38	-0.003 (p= 0.328)	-0.147 (p= 0.079)	-0.286 (p= 0.006)	NSI
Reasoning and problem solving					
NAB mazes	0.25	-0.123 (p= 0.277)	-0.236 (p= 0.011)	-0.260 (p= 0.024)	NSI
Social Cognition					
MSCEIT: managing emotions	0.32	0.158 (p= 0.151)	0.164 (p= 0.066)	-0.276 (p= 0.013)	NSI

All analyses were adjusted for sex, education level, diagnosis, and antipsychotic treatment.

Abbreviations: EP= Early psychosis; BACS-SC= Brief Assessment of Cognition in Schizophrenia-Symbol Coding; CPT-IP= Continuous Performance Test-Identical Pairs; WMS-III= Wechsler Memory Scale – 3rd Edition; HVLT-R= Hopkins Verbal Learning Test-Revised; BVMT-R= Brief Visuospatial Memory Test-Revised; NAB= Neuropsychological Assessment Battery; MSCEIT= Mayer-Salovey-Caruso Emotional Intelligence Test.

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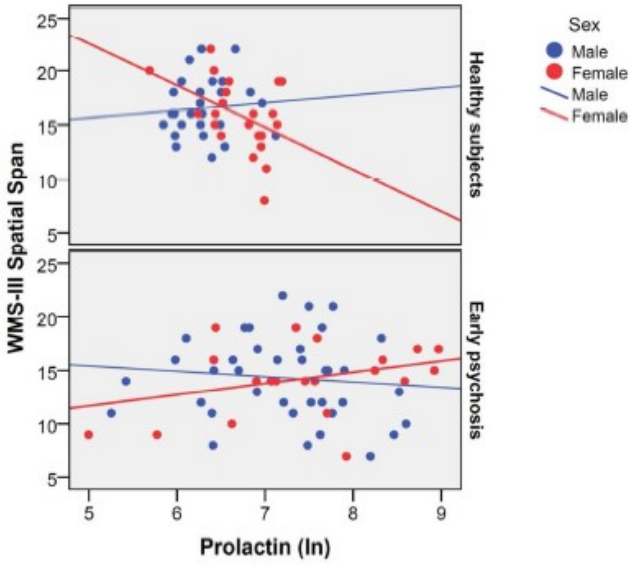
Table 5. Results of the multiple linear regression analyses exploring the association between prolactin and cognitive tasks in patients with an early psychosis.

	R^2	Prolactin	Female sex	Education level	Antipsychotic treatment	PANSS negative factor	Female sex x prolactin
Speed of processing							
Trail making test, part A (seconds)	0.43	0.436 (p= 0.010)	0.757 (p= 0.077)	-0.248 (p= 0.036)	-0.276 (p= 0.041)	-0.506 (p<0.001)	-0.938 (p=0.032)
BACS-SC	0.38	-0.355 (p= 0.038)	-0.688 (p= 0.111)	0.413 (p= 0.001)	-0.022 (p= 0.868)	-0.268 (p= 0.038)	
Category fluency: animal naming	0.34	-0.323 (p= 0.083)	-1.214 (p= 0.010)	0.161 (p= 0.205)	0.043 (p= 0.776)	-0.442 (p= 0.002)	1.196 (p= 0.017)
Attention and vigilance							
CPT-IP	0.41	0.014 (p= 0.910)	0.076 (p= 0.503)	0.447 (p< 0.001)	-0.033 (p= 0.797)	-0.316 (p= 0.013)	
Working memory							
WMS-III spatial span	0.27	0.105 (p= 0.446)	-0.069 (p= 0.581)	0.437 (p= 0.001)	0.001 (p= 0.993)	-0.183 (p= 0.187)	
Letter-number span	0.13	0.088 (p= 0.585)	-0.053 (p= 0.717)	0.270 (p= 0.065)	0.003 (p= 0.984)	-0.188 (p= 0.219)	
Verbal learning							
HVLT-R	0.34	0.134 (p= 0.309)	0.127 (p= 0.289)	0.291 (p= 0.022)	-0.135 (p= 0.335)	-0.321 (p= 0.017)	
Visual learning							
BVMT-R	0.27	0.088 (p= 0.532)	-0.132 (p= 0.303)	0.297 (p= 0.026)	-0.031 (p= 0.841)	-0.337 (p= 0.019)	
Reasoning and problem solving							
NAB mazes	0.27	-0.07 (p= 0.616)	-0.271 (p= 0.038)	0.183 (p= 0.168)	0.156 (p= 0.291)	-0.336 (p= 0.018)	
Social cognition							
MSCEIT: managing emotions	0.37	0.252 (p= 0.064)	0.286 (p= 0.020)	0.286 (p= 0.022)	0.017 (p= 0.903)	-0.338 (p= 0.011)	

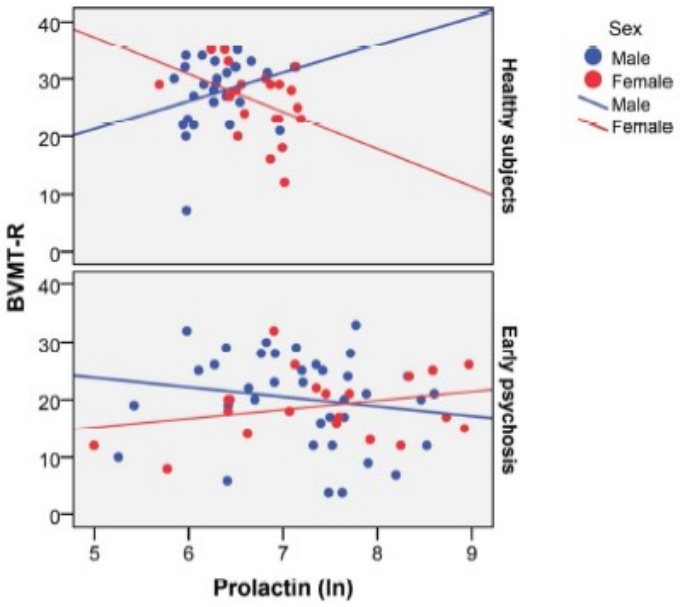
All analyses were adjusted for sex, education level, antipsychotic treatment and negative symptoms.

Abbreviations: BACS-SC= Brief Assessment of Cognition in Schizophrenia-Symbol Coding; CPT-IP= Continuous Performance Test-Identical Pairs; WMS-III= Wechsler Memory Scale – 3rd Edition; HVLT-R= Hopkins Verbal Learning Test-Revised; BVMT-R= Brief Visuospatial Memory Test-Revised; NAB= Neuropsychological Assessment Battery; MSCEIT= Mayer-Salovey-Caruso Emotional Intelligence Test; PANSS= Positive and Negative Syndrome Scale.



Supplementary material. Figure 1S.

190x172mm (216 x 216 DPI)



Supplementary material. Figure 2S.

189x178mm (213 x 213 DPI)

Table 1S. MATRICS Consensus Cognitive Battery tests and cognitive domains.

Cognitive domain	Neuropsychological test
Speed of processing	Brief Assessment of Cognition in Schizophrenia-Symbol Coding
	Category Fluency-Animal naming
	Trail Making Test Part A
Attention and vigilance	Continuous Performance Test-Identical Pairs
Working memory	WMS-III Spatial Span
	University of Maryland Letter-Number Span
Verbal learning	Hopkins Verbal Learning Test-Revised
Visual learning	Brief Visuospatial Memory Test-Revised
Reasoning and problem solving	Neuropsychological Assessment Battery-Mazes
Social cognition	Mayer-Salovey-Caruso Emotional Intelligence Test-Managing Emotions

On all cognitive tests except the Trail Making Test (TMT), higher scores reflect better cognitive performance. As the TMT is measured in seconds, greater scores reflect poorer cognitive performance.

Table 2S. Prolactin levels after antipsychotic treatment in 60 patients with early psychosis.

	Male (N=39)		Female (N=21)		
Prolactin levels (pmol/L) after antipsychotic treatment	N	Mean (SD)	N	Mean (SD)	P value
None (N=11)	7	1048.9 (943.2)	4	993.3 (599.6)	0.726
Risperidone/paliperidone (N=20)	14	2601.7 (1265.1)	6	2779.9 (1731.8)	0.859
Olanzapine/quetiapine (N=15)	12	1261.7 (1276.3)	3	1389.6 (484.6)	0.449
Aripiprazole (N=5)	1	613.0	4	2306.3 (3704.2)	NA
Other (polytherapy [N=8] or perphenazine [N=1])	5	2024. (995.5)	4	4868.0 (2452.5)	0.052

Abbreviations: SD=Standard deviation; NA=Not assessed.

Table 3S. Sex differences in cognitive performance in 20 patients receiving risperidone or paliperidone monotherapy.

	Male (N=14)	Female (N=6)	P value
Cognitive testing (MCCB)			
Speed of processing			
Trail making test, part A (seconds)†	39.6 (14.4)	33.0 (6.9)	0.458
BACS-SC	46.4 (10.3)	47.5 (9.6)	0.827
Category fluency: animal naming	18.4 (4.6)	19.2 (4.2)	0.731
Attention and vigilance			
CPT-IP	1.83 (0.63)	2.13 (0.54)	0.330
Working memory			
WMS-III spatial span	14.8 (4.1)	14.3 (4.7)	0.830
Letter-number span	12.9 (1.8)	13.0 (2.4)	0.936
Verbal learning			
HVLT-R	23.6 (4.5)	25.8 (2.8)	0.274
Visual learning			
BVMT-R	21.4 (6.6)	20.8 (4.3)	0.843
Reasoning and problem solving			
NAB mazes	19.1 (5.7)	18.7 (5.2)	0.862
Social cognition			
MSCEIT: managing emotions	83.3 (8.3)	94.7 (8.5)	0.014

†For all cognitive tests, higher scores reflect better cognitive performance, with the exception of the Trail Making Test. As this test is measured in seconds, lower scores reflect better cognitive performance.

Abbreviations: BACS-SC=Brief Assessment of Cognition in Schizophrenia-Symbol Coding; CPT-IP=Continuous Performance Test-Identical Pairs; WMS-III=Wechsler Memory Scale – 3rd Edition; HVLT-R=Hopkins Verbal Learning Test-Revised; BVMT-R=Brief Visuospatial Memory Test-Revised; NAB=Neuropsychological Assessment Battery; MSCEIT=Mayer-Salovey-Caruso Emotional Intelligence Test.

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Original article 1

Improvement in cognitive abilities following cabergoline treatment in patients with a prolactin-secreting pituitary adenoma

Itziar Montalvo[a], Marta Llorens[a], Laia Caparrós[a], Montserrat Pamias[a], Jordi Torralbas[a], Olga Giménez-Palop[b], Assumpta Caixàs[b], Diego J. Palao[a] and Javier Labad[a]

Hyperprolactinaemia may affect sexual and reproductive functioning. However, recent studies suggest that increased prolactin levels may also have negative effects on cognition. We aimed to study whether the reduction in prolactin levels by cabergoline in patients with hyperprolactinaemia is followed by an improvement in cognitive tasks. We studied seven patients with hyperprolactinaemia caused by a prolactinoma that had an indication to start treatment with cabergoline. All patients were assessed twice (baseline and 6–12 months after cabergoline treatment) with a cognitive battery. Plasma prolactin levels were determined. We found a significant improvement in the speed of processing, working memory, visual learning and reasoning and problem-solving domains after cabergoline treatment. Improvements in speed of processing and reasoning and problem solving were greater in patients with baseline prolactin levels above the median. In summary, a reduction in prolactin levels by cabergoline in patients with hyperprolactinaemia is followed by an improvement in cognitive abilities. This finding suggests that prolactin may be involved in cognitive processes, although cabergoline could also have procognitive effects that are independent of prolactin changes. Further clinical trials are needed to confirm the potential cognitive-enhancement properties of cabergoline in patients with chronic hyperprolactinaemia. *Int Clin Psychopharmacol* **00:000–000**

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Keywords: cabergoline, cognition, dopamine agonist, prolactin, prolactinoma

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Introduction

Amenorrhoea, galactorrhoea, sexual dysfunction and infertility are the most widely studied consequences of hyperprolactinaemia (Horseman and Gregerson, 2013). Recent studies in nonpsychiatric (Henry and Sherwin, 2011; Bala *et al.*, 2016) and psychiatric populations (Montalvo *et al.*, 2014), as well as in animal models (Torner *et al.*, 2013), suggest that hyperprolactinaemia may have a negative effect on cognitive abilities. However, no previous studies have explored whether the reduction in prolactin levels is followed by an improvement in cognitive tasks.

Prolactinomas are adenomas of the pituitary gland that cause hyperprolactinaemia and require treatment with dopamine agonists (e.g. cabergoline) when prolactin-related symptoms appear. Although a recent study (Bala *et al.*, 2016) carried out in patients with a prolactinoma suggests that overproduction of prolactin causes memory and attention impairments, no previous studies have explored whether the reduction in prolactin levels by dopamine agonists is followed by an improvement in cognitive tasks. Thus, the main aim of our study was to carry out a preliminary study to explore this issue.

Patients and methods

Patients

We studied 10 patients who had hyperprolactinaemia caused by a prolactinoma and had received an indication to start treatment with cabergoline. All prolactinomas were microprolactinomas (< 10 mm in diameter). Participants were recruited from the Endocrinology Department of Corporació Sanitària Parc Taulí (Sabadell, Spain). Exclusion criteria were mental illness, prolactin-elevating drugs, substance abuse or dependence, mental retardation, dementia, endocrinological disorder other than hyperprolactinaemia, autoimmune diseases and pregnancy.

All patients provided written informed consent before starting the study. We had previously obtained study approval by the local ethics committee. All patients completed a baseline visit before starting cabergoline treatment. We aimed to follow-up with patients during a second visit 6–12 months after the baseline visit. Of the 10 patients, seven completed the follow-up visit and three patients did not complete the follow-up visit because of pregnancy, a change in the place of residence and the refusal to take cabergoline.

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Clinical assessment

All patients were screened using the 12-Item General Health Questionnaire (Sanchez-Lopez and Dresch, 2008) to assess their overall psychological well-being and thus to ensure that they had no current anxiety or mood symptoms. All participants had a 12-Item General Health Questionnaire score less than 4.

Cognitive functioning was assessed at baseline and at follow-up. To assess six different cognitive domains, we used nine tests from the MATRICS Consensus Cognitive Battery (MCCB) (Nuechterlein *et al.*, 2008), without administering the social cognition task. The following tests were administered: the Brief Assessment of Cognition in Schizophrenia-Symbol Coding (speed of processing), a Category Fluency-Animal Naming test (speed of processing), the Trail Making Test Part A (speed of processing), Continuous Performance Test-Identical Pairs (attention and vigilance), WMS-III Spatial Span (working memory), University of Maryland Letter-Number Span (working memory), Hopkins Verbal Learning Test-Revised (verbal learning), Brief Visuospatial Memory Test-Revised (visual learning) and Neuropsychological Assessment Battery-Mazes (reasoning and problem solving). For visual learning, alternate forms of the Brief Visuospatial Memory Test-Revised were used to minimize practice effects.

We decided to use this cognitive battery because the MCCB has shown practicality of administration, high test–retest reliability and minimal practice effects. Moreover, we had previously found a relationship between prolactin levels and cognitive functioning in some MCCB tasks in a study that included patients with a psychotic disorder (Montalvo *et al.*, 2014). For each cognitive domain, we used the age-adjusted and sex-adjusted *T*-scores generated by the MCCB computer-scoring program. A neurocognitive composite score was calculated using the *T*-scores for the six cognitive domains assessed.

Hormonal measures

A fasting blood sample was obtained in the morning under resting conditions to determine unstimulated plasma prolactin levels. Prolactin concentrations were measured using an electrochemiluminescence immunoassay system with the Elecsys Prolactin II Assay (Roche Diagnostics, Indianapolis, Indiana, USA). The sensitivity of the prolactin assay was 0.047 ng/ml. The intra-assay and interassay coefficients of variation were under 6%.

Statistical analyses

The statistical package for the social sciences (SPSS), version 19.0 for Windows (IBM Corporation Software Group, Somers, New York, USA) was used for statistical analysis. Changes in cognitive tasks after cabergoline treatment were assessed using a paired *t*-test. *P* values less than 0.05 were considered significant. We also aimed to explore whether those patients with higher prolactin levels differed in their cabergoline treatment response during cognitive tasks. For this purpose, we considered two groups on the basis of the median values of the baseline prolactin of all patients who completed the follow-up study. A median value of 72.3 ng/ml divided the sample into two groups (very high levels vs. high levels). A repeated-measures analysis of variance was carried out to assess whether there was an interaction effect between time and prolactin group, which would mean that the treatment response differed depending on the baseline prolactin levels.

We also explored whether changes in prolactin levels (difference between baseline and final visits) correlate with cognitive changes after cabergoline treatment. Cognitive changes for each of the nine tests were calculated using *z*-scores. For each cognitive task, the difference between baseline and final cognitive raw scores was divided by the SD of the baseline measure. Spearman's correlation was used to explore the relationship between prolactin and cognitive changes.

Results

Prolactin and cognitive changes

Demographic and clinical data of all seven participants who completed the follow-up study are shown in Table 1. Most patients were women (85.7%). The mean (SD) age of the sample was 39.5 (3.8) years. As expected, we found that prolactin levels decreased after cabergoline treatment in all patients (Table 2). We found a significant improvement in the speed of processing, working memory, visual learning and reasoning and problem-solving domains between the baseline and the follow-up visit (Table 2).

Cognitive changes by prolactin group (baseline prolactin levels below vs. above the median)

In the repeated-measures analysis of variance analysis, a significant effect for time (baseline visit vs. post-cabergoline visit) was found for the speed of processing, working memory, visual learning and reasoning and problem-solving domains (Table 3). Moreover, a significant interaction effect between time and prolactin group was found for processing speed and reasoning and problem solving (Table 3). This indicated that the degree of change in these two cognitive tasks differed by prolactin group. As observed in Fig. 1, the improvement in these two domains was greater in patients with baseline prolactin levels above the median. In relation to the overall neurocognitive composite score, we found a significant time effect (but not the interaction between time and prolactin group).

Correlation analyses

In the correlation analyses, of all nine cognitive tests, only the Trail Making Test was associated with prolactin changes ($r = -0.76$, $P = 0.049$). As this processing speed task is measured in seconds, a negative relationship

Table 1 Demographic and clinical data of all seven participants who completed at least one follow-up visit (at 6 or 12 months) after cabergoline treatment

Case	Age	Sex	Education (years)	Visit	Cabergoline dose (mg/week)	Prolactin (ng/ml)	SOP	AV	WM	Verbal learning	Visual learning	RPS
1	41	Female	8	Baseline	0	118.6	47	52	37	32	33	38
				Post-treatment (6 months)	0.5	13.99	66	47	50	43	55	49
2	41	Female	11	Baseline	0	55.84	49	45	46	50	59	50
				Post-treatment (12 months)	0.25	18.0	56	NA	48	50	61	53
3	36	Female	9	Baseline	0	46.42	27	24	28	26	39	37
				Post-treatment (12 months)	0.25	7.67	29	31	36	35	46	42
4	40	Female	12	Baseline	0	75.53	52	51	52	62	58	46
				Post-treatment (6 months)	0.5	23.22	67	55	52	48	67	60
5	34	Male	10	Baseline	0	249.9	37	41	40	38	56	55
				Post-treatment (12 months)	0.25	7.29	49	64	51	31	64	63
6	44	Female	10	Baseline	0	72.27	59	64	62	53	57	66
				Post-treatment (12 months)	0.5	41.84	68	60	67	50	71	70
7	42	Female	14	Baseline	0	43.73	69	54	54	53	65	53
				Post-treatment (12 months)	0.25	15.11	63	67	58	62	70	61

Cognitive data are represented as age-adjusted and sex-adjusted *T*-scores for each cognitive domain.
AV, attention and vigilance; NA, not assessed; RPS, reasoning and problem solving; SOP, speed of processing; WM, working memory.

Table 2 Prolactin and cognitive changes after cabergoline treatment in seven patients with a prolactinoma

	Baseline visit	Post-treatment visit	*P* value[a]
Prolactin (ng/ml)	94.6 (73.0)	18.2 (11.8)	0.041
MCCB cognitive tests (raw data)			
Speed of processing			
Trail Making Test, part A (s)[b]	30.1 (8.6)	25.1 (10.7)	0.195
Brief Assessment of Cognition in Schizophrenia-Symbol Coding	57.4 (12.4)	65.1 (12.5)	0.006
Category fluency: animal naming	24.3 (5.7)	26.6 (6.2)	0.410
Attention and vigilance			
Continuous Performance Test-Identical Pairs	2.8 (0.9)	3.2 (0.8)	0.205
Working memory			
Working Memory-III Spatial Span	16.6 (3.2)	18.3 (2.5)	0.070
Letter-number span	12.4 (3.5)	14.1 (3.3)	0.045
Verbal learning			
Hopkins Verbal Learning Test-Revised	25.3 (7.0)	26.1 (5.4)	0.669
Visual learning			
Brief Visuospatial Memory Test-Revised	26.6 (6.5)	32.1 (4.7)	0.009
Reasoning and problem solving			
Neuropsychological Assessment Battery mazes	18.7 (5.5)	22.3 (3.8)	0.012
MCCB cognitive domains (*T*-scores)[c]			
Speed of processing	48.6 (13.8)	56.9 (14.1)	0.039
Attention and vigilance	47.7 (13.7)	54.0 (13.3)	0.204
Working memory	45.3 (12.0)	51.7 (9.5)	0.014
Verbal learning	44.9 (13.0)	45.6 (10.4)	0.848
Visual learning	52.4 (11.7)	62.0 (8.9)	0.009
Reasoning and problem solving	49.3 (10.1)	56.9 (9.4)	0.002
Neurocognitive composite factor	47.6 (11.7)	54.6 (10.2)	0.002

Data are mean (SD).
P values (two-tailed) are shown.
Significance was set at $P < 0.05$.
MCCB, MATRICS Consensus Cognitive Battery.
[a]A paired *t*-test was applied.
[b]For all cognitive tests, higher scores reflect a better cognitive performance, with the exception of the Trail Making Test. As this test is measured in seconds, lower scores reflect a better cognitive performance.
[c]Age-adjusted and sex-adjusted *T*-scores.

indicates that a greater reduction in prolactin levels after cabergoline treatment is associated with improved processing speed. Changes in overall cognition, as measured with the neurocognitive composite score, were not associated with prolactin changes.

Discussion

Our preliminary findings from a case series of patients with hyperprolactinaemia secondary to a prolactinoma suggest that a reduction in prolactin with cabergoline improves cognition in several domains. To our knowledge, this is the first study to find a cognitive-enhancement effect of cabergoline in patients with hyperprolactinaemia.

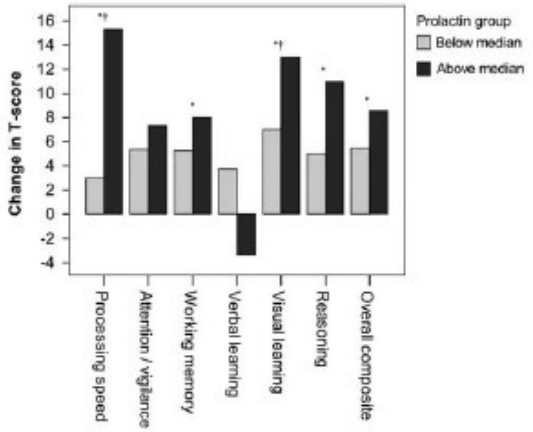
Cabergoline as a cognitive enhancer

Cabergoline is a potent dopamine D2 agonist and a weak D1 agonist one that could improve cognition by several distinct mechanisms. The first is by D2 agonism on the

Table 3 Within-patient effects of the repeated-measures analysis of variance considering the interaction between time (baseline visit vs. postcabergoline visit) and prolactin group (below or above the median)

	Time effect			Time × prolactin group effect		
	F	*P* value	η^2	*F*	*P* value	η^2
Speed of processing	18.16	0.008	0.78	8.22	0.035	0.62
Attention and vigilance	1.73	0.259	0.30	0.04	0.846	0.01
Working memory	11.34	0.020	0.69	0.49	0.516	0.09
Verbal learning	0.003	0.956	0.001	0.96	0.372	0.16
Visual learning	17.14	0.009	0.77	1.54	0.269	0.24
Reasoning and problem solving	68.57	<0.001	0.93	9.84	0.027	0.66
Neurocognitive composite score (overall)	40.04	0.003	0.91	1.98	0.232	1.98

Fig. 1



Cognitive performance in patients with prolactin levels above or below the median (72.3 ng/ml). *$P < 0.05$ for the time effect (baseline visit vs. postcabergoline visit). †$P < 0.05$ for the prolactin group × time effect.

striatal D2 receptors, which modulate cognitive processes and enhance D1 receptor expression (Stelzel *et al.*, 2013). Second, D1 and D2 agonisms on the prefrontal cortex may contribute towards the improvement in cognitive domains associated with prefrontal cortex activity (executive functions and working memory) (Puig and Miller, 2014). Finally, D2 agonism on the tuberoinfundibular pathway causes a reduction in prolactin levels. We believe that this last mechanism (D2 agonism on the tuberoinfundibular pathway) is the main reason for cognitive improvement by cabergoline because a greater effect was found in patients with higher baseline prolactin levels.

Cognitive domains and prolactin

Of all six cognitive domains that were assessed in our study, we found a significant improvement in four (speed of processing, working memory, visual learning and reasoning and problem solving) after cabergoline treatment. For two specific domains (speed of processing and reasoning and problem solving), the improvement was more evident for patients with higher baseline prolactin levels. These results are in agreement with our previous study that included patients with early psychosis and also found a negative relationship between prolactin and performance in these two cognitive tasks (Montalvo *et al.*, 2014). In that study, which included patients with a psychotic disorder at early stages of the illness and individuals at high risk of psychosis [at-risk mental states ARMS)], prolactin levels were associated negatively with processing speed in both groups and with impaired reasoning and problem solving in ARMS patients. It is noteworthy that most ARMS individuals were not receiving antipsychotic treatment, lending support to the hypothesis that hyperprolactinaemia may affect cognitive processes independent of antipsychotic treatment. Moreover, in those early psychotic patients receiving antipsychotic treatment, increased prolactin levels mediated the negative effects of prolactin-elevating antipsychotics on processing speed.

Limitations and strengths

The main limitation of our study is the small sample size. Our results are preliminary and need to be replicated in larger samples before drawing definitive conclusions. However, although the sample size was small, the post-hoc statistical power was adequate for some cognitive domains (100% reasoning and problem solving, 92% for speed of processing, 91% for visual learning and 77% for working memory) because the effect size was large (the partial η^2 values for all four domains were >0.77). The analyses of attention and vigilance or verbal learning were underpowered as the effect sizes of the changes in these domains were smaller.

The main strength of our study is that it is the first to show that cabergoline treatment of patients with a prolactinoma is associated with improved cognitive performance. If our findings are replicated in further studies, they may have potential clinical implications. Currently, the monitoring of hyperprolactinaemia side effects is focused on sexual and reproductive functions. However, our study suggests that prolactin may also have brain effects that influence cognitive processes, which should be considered when treating patients with hyperprolactinaemia. These patients may benefit from cabergoline treatment to improve their cognitive abilities. This

knowledge may be particularly important for patients with psychotic disorders, who can suffer from chronic hyperprolactinaemia (secondary to D2 receptor blockade in the tuberoinfundibular dopaminergic pathway by antipsychotic drugs) and cognitive alterations, which are determinants of functional outcomes. A potential problem in treating psychotic patients with cabergoline is the risk of worsening their psychotic symptoms or triggering a psychotic relapse because of D2 agonism on the mesolimbic pathway (Chang *et al.*, 2008). However, open-label trials have reported reductions in prolactin levels with relatively low doses of cabergoline (between 0.5 and 1 mg/week) without worsening the psychotic symptoms (Cavallaro *et al.*, 2004; Coronas *et al.*, 2012). A recently published large study (Kalkavoura *et al.*, 2013) using greater doses (0.25, 0.5 and 1 mg/day) for 6 months even reported an improvement in the severity of psychotic symptoms without psychotic exacerbations. All of the above studies suggest that cabergoline may be a safer treatment than was initially believed.

However, we have to underscore that our results only apply to patients with a prolactinoma and that the potential treatment of other populations with chronic hyperprolactinaemia, particularly those patients with a psychotic disorder, needs to be further studied.

Conclusion

In summary, our study suggests that the reduction in prolactin levels by cabergoline in patients with hyperprolactinaemia is followed by an improvement in cognitive abilities. This suggests that prolactin may be involved in cognitive processes, although cabergoline could also have procognitive effects that are independent of prolactin changes. Further clinical trials are needed to confirm the potential cognitive-enhancement properties of cabergoline in patients with chronic hyperprolactinaemia.

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Itziar Montalvo, Olga Giménez-Palop and Javier Labad designed the study and wrote the protocol. Javier Labad carried out the statistical analysis. Itziar Montalvo, Marta Llorens and Laia Caparròs performed the literature searches. Itziar Montalvo wrote the first draft of the manuscript, which was supervised by Javier Labad and Olga Giménez-Palop. Assumpta Caixàs, Jordi Torralbas, Marta Llorens and Itziar Montalvo participated in the recruitment and obtained clinical data. Montserrat Pamias and Diego Palao contributed towards the interpretation of the results and discussion, along with all other authors. All authors contributed to and have approved the final manuscript.

Conflicts of interest

Javier Labad and Itziar Montalvo have received honoraria for lectures or advisory boards from Janssen-Cilag, Otsuka or Lundbeck. For the remaining authors there are no conflicts of interest.

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