Universitat Autònoma de Barcelona

# ESTIMULACIÓN CEREBRAL PROFUNDA EN ESQUIZOFRENIA RESISTENTE

**Alexandra Roldán Bejarano**

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Tesis Doctoral presentada por:

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para obtener el grado de Doctor por la Universitat Autònoma de Barcelona

DOCTORAT EN PSIQUIATRIA
DEPARTAMENT DE PSIQUIATRIA I MEDICINA LEGAL
FACULTAT DE MEDICINA
UNIVERSITAT AUTÒNOMA DE BARCELONA
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Barcelona, 2020

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**Certifican**:

Que han supervisado la **Tesis Doctoral** titulada:

ESTIMULACIÓN CEREBRAL PROFUNDA EN ESQUIZOFRENIA RESISTENTE

realizada por **Alexandra Roldán Bejarano** y consideran que es apta para el trámite de lectura y defensa pública delante de un tribunal, para optar al grado de Doctor por la Universistat Autònoma de Barcelona.

Por tal motivo queda constancia en el presente documento en Barcelona, a 18 de noviembre de 2020.

Firmado,

Dra. Iluminada Corripio Collado

Dra. Maria J. Portella

A mis padres y a mi yaya.
A Kilian, para darle fuerza en su camino.
A mis amigos

«La utopía está en el horizonte. Camino dos pasos, ella se aleja dos pasos y el horizonte se corre diez pasos más allá. Por mucho que camine nunca la alcanzaré. Entonces, ¿para qué sirve la utopía? Para eso, sirve para caminar».

**Eduardo Galeano**

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A mis padres, sobre todo por el cariño y el amor incondicional que me han dado desde que tengo recuerdo. Por haberme educado con valores como el respeto, la sencillez y la humildad, que creo son imprescindibles para apreciar lo bueno de la vida. Por poner todo su esfuerzo dedicado a que pudiera llegar a donde quisiera. Sin duda, en ellos tengo la prueba que con perseverancia se consigue aquello que anhelas, pero sin olvidar pasárselo bien. Gracias por estar ahí siempre.

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# PRÓLOGO

La presente tesis se ha elaborado entre los años 2016 y 2020 durante mi ejercicio como psiquiatra en el Hospital de la Santa Creu i Sant Pau y, en parte, como becaria del Institut de Recerca mediante un Contrato Río Hortega. Se presenta en forma de compendio de publicaciones y la componen los siguientes dos estudios, publicados en revistas internacionales indexadas y con factor de impacto.

## Estudio 1

Corripio, I., Roldán, A., Sarró, S., McKenna, P. J., Alonso-Solís, A., Rabella, M., … Portella, M. J. (2020). Deep brain stimulation in treatment resistant schizophrenia: A pilot randomized cross-over clinical trial. EBioMedicine, 51. https://doi.org/10.1016/j.ebiom.2019.11.029

## Estudio 2

Roldán, A., Portella, M. J., Sampedro, F., Alonso-Solís, A., Sarró, S.,Rabella, M., …Corripio, I. Brain Metabolic Changes in Patients With Treatment Resistant Schizophrenia Treated With Deep Brain Stimulation: A Series of Cases. J Psychiatr Res. 2020 Aug;127:57-61. https://doi: 10.1016/j.jpsychires.2020.05.016.

Asimismo, se añaden otros cuatro artículos elaborados durante los años de estudiante de doctorado y relacionados con el motivo de esta tesis, los cuales se incluyen en el anexo. Dos de ellos están ya publicados en revistas internacionales y, otros dos, pendientes de publicación.

## Estudio 3

Molins, C., Roldán, A., Corripio, I., Isohanni, M., Miettunen, J., Seppälä, J., … Jääskeläinen, E. (2016). Response to antipsychotic drugs in treatment-resistant schizophrenia: Conclusions based on systematic review. Schizophrenia Research, 178(1–3), 64–67. https://doi.org/10.1016/j.schres.2016.09.016

## Estudio 4

Galling, B., Roldán, A., Hagi, K., Rietschel, L., Walyzada, F., Zheng, W., … Correll, C. U. (2017). Antipsychotic augmentation vs. monotherapy in schizophrenia: systematic review, meta-analysis and meta-regression analysis. World Psychiatry, 16(1), 77–89. https://doi.org/10.1002/wps.20387

## Estudio 5

Corripio, I., Roldán A., McKenna PJ., Sarró, S., Alonso-Solís, A., Salgado, …Portella, MJ. Target selection for deep brain stimulation in treatment resistant schizophrenia. Pendiente de aceptación.

## Estudio 6

Sampedro, F., Roldán, A., Alonso-Solís, A., Grasa, EM., Portella, MJ., …Corripio, I. Gray matter microstructural alterations in schizophrenia patients with treatment-resistant auditory verbal hallucinations. Bajo revision en la Journal of Psychiatric Research.

Además, a lo largo de estos años la candidata a doctoranda ha realizado difusión de estos estudios, en congresos de psiquiatría nacionales e internacionales, en forma de los pósteres o comunicaciones que se detallan a continuación:

## PÓSTERES:

· Roldán, A., Sarró, S., Rabella, M., Sampedro, F., Alonso-Solís, A., Grasa, EM., Portella, MJ., Pérez, V., Àlvarez, E., Molet, J., Rodríguez, R., McKenna, PJ., Pomarol-Clotet, E., Corripio, I. Deep Brain Stimulation in Treatment Resistant Schizophrenia: PET changes post-stimulation. 31th European Congress of Neuropsychopharmacology (ECNP), 2018.

· Roldán, A., Sarró, S., Rabella, M., Sampedro, F., Alonso-Solís, A., Portella, MJ., Ana M. Díaz, Àlvarez, E., Molet, J., Rodríguez, R., McKenna, PJ., Pomarol-Clotet, E., Corripio, I. Estimulación Cerebral Profunda en Esquizofrenia Resistente al Tratamiento: datos preliminares de los cambios en PET. XXI Congreso nacional de Psiquiatría, Granada 2018.

· Corripio, I., Pomarol-Clotet, E., Peter McKenna PJ., Sarró, S., Puigdemont, D., Molet, J., Roldán, A. Deep Brain Stimulation: first trial in treatment-resistant schizophrenia. III International Brain Stimulation Conference. Vancouver, 2019.

· Post-stimulation PET changes in the first Deep Brain Stimulation in Treatment Resistant Schizophrenia trial. III International Brain Stimulation Conference. Vancouver, 2019.

## COMUNICACIONES:

· Alexandra Roldán. Conferencia invitada en les Jornades Intensives en Patologies Resistents (8ª edición), Fidmag Germanes Hospitalàries, 2019.

· Alexandra Roldán. Tratamientos biológicos no farmacológicos. Ponencia invitada en el VIII Foro Internacional de Esquizofrenia Cibersam, 2019.

· Alexandra Roldán. Conferencia invitada en les Jornades Intensives en Patologies Resistents (7ª edición), Fidmag Germanes Hospitalàries, 2018.

· Alexandra Roldán. Estimulación Cerebral Profunda en Esquizofrenia Resistente: Sant Pau/Fidmag trial. Comunicación oral en el VII Foro Internacional de Esquizofrenia Cibersam, 2018.

· Roldán, A., Sarró, S., Rabella, M., Sampedro, F., Alonso-Solís, A., Grasa, EM., Portella, MJ., Pérez-Solà, V., Àlvarez, E., Molet, J., Rodríguez, R., McKenna, PJ., Pomarol-Clotet, E., Corripio, I. Deep Brain Stimulation in Treatment Resistant Schizophrenia: post-stimulation PET changes. Comunicación oral en el 31th European Congress of Neuropsychopharmacology (ECNP), 2018.

# ACRÓNIMOS

**AMPc**: Adenosín monofosfato cíclico
**AS**: del inglés, Associative Striatum (estriado asociativo)
**ASL**: del inglés, Arterial Spin Labeled
**ATV**: área tegmental ventral
**BOLD**: del inglés, Blood-Oxygen-Level Dependent contrast imaging (contraste de imagen dependiente del nivel de oxigenación de la sangre)
**CBF**: del inglés, Cerebral Blood Flow (flujo de sangre cerebral)
**CCA**: córtex cingulado anterior
**CDS**: escala calgary para la depresión
**Cg25**: área Broadman Cg25
**CGI**: del inglés, Clinical Global Impression (escala de impresión clínica global)
**CGIi**: del inglés, Clinical Global Impression (escala de impresión clínica global de mejoría global)
**CGIs**: del inglés, Clinical Global Impression (escala de impresión clínica global de gravedad)
**CI**: coeficiente intelectual
**CPF**: córtex prefronatal
**CPFm**: córtex prefrontal medial
**CPFDL**: córtex prefrontal dorsolateral
**DA**: dopamina
**DMN**: del inglés, Default Mode Network (red neuronal por defecto)
**DTI**: del inglés, Diffusion Tensor Imaging (neuroimagen por tensión de difusión)
**ECP**: estimulación cerebral profunda
**EEAG**: escala de evaluación de la actividad global
**EPSC**: del inglés, Evoked Postsynaptic Current (corriente post-sináptica evocada)
**ERT**: esquizofrenia resistente al tratamiento
**ESRS**: del inglés, Extrapyramidal Symptom Rating Scale (escala de síntomas extrapiramidales)
**FA**: anisotropía fraccional
**FDA**: del inglés, Food and Drug Administration
**FDG**: fluorodesoxiglucosa
**fMR**: del inglés, functional Magnetic Resonance (resonancia magnética funcional)
**GABA**: ácido gamma aminobutírico
**GDNF**: del inglés, Glial cell-derived neurotrophic factor (factor neurotrófico derivado de la línea celular glial)
**Glu**: glutamato
**GPe**: globo pálido externo
**GPi**: globo pálido interno
**GPv**: globo pálido ventral
**HFS**: del inglés, High Frequency Stimulation (estimulación de alta frecuencia)
**MFB**: del inglés, Medial Forebrain Bundle
**MR**: del inglés, Magnetic Resonance (resonancia magnética)
**MRS**: del inglés, Magnetic Resonance Spectroscopy (espectroscopía por resonancia magnética)
**MSN**: núcleo septal medial
**NAc**: núcleo accumbens
**NMDA**: N-metil-D-aspartato
**OFC**: córtex orbito-frontal
**PANSS**: del inglés, Positive and Negative Syndrome Scale (escala del síndrome positivo y negativo de la esquizofrenia)
**PKA**: protein-kinasa A
**PPI**: inhibición pre-pulso
**PSP**: del inglés, Personal and Social Performance (escala de funcionamiento personal y social)
**rCBF**: del inglés, regional Cerebral Blood Flow (flujo de sangre cerebral regional)
**SANS**: escala para síntomas negativos de la esquizofrenia
**SB**: sustancia blanca
**SFS**: del inglés, Social Functioning Scale (escala de funcionalidad social)
**SG**: sustancia gris
**SgACC**: córtex cingulado anterior subgenual
**SMS**: del inglés, Sensorimotor Striatum (estriado sensorimotor)
**SN**: sustancia negra
**SNr**: Sustancia negra pars reticulada
**SNpc**: Sustancia negra pars compacta
**SPECT**: del inglés, Single Photon Emission Computed Tomography (tomografía computerizada por emisión de fotones)
**TDR**: trastorno depresivo mayor resistente al tratamiento
**TMD**: tálamo mediodorsal o núcleo mediodorsal del tálamo
**TOC**: trastorno obsesivo-compulsivo
**STN**: núcleo subtalámico
**TEC**: terapia electroconvulsiva
**UKU**: escala de efectos secundarios Udvalg für Kliniske Undersogelser
**VC/VS**: del inglés, Ventral Capsule/Ventral Striatum (cápsula ventral/estriado ventral)
**VS**: del inglés, Ventral Striatum (estriado ventral)
**WAIS**: del inglés, Wechsler Adult Intelligence Scale (escala wechsler de inteligencia para adultos)

# 1. INTRODUCCIÓN

## 1.1. LA ESQUIZOFRENIA Y LA ESQUIZOFRENIA RESISTENTE

La esquizofrenia es un trastorno mental altamente incapacitante que afecta a alrededor del 1% de la población y que se caracteriza por la aparición de síntomas psicóticos positivos (delirios, alucinaciones auditivas, desorganización del pensamiento, etc.), negativos (apatía, alogia, aplanamiento afectivo, asociabilidad, etc.) y cognitivos (alteraciones de funciones ejecutivas, atención y memoria) (Kahn et al., 2015). El debut de la enfermedad suele aparecer en la adolescencia o adultez temprana, y a menudo está precedido por la 'fase prodrómica', que consiste en un declive de funciones ejecutivas y sociabilidad durante la adolescencia temprana (Kahn et al., 2015). El pico de incidencia del primer episodio psicótico se encuentra entre los 20-24 años para los varones y los 29-32 años para las mujeres (Stilo & Murray, 2010), con una incidencia algo más frecuente en hombres (riesgo relativo de 1.4/1).

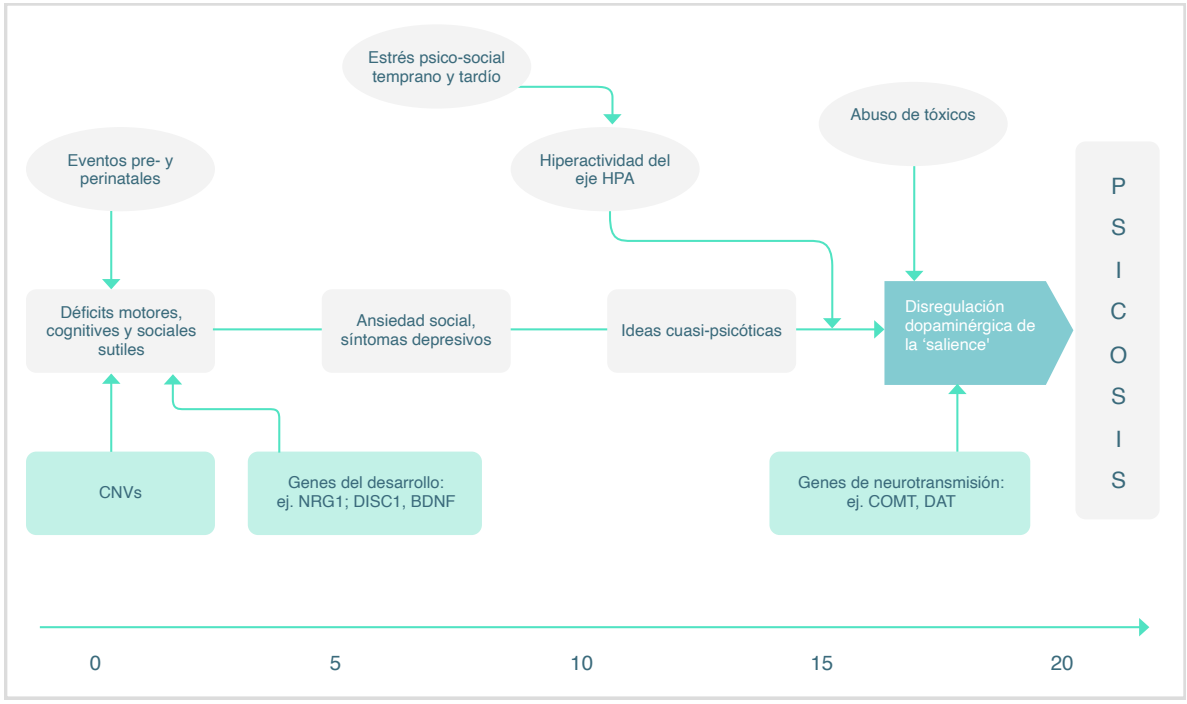


Figura 1. Factores de riesgo para el desarrollo de esquizofrenia (adaptada de Stilo & Murray, 2010). Acrónimos: CNVs: del inglés, copy-number variant; HPA: Eje- hipotálamo-pituitario-adrenal

En cuanto a la etiopatotogenia de la esquizofrenia, la evidencia actual apoya la comúnmente denominada 'hipótesis del neurodesarrollo'. Esta hipótesis trata de explicar cómo diversos factores inciden sobre la organización histológica y estructural de circuitos neuronales, alterando el proceso normal de desarrollo cerebral en estos pacientes (Mjellem & Kringlen, 2001). Se han descrito desde factores biológicos, como la genética o eventos pre y perinatales (complicaciones durante el embarazo o el parto, infecciones o malnutrición materna), a factores ambientales como el estrés psico-social (impacto de los ambientes urbanos, estados migratorios o eventos vitales estresantes durante la infancia) o el consumo de sustancias. En la figura 1 (adaptada de Stilo & Murray, 2010) se resumen los distintos factores implicados en la hipótesis del neurodesarrollo.

Sin embargo, el periodo de latencia entre el desarrollo embrionario y la aparición de los primeros síntomas, el deterioro durante los primeros años de enfermedad y la progresión sintomática y de los cambios en la neuroimagen de estos pacientes también han apoyado durante años la 'hipótesis neurodegenerativa'. Esta hipótesis expone la idea de que la enfermedad mantiene un curso degenerativo que afecta a la pérdida de la función neurológica y conlleva en estos pacientes un deterioro cognitivo (Pino et al., 2014). El proceso neurodegenerativo en pacientes con esquizofrenia es evidente en estudios donde se observa la presencia de neurotoxicidad, de alteraciones morfológicas en el cerebro (como la reducción de los lóbulos frontal y temporal, así como un alargamiento de ventrículos) o en los que parece que el tratamiento antipsicótico disminuye la progresión de la enfermedad. Por todo ello, algunos autores apoyan un modelo integrativo basado en un trastorno del neurodesarrollo progresivo, como una condición en que el neurodesarrollo estaría alterado y progresa de manera variable entre los diferentes individuos (Insel, 2010).

Esto explicaría también que el pronóstico de la esquizofrenia pueda variar desde la recuperación completa hasta la cronicidad, a menudo con un curso de la enfermedad con frecuentes remisiones y recaídas (ver figura 2).

Se ha estimado que los pacientes con esquizofrenia presentan una esperanza de vida 20 años menor que la población general (Laursen, Mortensen, Maccabe, Cohen, & Gasse, 2014) y generalmente experimentan serias alteraciones en múltiples dominios de la vida diaria, incluyendo la habilidad para mantener relaciones sociales, sostener un empleo o vivir de manera independiente (Harvey, 2014). Estos déficits generalmente persisten a pesar de que el paciente alcance la remisión de los síntomas psicóticos (Kahn et al., 2015).

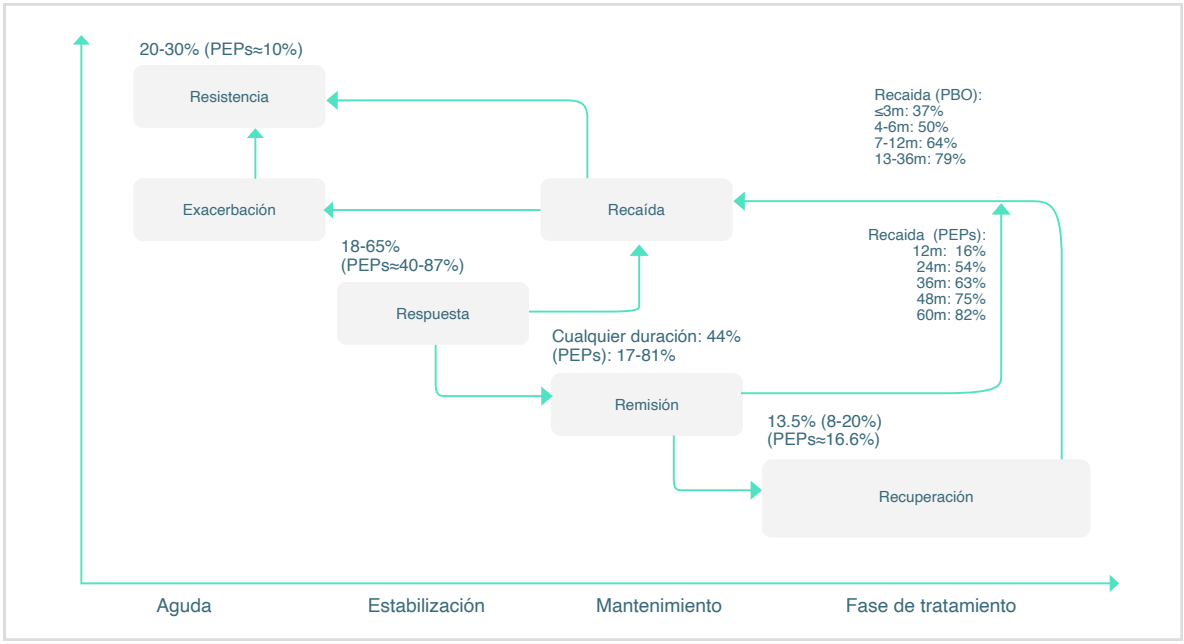


Figura 2. Fases de tratamiento y 'outcomes' en esquizofrenia (adaptada de CarbonM. & Correll, 2014). Acrónimos: PBO: placebo; PEP: primer episodio psicótico.

Además, se estima que alrededor de un 20-30% de los pacientes con diagnóstico de esquizofrenia no responden adecuadamente al tratamiento antipsicótico convencional (Siskind, Siskind, & Kisely, 2017), considerándolos pacientes resistentes al tratamiento (ver criterios consensuados en tabla 1) (Howes et al., 2017).

Estos pacientes experimentan síntomas permanentemente, los cuales originan una importante limitación funcional y en su calidad de vida, lo que a su vez que conlleva una profunda carga para sus familiares o cuidadores (Velligan, Brain, Bouérat Duvold, & Agid, 2019). Además, todo ello implica una mayor complejidad de tratamiento y un notable número de re-hospitalizaciones. Los pacientes resistentes generan, por tanto, un elevado gasto sanitario, que supondría entre el 60-70% de los costes del total en la esquizofrenia (Kennedy, Altar, Taylor, Degtiar, & Hornberger, 2014).

Entre los factores que se han asociado a la resistencia al tratamiento se encuentran: complicaciones obstétricas, historia familiar de esquizofrenia, mayor carga genética, menor edad de inicio de la enfermedad, mayor duración de la psicosis sin tratar, predominio de síntomas negativos y presencia de signos neurológicos leves (Leung, Gadelrab, Ntephe, McGuire, & Demjaha, 2019).

| DOMINIO Y SUBDOMINIO | REQUERIMIENTO MÍNIMO | REQUERIMIENTO ÓPTIMO |
|---|---|---|
| **Síntomas actuales** | | |
| Evaluación | Entrevista con una escala estandarizada (ej. PANSS, BPRS, SANS, SAPS) | Evaluación prospectiva del tratamiento utilizando una escala estandarizada |
| Gravedad | Al menos gravedad moderada | Al menos gravedad moderada y < del 20% de disminución de síntomas durante un ensayo prospectivo u observación durante ≥ 6 semanas |
| Duración | ≥12 semanas | ≥12 semanas; especificando la duración de la resistencia al tratamiento |
| Malestar subjetivo | No requerida | No requerida |
| Funcionalidad | Al menos moderada alteración de la funcionalidad evaluada con una escala validad (ej. SOFAS) | Al menos moderada alteración de la funcionalidad evaluada con una escala validad (ej. SOFAS) |
| **Tratamiento adecuado** | | |
| Evaluación de respuesta anterior | La información debe recogerse de informes del paciente/cuidador, cursos clínicos, recuento de comprimidos, etc. | La información debe recogerse de informes del paciente/cuidador, cursos clínicos, recuento de comprimidos, etc. |
| Duración | ≥6 semanas a dosis terapéuticas; registro de dosis mínima y media (DE) para cada episodio de tratamiento | ≥6 semanas a dosis terapéuticas; registro de dosis mínima y media (DE) para cada episodio de tratamiento |
| Dosis | Equivalente a ≥600 mg de clorpromazina al día, registro de dosis mínima y media (DE) para cada tratamiento | Equivalente a ≥600 mg de clorpromazina al día, registro de dosis mínima y media (DE) para cada tratamiento |
| Número de antipsicóticos | ≥2 episodios de tratamiento anterior con diferentes antipsicóticos, especificando número medio de ensayos de tratamiento fallidos | ≥2 episodios de tratamiento anterior con diferentes antipsicóticos, al menos uno de ellos con antipsicóticos de liberación prolongada (durante 4 meses mínimo), especificando número medio de ensayos de tratamiento fallidos |
| Adherencia | ≥80% de las dosis prescritas (la adherencia debe evaluarse mediante 2 fuentes, especificar los métodos utilizados para establecer la adherencia). Monitorizar niveles plasmáticos de antipsicóticos al menos en una ocasión | Los mismos que para criterios mínimos, además de medir los niveles plasmáticos de antipsicóticos al menos en 2 ocasiones con al menos 2 semanas de diferencia (sin advertir al paciente) |
| **Dominio de síntomas** | Positivos, negativos, cognitivos | Los mismos que en criterios mínimos |
| **Curso de la enfermedad** | Inicio temprano (un año desde el inicio de la enfermedad), inicio a medio término (1-5 años tras el inicio de la enfermedad), inicio tardío (> 5 años tras el inicio de enfermedad) | Los mismos que en criterios mínimos |
| **Ultra-resistencia al tratamiento** | Cumple los criterios anteriores para la resistencia al tratamiento y además, falta de respuesta a un tratamiento adecuado con clozapina | Los mismos que en criterios mínimos |

Tabla 1. Criterios de consenso para la evaluación y definición de la Esquizofrenia Resistente al Tratamiento (adaptada de Howes et al., 2017).

## 1.1.1. Neurobiología de la esquizofrenia

Los mecanismos neurobiológicos que subyacen a los síntomas de la esquizofrenia no están todavía completamente dilucidados. La teoría más comúnmente aceptada es la 'hipótesis dopaminérgica'. Ésta se basa en la existencia de una desregulación en la modulación del sistema dopaminérgico cerebral, como resultado de una combinación de múltiples factores de riesgo ambientales y genéticos (Howes & Kapur 2009). A continuación se presenta un breve repaso de los factores neurobiológicos implicados en el sistema dopaminérgico, como son las vías dopaminérgicas y sus circuitos corticales relacionados, los receptores de las células de dopamina, así como un resumen de los hallazgos más relevantes en estudios de neuroimagen realizados en pacientes con esquizofrenia.

### 1.1.1.1. Vías dopaminérgicas

Clásicamente se han descrito 4 vías dopaminérgicas principales (Figura 3): la vía tuberoinfundibular, la vía nigroestriatal, la vía mesocortical y la vía mesolímbica. Existe también una quinta vía, descubierta más recientemente en primates, que inervaría el tálamo y podría estar implicada en mecanismos de mantenimiento de la vigilia, sin existir evidencia todavía de un funcionamiento anormal de esta quinta vía dopaminérgica en la esquizofrenia (Stahl, 2008).

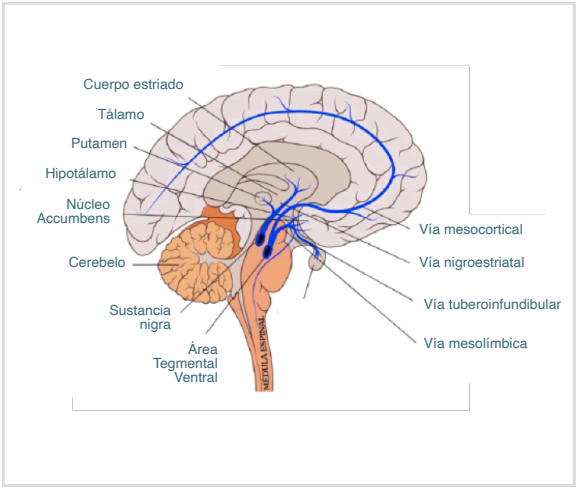


Figura 3. Representación esquemática de las vías dopaminérgicas.

• El sistema dopaminérgico tuberoinfundibular se compone de neuronas dopaminérgicas que proyectan desde el núcleo arqueado del hipotálamo hacia la hipófisis anterior. Normalmente estas neuronas están activas e inhiben la secreción de prolactina. Un bloqueo de los receptores dopaminérgicos mediado por fármacos antipsicóticos podría alterar el funcionamiento de esta vía, produciendo una elevación de niveles de prolactina que podría conllevar galactorrea, amenorrea y, posiblemente, disfunción sexual.

• La vía dopaminérgica nigroestriatal consiste en neuronas cuyos cuerpos celulares se originan en la sustancia negra del tronco del encéfalo y finalizan en terminales axonales de los ganglios basales o del cuerpo estriado. Esta vía forma parte del sistema nervioso extrapiramidal y controla los movimientos motores, por lo que un bloqueo de los receptores dopaminérgicos en esta vía produciría trastornos del movimiento (rigidez, acinesia o bradicinesia, distonía, acatisia, etc.).

• El sistema dopaminérgico mesocortical parte desde cuerpos celulares localizados en el área tegmental ventral del tronco del encéfalo y se dirige al córtex prefrontal. Los haces de esta vía que conectan con el córtex prefrontal dorsolateral se relacionan con la regulación de las funciones ejecutivas, mientras que los haces que llegan a partes ventromediales del córtex prefrontal se vinculan a funciones relacionadas con la regulación de las emociones y el afecto. Un déficit en la actividad dopaminérgica en esta vía podría explicar los síntomas cognitivos y negativos de la enfermedad.

• La vía dopaminérgica mesolímbica también se proyecta desde el área tegmental ventral a los terminales axonales de ciertas áreas límbicas del cerebro, como el núcleo accumbens en el estriado ventral. Se cree que esta vía tiene un importante papel en diversos comportamientos relacionados con la emoción y en la producción de síntomas positivos como los delirios y las alucinaciones. Esta vía es además importante para la motivación, el placer y la recompensa, por lo que también podría tener cierta implicación en los síntomas negativos de la enfermedad.

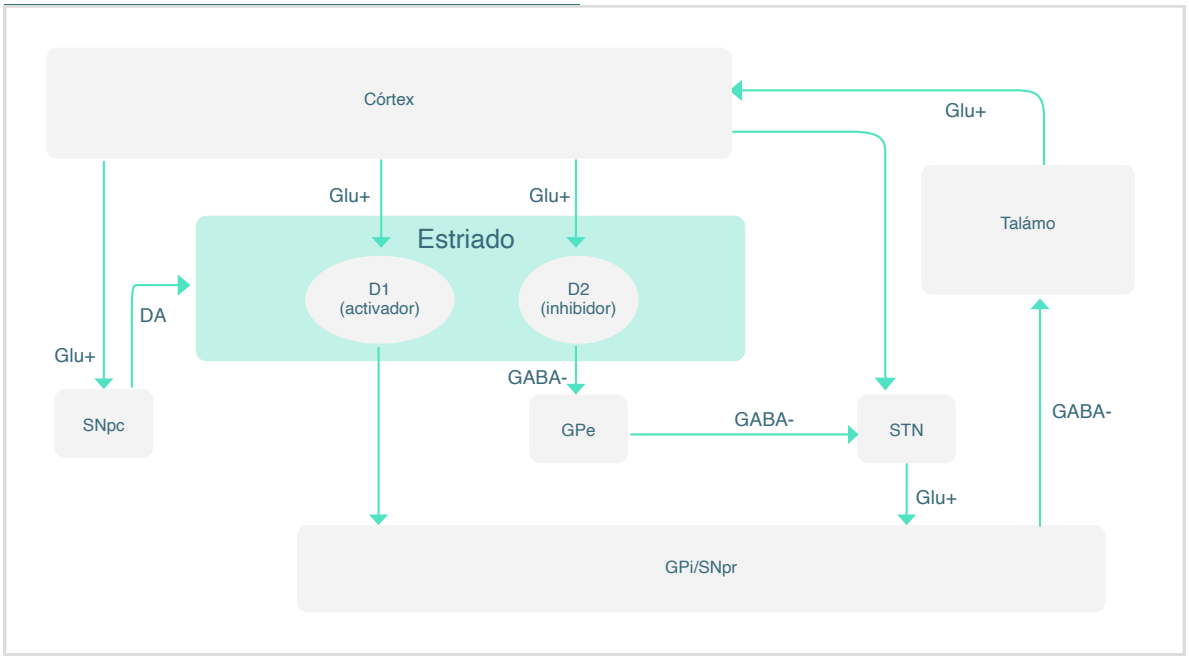


Figura 4. Representación simplificada del circuito sensori-motor. Abreviaciones: GPi, globo pálido interno; GPe, globo pálido externo; SNpr, sustancia nigra pars reticulada; SNpc, sustancia nigra pars compacta; STN, núcleo subtalámico.

## 1.1.1.2. Circuitos implicados en el sistema dopaminérgico

Las conexiones neuronales que unen el córtex cerebral con los ganglios basales se encuentran estrechamente relacionadas con la modulación del sistema dopaminérgico. El núcleo estriado, input principal de los ganglios basales, trabaja conjuntamente con el córtex, el tálamo y las células dopaminérgicas del tronco del encéfalo para modular la transmisión de dichas vías mediante circuitos cortico-estriatales. Se han definido a nivel teórico tres circuitos paralelos e interconectados entre ellos, que parcelan de manera efectiva el estriado en subdivisiones funcionales, según el núcleo diana de la red y sus 'inputs' y 'outputs' específicos. Se trata de los circuitos sensorimotor, límbico y asociativo (Hoover & Strick, 1993).

### • Circuito sensorimotor

La corteza cerebral envía aferencias excitatorias mediadas por glutamato hacia el estriado, siendo el putamen el núcleo principal de entrada. Desde este núcleo se originan dos vías motoras: la vía directa se inicia desde el estriado al globo pálido interno (GPi) y a la sustancia negra pars reticulata (SNr). Estas áreas proyectan, a su vez, hacia el tálamo motor y, desde allí, de nuevo a la corteza motora suplementaria, dentro del córtex prefrontal (Hoover & Strick, 1993). La vía indirecta proyecta desde el putamen hacia el globo pálido externo (GPe), este núcleo envía neuronas inhibitorias al núcleo subtalámico (STN), el cual, a su vez, proyectará neuronas glutamatérgicas a los núcleos de salida GPi y SNr (Haber, 2014). Asimismo, el STN también recibe proyecciones directas de todo el córtex frontal, conociéndose esta vía como 'hiperdirecta' (Figura 4).

Ambas vías (directa e indirecta) modulan la actividad excitatoria o inhibitoria de la corteza frontal, respectivamente. A través de la activación de la vía directa se produciría una disminución de la actividad de las proyecciones inhibitorias del GPi al tálamo, lo que conllevaría un incremento de la actividad talámica y, por tanto, una activación del córtex. En cambio, la activación de la vía indirecta produciría una inhibición talámica y, en consecuencia, una disminución de la actividad de la corteza frontal.

Además, dentro de este circuito motor, existiría una vía dopaminérgica asociada a la sustancia negra pars compacta (SNpc) que, mediante proyecciones nigroestriatales, también modularía la información desde el circuito límbico ventral hacia el córtex mediante la activación de la vía directa (rica en receptores dopaminérgicos D1) o indirecta (rica en receptores D2), dependiendo de las neuronas sobre las que la SNpc proyecte.

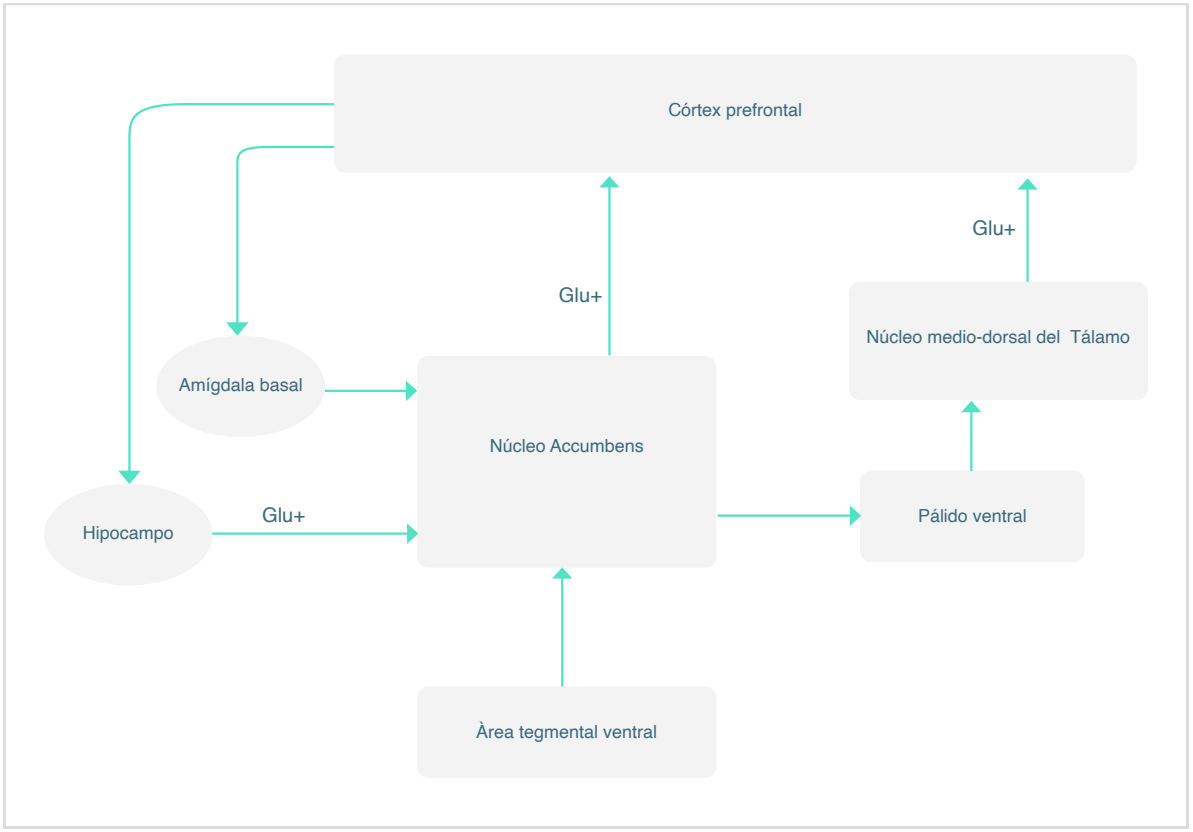


Figura 5. Representación esquemática del circuito límbico

## • Circuito límbico

El principal protagonista de este circuito dentro de los ganglios basales es el estriado ventral, siendo el núcleo de entrada principal el núcleo accumbens (NAc). Desde este área se envían aferencias hacia el globo pálido ventral (GPv), continuando su proyección hacia el tálamo mediodorsal (TMD) y, desde aquí, hacia la denominada corteza límbica, que incluiría el córtex cingulado anterior (CCA), algunas regiones del córtex orbito-frontal (OFC) y el córtex prefrontal medial (CPFm). Desde estas áreas corticales se cerraría el circuito mediante nuevas proyecciones al NAc (Figura 5). Se ha propuesto que el córtex límbico, y por tanto este circuito, estaría relacionado con la recompensa, la motivación, la cognición y el control de las emociones. Además, el NAc es un núcleo importante dentro del sistema dopaminérgico, ya que recibe proyecciones desde el área tegmental ventral (ATV). Esta vía (mesolímbica), como se ha comentado anteriormente, es imprescindible en los mecanismos de motivación y refuerzo de la conducta. Asimismo, el NAc recibiría inputs desde el hipocampo y la amígdala basolateral, contribuyendo a la integración de la información (Figura 5) (Haber, 2014; Hoover & Strick, 1993).

## • Circuito asociativo

El núcleo de entrada principal de este circuito se localizaría en la cabeza del caudado, que envía proyecciones al GPi y a la SNr, alcanzando desde estas áreas el núcleo talámico ventral anterior, el cual proyectaría sus aferencias hacia el córtex prefrontal dorsolateral (CPFDL), así como al OFC medial y lateral. Este circuito estaría implicado en las llamadas funciones ejecutivas, como son la planificación y ejecución de tareas (Haber, 2014)

Tradicionalmente, se han definido estos tres circuitos (sensorimotor, límbico y asociativo) separadamente y con funciones paralelas. Estudios más recientes en primates han evidenciado que muy probablemente estos tres circuitos estarían superpuestos e interconectados entre sí, definiendo un modelo que permitiría la canalización de información entre ellos (Figura 6) y, por tanto, una coordinación funcional que proporcionaría la capacidad de desarrollar comportamientos complejos (McCutcheon, Abi-Dargham, & Howes, 2019).

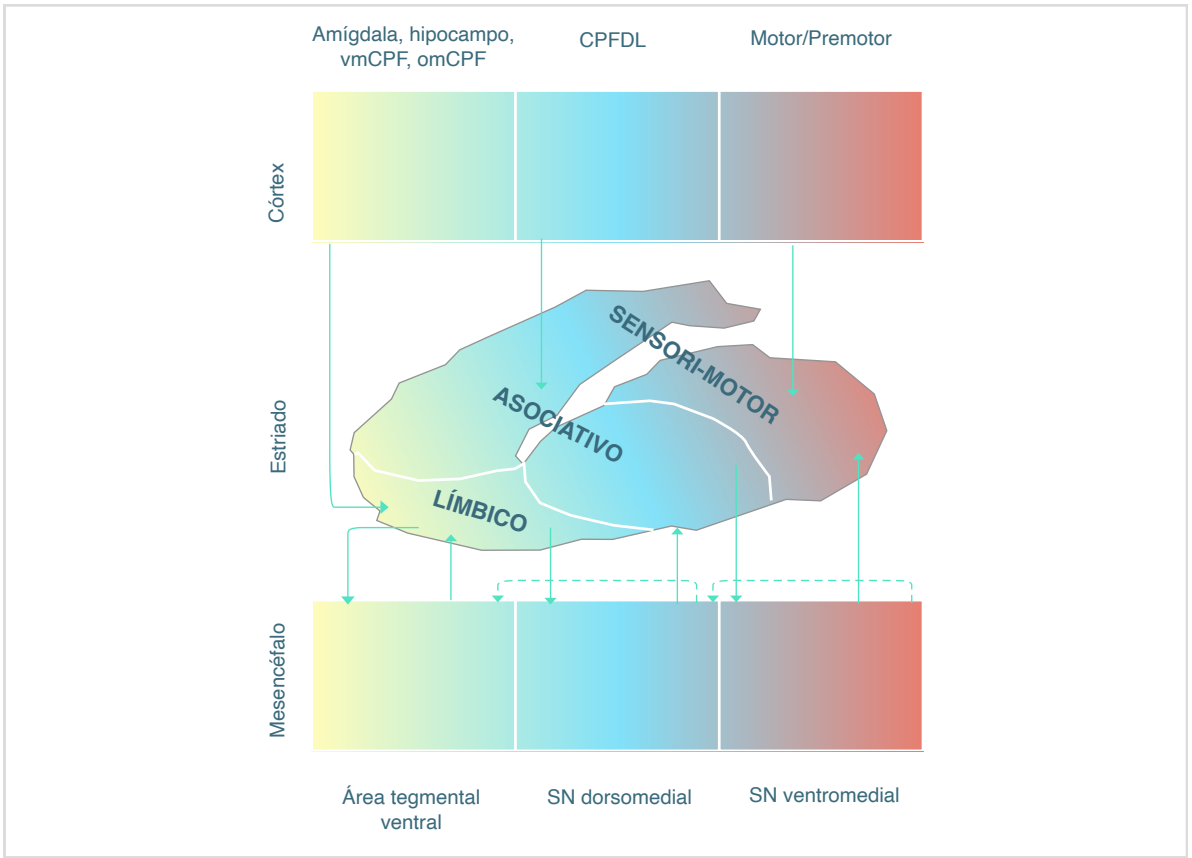


Figura 6. Resumen de los estudios de rastreo en primates que mapean las conexiones entre el córtex, estriado y mesencéfalo. El estriado en primates puede dividirse en el NAc, tubérculo olfactorio, núcleo caudado y putamen. Las conexiones cortico-estriatales discurrirían en tres vías paralelas. Las áreas corticales motoras proyectarían al putamen caudal; el CPFDL al caudado y al putamen rostral; mientras que las áreas límbicas proyectarían al estriado ventral; denominándose estas subdivisiones estriado sensorimotor, estriado asociativo y estriado límbico, respectivamente. A su vez el estriado mantendría conexiones con el mesencéfalo: el ATV y SN medial proyectarían al estriado límbico, mientras que el área más central/ventrolateral de la SN proyectaría al estriado asociativo y sensorimotor. El estriado, a su vez, presenta eferencias de nuevo al mesencéfalo. Además de estas conexiones recíprocas, las conexiones de retroalimentación estriato-nigro-estriatales permiten transferir información mediante el estriado desde áreas límbicas a motoras, a través del estriado asociativo (adaptada de McCutcheon et al., 2019).

### 1.1.1.3. Receptores dopaminérgicos

Existen cinco tipos de receptores dopaminérgicos (D1 a D5), que se codifican en los humanos por los genes DRD1 a DRD5, respectivamente; y median todas las funciones fisiológicas del neurotransmisor catecolaminérgico de la dopamina. Se trata de receptores metabotrópicos (acoplados a proteínas G), los cuales se clasifican a su vez en dos categorías (Beaulieu & Gainetdinov, 2011):

1) La familia RD1-like, formada por los receptores D1 y D5, que se localizan en las células receptoras de dopamina, principalmente a nivel post-sináptico.

2) La familia RD2-like, que comprende los receptores D2, D3 y D4, pudiendo hallarse a nivel post-sináptico y como autorreceptores pre-sinápticos de las neuronas dopaminérgicas.

Los diferentes tipos de receptores dopaminérgicos presentan diferentes localizaciones a nivel cerebral. La mayor representación de los receptores D1 y D5 se encontraría en el estriado, NAc, SNr y bulbo olfatorio. Los RD2 se hallarían en el estriado, y en menor medida, en el hipocampo y tálamo. Los receptores RD3 estarían presentes mayormente en áreas límbicas cerebrales y los RD4 en córtex prefrontal e hipocampo (Beaulieu & Gainetdinov, 2011).

El mecanismo más comúnmente aceptado para la activación de los receptores dopaminérgicos es el mediado a través de proteínas G, lo que conllevaría la estimulación de segundos mensajeros. En el caso de la familia de receptores D1, producirían adenosín monofosfato cíclico (AMPc) y la activación de la protein-kinasa A (PKA). En cambio, la familia D2 (D2, D3 y D4) regularía de manera negativa la producción de AMPc, resultando en una disminución de la actividad de la PKA. Por tanto, las respuestas intracelulares podrían diferir de un grupo celular a otro tras la activación del mismo receptor, dependiendo del estado neuronal presente en el momento de la estimulación (Beaulieu & Gainetdinov, 2011).

### 1.1.1.4. Estudios de neuroimagen

#### • Estudios de neuroimagen estructural

Las anormalidades estructurales cerebrales en la esquizofrenia han sido ampliamente estudiadas a lo largo de los años. En estudios de meta-análisis con amplias muestras de pacientes diagnosticados de esquizofrenia se ha evidenciado un menor volumen hipocampal, en comparación con controles sanos, seguido de un menor volumen en amígdala, tálamo, núcleo accumbens y volúmenes intracraneales, así como volúmenes aumentados en ventrículos laterales y globo pálido (Van Erp et al., 2016). Las personas afectas de esquizofrenia también presentan en comparación con controles sanos un adelgazamiento cortical generalizado y una superficie cortical disminuida, principalmente en regiones frontales y temporales. Las diferencias en el adelgazamiento cortical se correlacionarían negativamente con la dosis de tratamiento, la gravedad de los síntomas y la duración de la enfermedad; mientras que su relación sería positiva con la edad de inicio de la enfermedad (Van Erp et al., 2018). Los estudios que comparan pacientes diagnosticados de esquizofrenia resistente al tratamiento (ERT) con pacientes respondedores muestran, en los primeros, una mayor disminución de sustancia gris en áreas frontales (Mouchlianitis, McCutcheon, & Howes, 2016).

Además, la neuroimagen por tensor de difusión (DTI, por sus siglas en inglés) permite el estudio de la microestructura de la sustancia blanca, mostrando en pacientes con esquizofrenia una anisotropía fraccional (FA, por sus siglas en inglés) disminuida (que refleja el grado de libertad de las moléculas de agua que difunden en todas direcciones), en comparación con controles. Esto ocurre típicamente en los tractos de fibras que conectan los lóbulos frontal y temporal (Kubicki & Shenton, 2014). Sin embargo, hallazgos meta-analíticos recientes han sugerido que la disminución de FA podría ser más generalizada, afectando a la mayor parte de regiones de sustancia blanca, aunque con mayores efectos sobre tractos cortico-talámicos e inter-hemisféricos, incluyendo la corona radiada y el cuerpo calloso (Kelly et al., 2018). Los pocos estudios que comparan pacientes con ERT versus respondedores publicados hasta la fecha, han mostrado resultados inconsistentes (Mouchlianitis, McCutcheon, & Howes, 2016).

#### • Estudios de neuroimagen funcional

La neuroimagen funcional proporciona una visión dinámica del funcionamento cerebral, permitiendo observar la activación de diferentes estructuras durante la realización de tareas cognitivas o en estado de reposo. Los estudios de neuroimagen iniciales medían el flujo cerebral vascular a través de la inhalación de 133Xenon u otros radiotrazadores mediante la tomografía computerizada por emisión de fotones (SPECT, por sus siglas en inglés); mientras que las técnicas

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Las alteraciones en el metabolismo y flujo vascular cerebral han sido demostradas en un meta-análisis de estudios SPECT y PET (Hill et al., 2004). Se identificó una hipo-frontalidad en pacientes con esquizofrenia, aunque con un tamaño del efecto pequeño-medio, siendo éste mayor a mayor tiempo de evolución de la enfermedad. Este mismo meta-análisis también demostró una hipo-frontalidad relacionada con un menor rendimiento en tareas ejecutivas, vigilancia y memoria. En otro meta-análisis de estudios PET y fMR en pacientes con esquizofrenia  a los que se realizaban tareas de 'memoria de trabajo', se halló, además de esta hipo-frontalidad, una activación aumentada en el cingulado anterior y regiones frontales izquierdas (Glahn et al., 2005). También se ha descrito un estado de reposo anormal de la actividad cerebral en estudios  PET, fMR y ASL, identificando una hipoactivación en el CPF ventromedial, hipocampo izquierdo, córtex cingulado posterior y precuneus, así como una hiperactivación en el giro lingual bilateral, en comparación con controles (Kühn & Gallinat, 2013). Un estudio de nuestro mismo grupo de investigación que evaluaba la conectividad funcional en estado de reposo mediante fMR, comparando pacientes con alucinaciones auditivas persistentes y pacientes con esquizofrenia respondedores al tratamiento, observó que los pacientes resistentes mostraban una mayor conectividad entre el CPF dorsomedial y otras áreas frontotemporales, así como una conectividad disminuida entre el CPF ventromedial y áreas del córtex cingulado (Alonso-Solís et al., 2015). Por último, en una revisión sistemática de estudios ASL en esquizofrenia, los autores identificaron disminuciones del flujo cerebral en el lóbulo frontal, giro frontal medio izquierdo, giro frontal inferior y língula, cuneus, giro medio occipital y fusiforme, cingulado anterior y lóbulo parietal, mostrando únicamente el putamen un aumento del flujo cerebral en estos pacientes (Guimarães, Machado-de-Sousa, Crippa, Guimarães, & Hallak, 2016). En un único estudio llevado a cabo con ASL en pacientes con ERT, los pacientes con alucinaciones persistentes mostraron un aumento del flujo cerebral en el giro temporal superior izquierdo y supramarginal derecho, así como en el córtex temporoparietal, en comparación con pacientes respondedores (Wolf et al., 2012).

## • Estudios de neuroimagen de la neuroquímica cerebral

Para investigar los cambios químicos cerebrales se han empleado técnicas de PET, SPECT y resonancia magnética por espectroscopía (MRS, por sus siglas en inglés). Los estudios de PET han examinado, principalmente, los receptores de interés en la esquizofrenia, como la dopamina, la serotonina, el ácido gamma aminobutírico (GABA) y el glutamato.

En el caso de la dopamina (DA), el radiotrazador del precursor de la DA L-dihidroxi-fenilalanina, permite la medición de su recaptación y conversión en las neuronas dopaminérgicas, aportando un índice de la capacidad de síntesis de DA. De forma alternativa, escaneando la competición entre la DA endógena y los radioligandos específicos a receptores dopaminérgicos post-sinápticos, se puede determinar los niveles basales de DA (mediante la depleción de la DA endógena utilizando componentes como la α-metil-paratirosina), así como la magnitud de la liberación de DA (a través de cambios farmacológicos o psicológicos). Los meta-análisis de estudios utilizando técnicas de PET o SPECT, muestran que existe un robusto aumento en la síntesis y liberación de dopamina estriatal en la psicosis (McCutcheon et al., 2019). Aunque los estudios iniciales de PET y SPECT de la función dopaminérgica presináptica eran capaces de delimitar las subdivisiones anatómicas del estriado, no disponían de resolución suficiente como para poder distinguir de manera precisa entre las subdivisiones funcionales. Sin embargo, el desarrollo de dispositivos de PET de

subdivisiones funcionales, señalando el estriado asociativo como la región en la que se encuentran mayores diferencias en cuanto a función dopaminérgica, tras comparar pacientes con esquizofrenia y controles sanos (Howes et al., 2013; Kegeles et al., 2010; McCutcheon, Beck, Jauhar, & Howes, 2018; Mizrahi et al., 2012).

Aunque diferentes estudios han demostrado una elevación discreta pero significativa de los receptores dopaminérgicos D2 en pacientes libres de tratamiento o naïve (Corripio et al., 2011, 2006; Pilowsky et al., 1994), no se han evidenciado alteraciones relevantes en los receptores dopaminérgicos D2/D3 en revisiones recientes. Esta discrepancia podría deberse a un enmascaramiento de la ocupación del receptor mediante el aumento de niveles de dopamina endógena, o bien a que las diferencias entre grupos en la afinidad del receptor no se detecten con los radioligandos antagonistas generalmente utilizados (McCutcheon et al., 2019).

En cuanto a receptores de otros neurotransmisores, un meta-análisis de estudios PET reportó una disminución de receptores serotoninérgicos 5-HT1 en el mesencéfalo y una disminución de receptores 5-HT2 en el neocórtex, sin evidenciarse cambios en el transportador de serotonina, en relación a controles sanos (Nikolaus, Müller, & Hautzel, 2016). El sistema glutamatérgico se ha investigado también utilizando PET y MRS, sugiriendo en una revisión de estos estudios una hipofunción de los receptores N-metil-D-aspartato (NMDA) en la esquizofrenia (Poels et al., 2014). En cuanto al neurotransmisor GABA, no se han hallado diferencias en cuanto a sus niveles entre pacientes con esquizofrenia y controles sanos (Schür et al., 2016). Sin embargo, el dinamismo de estos neurotransmisores podría ser diferente en pacientes que reciben tratamiento y en los que no, y podría contribuir en los resultados inconsistentes hallados hasta el momento. De manera similar ocurre con aquellos meta-análisis de estudios que evalúan las alteraciones de niveles de glutamato con MRS, pudiendo reportar tanto una disminución de glutamato y un aumento de glutamina en regiones frontales mediales (Marsman et al., 2013), como una elevación de glutamato en ganglios basales, y de glutamina en el tálamo y el lóbulo temporal medial (Merritt, Egerton, Kempton, Taylor, & McGuire, 2016), sin mostrar una disminución de los niveles de glutamato en ninguna región específica cerebral en pacientes con esquizofrenia.

Estos neurotransmisores no trabajan de manera aislada en el cerebro, así que las modificaciones o alteraciones en alguno de estos sistemas de neurotransmisión influirán en el resto; como ocurre, por ejemplo, en el caso de la regulación de la transmisión dopaminérgica del estriado, influenciada por los sistemas glutamatérgico y GABA.

Los recientes y limitados estudios en pacientes con ERT de neuroquímica cerebral se comentarán en el apartado siguiente.

| | MODALIDAD NEUROIMAGEN | HALLAZGOS |
|---|---|---|
| **Estructura cerebral** | MR estructural<br>DTI | Déficits de SG y SB generalizados, principalmente en regiones temporales y pre-frontales.<br><br>Disminución de volumen en hipocampo, amígdala, tálamo y NAc. |
| **Función cerebral** | PET, SPECT<br>fMR en reposo<br>ASL<br>fMR con tareas | Hipoperfusión prefrontal.<br><br>Función alterada de la red neuronal en reposo.<br><br>Alteración de la activación relacionada con tareas en regiones pre-frontales, cingulado anterior y temporales. |
| **Neuroquímica cerebral** | PET<br>MRS | Aumento de la síntesis y liberación de DA pre-sináptica estriatal**.<br><br>Alteraciones variables en niveles regionales de Glu y GABA. |

Tabla 2. Resumen de los principales hallazgos en estudios de neuroimagen en esquizofrenia (adaptado de Keshavan et al., 2019). Abreviaciones: ** Hallazgo más consistentemente replicado; ASL, resonancia magnética por perfusión de 'arterial spin labeled'; DA, dopamina; DTI, neuroimagen por tensor de difusión; GABA, ácido gamma aminobutírico; Glu, glutamato; MR, resonancia magnética; MRS, resonancia magnética por espectroscopía; fMR, resonancia magnética funcional; NAc, núcleo accumbens; PET, tomografía por emisión de fotones; SPECT, tomografía computerizada por emisión de fotones; SB, sustancia blanca; SG, sustancia gris.

### 1.1.1.5. Integrando conceptos desde la neurobiología a los síntomas

Teniendo en cuenta que el hallazgo de neuroimagen más consistentemente replicado en la esquizofrenia es un aumento en la síntesis y liberación de dopamina presináptica en el núcleo estriado, y dado el papel integrativo que representa este núcleo a nivel cerebral, por sus conexiones con el córtex y el mesencéfalo, una alteración funcional secundaria a una señal dopaminérgica aberrante podría justificar las alteraciones presentes en la esquizofrenia. Se ha sugerido por modelos preclínicos que esta alteración podría representar una "asincronía" de las neuronas dopaminérgicas, como una combinación entre una disminución en la liberación de la dopamina fásica adaptativa como respuesta a estímulos relevantes, que podría explicar los síntomas negativos de la enfermedad, junto con un aumento de la liberación de DA fásica espontánea, que justificaría los síntomas positivos (para una revisión sobre el tema consultar Maia & Frank, 2017). Por tanto, esta función dopaminérgica alterada se relacionaría con la conectividad de la red de 'salience', produciendo una atribución exagerada o aberrante a estímulos ambientales irrelevantes, traduciéndose en los síntomas positivos de la enfermedad (Howes & Kapur, 2009; Kapur, Mizrahi, & Li, 2005; McCutcheon et al., 2019). Además, diversos estudios han evidenciado una relación bidireccional entre la dopamina cortical y estriatal, con lo que un aumento de la señal DA estriatal podría disminuir la liberación de DA mesocortical (Krabbe et al., 2015; Simpson, Kellendonk, & Kandel, 2010; Slifstein et al., 2015), produciendo así las alteraciones cognitivas y síntomas negativos de la esquizofrenia (Figura 7) (Howes, Fusar-Poli, Bloomfield, Selvaraj, & McGuire, 2012; McCutcheon et al., 2019).

Sin embargo, la 'hipótesis dopaminérgica' también se ha considerado una simplificación de la circuitería neural que explicaría la esquizofrenia, dada la relativa baja respuesta al tratamiento con fármacos antagonistas dopaminérgicos. La hipótesis glutamatérgica ha ganado relevancia en los últimos años, sugiriendo un mal funcionamiento de los receptores glutamatérgicos NMDA en las interneuronas GABA que mediaría en la generación de una producción dopaminérgica mesolímbica excesiva (Howes, McCutcheon, & Sto-

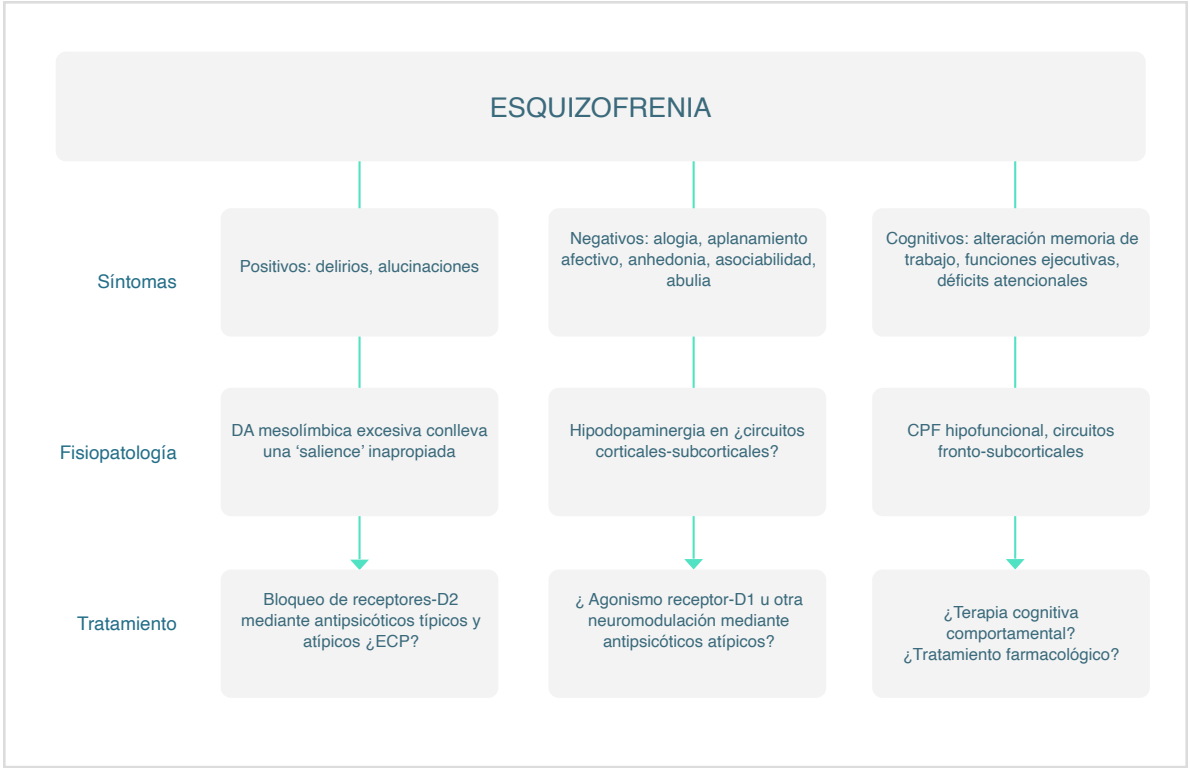


Figura 7. Relación entre sintomatología y fisiopatología de la esquizofrenia (adaptada de Mikell et al., 2009). Acrónimos: AD: dopamina; CPF: córtex pre-frontal.


Figura 8. Interacciones entre vías dopaminérgicas y glutamatérgicas (adaptada de Howes et al., 2015).

ne, 2015; Stahl, 2007). Por tanto, se ha sugerido una mayor complejidad en la neurobiología de la esquizofrenia, con interacciones entre neuronas dopaminérgicas, GABA y glutamatérgicas (Figura 8).

En este sentido, estudios recientes han sugerido que los pacientes diagnosticados de ERT podrían presentar una neurobiología diferente a la de aquellos pacientes respondedores (Leung et al., 2019), ya que no se ha observado en estudios de neuroimagen un aumento de DA a nivel estriatal en comparación con sujetos sanos (Demjaha, Murray, McGuire, Kapur, & Howes, 2012). Estos pacientes que no responden al tratamiento antipsicótico presentarían niveles de glutamato en CCA significativamente más elevados que controles sanos (Demjaha et al., 2014) y que pacientes diagnosticados de esquizofrenia respondedores al tratamiento (Mouchlianitis, Bloomfield, et al., 2016). Estos hallazgos se han replicado en primeros episodios de psicosis naïve (Egerton et al., 2018; Jauhar et al., 2018), con el objetivo de evitar los factores de confusión relacionados con la cronicidad de la enfermedad o el tratamiento antipsicótico continuado. Por todo ello, existen autores que han propuesto clasificar la esquizofrenia en dos subgrupos: la hiper- y la normo-dopaminérgica (Howes & Kapur, 2014).

## 1.1.2. Tratamiento de la esquizofrenia resistente al tratamiento

Son escasos los estudios dirigidos a evaluar la eficacia de los tratamientos antipsicóticos específicamente para la ERT. Por este motivo, los resultados obtenidos son en ocasiones inconsistentes y poco comparables, probablemente por variabilidades metodológicas, ya que en muchas ocasiones los criterios de elegibilidad de los pacientes son poco claros, las definiciones de resistencia son variables (Howes et al., 2017) y las dosis empleadas en los estudios son insuficientes (ver revisión en artículo 3 del Anexo; Molins et al., 2016).

Sin embargo, el tratamiento que ha demostrado mayor eficacia para los pacientes con ERT es la clozapina (Siskind, McCartney, Goldschlager, & Kisely, 2016), ya que se diferencia del resto de antipsicóticos en su potente acción antagonista sobre los receptores D4 de la dopamina (con una elevada expresión en vías mesocorticales) y su agonismo débil del receptor NMDA del glutamato (O'Connor & O'Shea, 2015). Aun así, el 40% de pacientes con ERT tampoco obtienen una respuesta adecuada a la clozapina (Siskind et al., 2017), denominándose recientemente a estos pacientes 'ultra-resistentes' (ver criterios consensuados en tabla 1) (Howes et al., 2017).

Otras estrategias farmacológicas, como el uso de combinaciones de fármacos antipsicóticos (ver artículo 4 del Anexo Galling et al., 2017), o la combinación de clozapina con otros antipsicóticos o con psicofármacos de acción glutamatérgica, tampoco han podido demostrar, hasta el momento, una eficacia claramente superior como para recomendar su uso en la práctica clínica diaria (Siskind et al., 2018; Wagner et al., 2019). El tratamiento de estos pacientes 'ultra-resistentes' añadiendo terapia electroconvulsiva (TEC) junto a clozapina, ha demostrado eficacia en alrededor del 50% de los casos en un estudio abierto cruzado de 8 semanas de duración (Petrides et al., 2015). Sin embargo, los mismos autores consideran que se requieren más estudios para asegurar la viabilidad del tratamiento y la persistencia de mejoría a largo plazo. Por todo ello, y dado que los fármacos antipsicóticos actuales presentan, en su gran mayoría, efectos secundarios indeseados, como efectos extrapiramidales o síndrome metabólico, se plantean nuevas estrategias terapéuticas para el tratamiento de estos pacientes resistentes.

## 1.2. ESTIMULACIÓN CEREBRAL PROFUNDA

La estimulación cerebral profunda (ECP) es una técnica neuroquirúrgica que se empezó a introducir en la década de los ochenta por el Dr. Benabid y cols. (Benabid, Pollak, Louveau, Henry, & De Rougemont, 1987) para el tratamiento del temblor en la enfermedad de Parkinson, alcanzando resultados similares a la talamotomía clásica. La US Food and Drug Administration (FDA) aprobó su uso para el temblor esencial en 1997, para la Enfermedad de Parkinson en 2002 y para la distonía en 2003. Posteriormente su uso se ha extendido a enfermedades psiquiátricas resistentes al tratamiento, como el Trastorno Obsesivo Compulsivo (aprobado por la FDA en 2009) o el Trastorno Depresivo Mayor, entre otras patología todavía bajo investigación. El tratamiento de la epilepsia refractaria con ECP también fue aprobado en Europa en 2010, pero no por la FDA.

La técnica consiste en la implantación de electrodos en determinadas áreas o núcleos cerebrales subcorticales mediante cirugía estereotáxica y bajo anestesia local. Estos electrodos (con diferentes contactos cada electrodo, generalmente cuatro en su parte distal) se conectan mediante cables de extensión subcutáneos a un generador de impulsos que se implanta a nivel infra-clavicular o abdominal. El generador consiste en una batería (recargable o no-recargable) que envía una señal eléctrica continua de alta frecuencia a la zona cerebral seleccionada. Además, la gran ventaja de esta técnica frente a la cirugía ablativa es que se trata de una técnica reversible y ajustable mediante un programador externo; es decir, que es posible apagar o encender la estimulación, así como modular la intensidad del impulso eléctrico, la frecuencia de estimulación y la amplitud del pulso generado en función del volumen de tejido cerebral que se desee estimular (Figura 9) (Miocinovic, Somayajula, Chitnis, & Vitek, 2013). Otra ventaja frente a la psicocirugía ablativa sería que, en el caso de ser necesario, el dispositivo también podría ser explantado sin generar ninguna pérdida de función del tejido cerebral.

## 1.2.1. Mecanismos de acción de la ECP

A pesar del éxito clínico de la ECP en algunas patologías, los mecanismos de acción por los que esta técnica muestra beneficios no están completamente esclarecidos. Se han propuesto múltiples hipótesis, prevaleciendo las teorías que se focalizan en que la estimulación induciría una disrupción de la actividad de circuitos patológicos cerebrales a través de cambios a nivel iónico, proteico, celular y de redes cerebrales. Aunque todavía no está claro qué efectos de la ECP son necesarios y suficientes para generar su acción terapéutica, sí parece estar establecido que la estimulación de alta frecuencia (>100Hz) produce respuestas en la circuitería cerebral, en comparación con la estimulación de menor frecuencia (Lozano et al., 2019).

Se han descrito (principalmente por estudios llevados a cabo en la enfermedad de parkinson y otros trastornos neurológicos) efectos fisiológicos agudos, efectos metabólicos más lentos y se ha sugerido también que la ECP pudiera producir un efecto neuroprotector o de neuroplasticidad a largo plazo (Aum & Tierney, 2018). En la figura 10 se muestran los mecanismos generales de acción de la ECP.

### 1.2.1.1. Efectos fisiológicos agudos

Desde una perspectiva biofísica, la inyección de corriente eléctrica a un tejido cerebral induce una despolarización neuronal mediante la generación de potenciales de acción a través de la apertura de canales de sodio dependientes de voltaje. Sin embargo, existe una diferencia importante entre los mecanismos de despolarización local y el efecto global observado en la actividad neuronal. Experimentos destinados a identificar la diana primaria de la ECP han demostrado que la estimulación de alta frecuencia (HFS, por sus

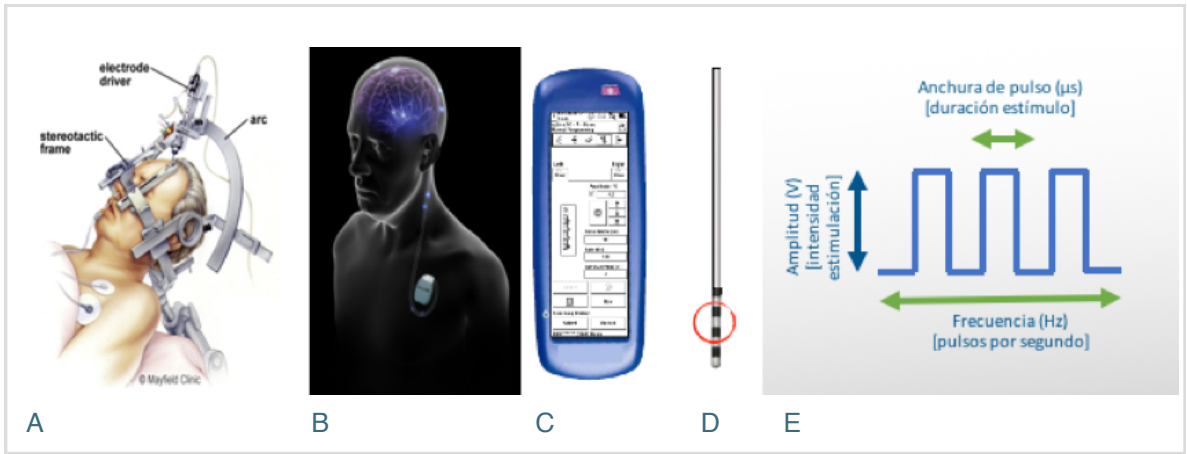


Figura 9.
A) Guía neuroquirúrgica estereotáxica para la implantación precisa de los electrodos en la diana terapéutica escogida.
B) Generador implantado a nivel infra-clavicular y cables de extensión subcutáneos.
C) Programador externo de la ECP.
D) Electrodo con 4 contactos distales.
E) Esquema de los 3 parámetros de pulso modulables con la ECP: amplitud (V), frecuencia (Hz) y anchura de pulso (µs).

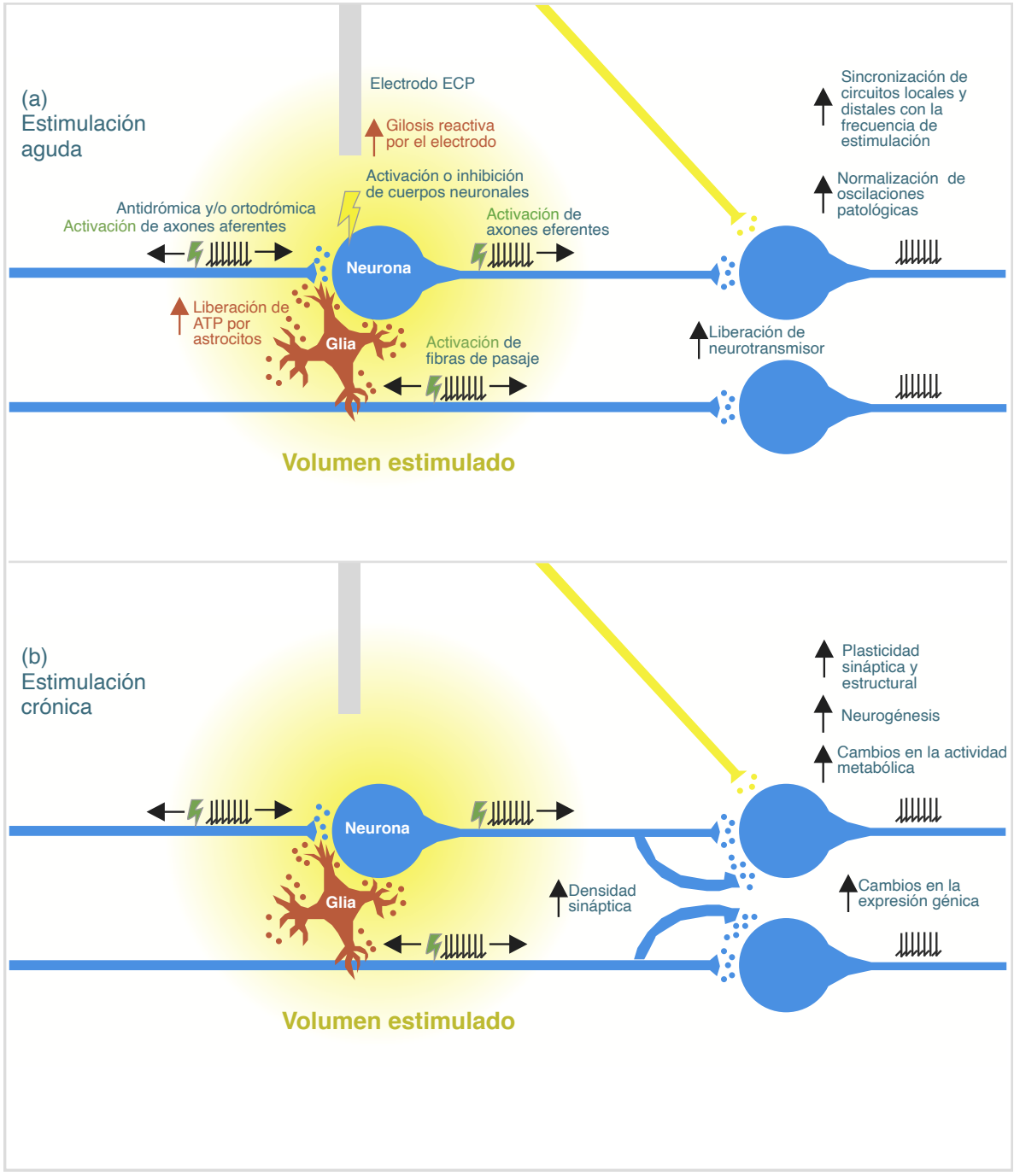


Fig 10. Mecanismos celulares generales de la ECP.
a) La estimulación aguda resulta en efectos complejos a nivel local y en circuitos distales en ambas direcciones. La simple inserción del electrodo provoca una respuesta inflamatoria que resulta en una gliosis reactiva al cabo de pocos días. Al activar la estimulación, la ECP produce sus efectos principalmente en axones aferentes y eferentes, de manera antidrómica y ortodrómica, así como en fibras de pasaje. También modula cuerpos neuronales y de glía, habiéndose descrito tanto patrones de activación como inhibitorios. La modulación de estas proyecciones puede normalizar oscilaciones patológicas en regiones distales mediante la sincronización de la actividad a la frecuencia de estimulación (frecuencia 'jamming'), y puede resultar un aumento en la liberación de neurotransmisores.
b) Los efectos de la estimulación crónica son menos conocidos, pero se han evidenciado efectos neuroplásticos. Cambios metabólicos estables y de plasticidad sináptica ocurren en el área de estimulación y a nivel distal, así como neurogénesis y proliferación de células progenitoras. Se ha sugerido también una plasticidad estructural en forma de cambios en la excitabilidad intrínseca, densidad sináptica y reorganización sináptica, probablemente secundaria a cambios en la expresión génica.

siglas en inglés) tiende a despolarizar axones, en mayor medida que el soma neuronal. Los potenciales de acción inducidos por la estimulación se propagan en ambas direcciones (ortodrómica y antidrómica) hacia las terminales axonales de la neurona. En este sentido, si los axones aferentes estimulados son inhibitorios (GABAérgicos), su activación mediante ECP suprimirá la actividad de las neuronas diana. Otros estudios han sugerido que la HFS sería capaz de producir una inhibición más directa mediante el bloqueo de la conducción axonal (Jensen & Durand, 2009). La mayoría de estudios, por tanto, han demostrado los efectos inhibitorios locales de la ECP ('inhibition hypothesis'). Sin embargo, otros estudios han descrito también un aumento en la actividad de disparo neuronal ('excitation hypothesis'), produciendo una excitación tanto de vías eferentes como aferentes en el lugar de estimulación. Esta controversia en cuanto a los efectos inhibitorios o excitatorios de la ECP se explicaría probablemente dependiendo del resultado 'neto' de la composición de los axones terminales inhibitorios (GABAérgicos) y excitatorios (glutamatérgicos) que se modulan con la ECP (Ashkan, Rogers, Bergman, & Ughratdar, 2017; Deniau, Degos, Bosch, & Maurice, 2010).

Otra hipótesis propuesta para explicar el mecanismo de la ECP es la 'disruption hypothesis', que propone que la HFS podría disociar las señales entrantes y salientes aberrantes del núcleo o área estimulada. Se ha demostrado que la ECP suprimiría la actividad oscilatoria patológica de bandas beta que ocurre en la generación de síntomas motores de la enfermedad de parkinson, resultando en una disrupción del flujo de información 'anormal' y preservación de aquellas vías que funcionan correctamente (Ashkan et al., 2017; Chiken & Nambu, 2016). Esta hipótesis se basaría en la 'jamming theory', descrita inicialmente por Benabid y cols. (Benabid, Benazzous, & Pollak, 2002), que postula que los pulsos de descarga axonal regulares de la ECP podrían prevenir que las neuronas retornasen a su actividad espontánea basal, incluyendo los patrones patológicos. Acorde con esta teoría, la ECP no reduciría el disparo neuronal sino que modularía su actividad patológica, produciendo cambios en amplias redes neuronales (Ashkan et al., 2017).

Para finalizar, además de la activación neuronal directa, se ha observado que la ECP también produciría una estimulación de las células gliales y, en especial, de los astrocitos. La estimulación de estas células contribuiría a la modulación del disparo neuronal, mediante la liberación de varios gliotransmisores como el glutamto, D-serina y ATP. La activación de los astrocitos también produciría efectos directos en el flujo vascular cerebral, causando un aumento o disminución de la actividad neuronal mediante un 'acoplamiento' neurovascular. Además, se ha sugerido que la mejoría observada con la microlesión de estructuras cerebrales tras la implantación inicial del electrodo, podría estar mediada por la gliosis reactiva y la consecuente inducción de células madres, conduciendo a una reorganización del circuito cerebral implicado (Ashkan et al., 2017; Fenoy, Goetz, Chabardès, & Xia, 2014; Vedam-Mai et al., 2012).

#### 1.2.1.2. Efectos metabólicos lentos

Además de la rápida modulación de la actividad neuronal, se han descrito varios cambios fisiológicos y metabólicos causados por la ECP en lugares distales a la localización del electrodo. Por ejemplo, se han demostrado cambios en la expresión de receptores D1, D2 y D3 extraestriatales en modelos animales tras la estimulación del STN (Carcenac et al., 2015), así como incrementos de los niveles de glutamato extracelular en el globo pálido y de GABA en SNr tras la estimulación del STN, los cuales sugerirían un aumento de la actividad neuronal en esas áreas. Asimismo, estudios realizados con PET también han revelado aumentos o disminuciones de flujo sanguíneo en zonas distales a las de estimulación (ver próximo apartado 1.2.4.4) (Aum & Tierney, 2018).

#### 1.2.1.3. Neuroplasticidad: ¿efecto neuroprotector a largo plazo?

El rol de la plasticidad con la ECP se apoyaría en estudios animales en los que se ha observado: 1) potenciación a corto-plazo de la corriente post-sináptica evocada (EPSC, por sus siglas en inglés), posiblemente en contexto de un aumento de liberación de glutamato; 2) potenciación a largo-plazo de la EPSC, asociada a cambios en proteínas post-sinápticas; y 3) depresión a largo-plazo, indicando una modificación de la regulación pre-sináptica (Agnesi, Johnson, & Vitek, 2013).

La ECP ha demostrado también aumentar la expresión de diversas moléculas neurotróficas, incluyendo el factor neurotrófico derivado del cerebro (BDNF, por sus siglas en inglés) y el factor neurotrófico derivado de la línea celular glial (GDNF, por sus siglas en inglés) (Gondard et al., 2015; Selvakumar, Alavian, & Tierney, 2015), potentes factores de supervivencia para las neuronas dopaminérgicas cerebrales. También se ha evidenciado en modelos animales de enfermedad

de parkinson un efecto neuronal protector de muerte celular (Wallace et al., 2007), aunque esta evidencia no se ha podido demostrar todavía como efecto de la ECP en humanos.

### 1.2.1.4. Mecanismo de acción en los trastornos mentales

Al contrario del uso de la ECP en los trastornos del movimiento o el dolor, se ha propuesto que los mecanismos por los que la ECP actuaría en los trastornos mentales consistiría en una modificación de los tractos de sustancia blanca implicados en redes cortico-estriatales más que una modulación de la sustancia gris cerebral. Ejemplos de ello serían la estimulación de la parte ventro-caudal del limbo anterior de la cápsula interna en el caso del trastorno obsesivo compulsivo (TOC) o el 'medial forebrain bundle' (MFB) en el caso del trastorno depresivo mayor (Ashkan et al., 2017). Aun así, hay demasiados pocos estudios en pacientes como para comprender el mecanismo de acción de la ECP en trastornos psiquiátricos.

En modelos animales de TOC, se ha observado que la estimulación de NAc, o su estructura adyacente la cápsula ventral/estriado ventral (VC/VS, por sus siglas en inglés), puede disminuir la hiperactividad fronto-estriatal, disminuir las oscilaciones patológicas de baja frecuencia, liberar DA estriatal y aumentar marcadores de neuroplasticidad como el BDNF en el córtex. Por tanto, la ECP implantada en estas localizaciones podría promover alteraciones neuroplásticas complejas que 'de-potenciarían' circuitos cortico-estriatales que se encuentran hiperactivados en el TOC, en parte mediante la tonificación de la inhibición en feedback del estriado (Veerakumar & Berton, 2015). La ECP en el STN también se utiliza para el tratamiento del TOC, pero sus mecanismos de acción están menos estudiados.

En modelos animales de depresión mayor, la estimulación del área análoga al córtex cingulado subcalloso, involucraría a neuronas de regiones distales al lugar estimulado (como la amígdala, el córtex piriforme/ínsula, el núcleo monoaminérgico y el núcleo dorsal del rafe) y que podrían conducir a modificaciones en la liberación de serotonina (Hamani et al., 2014; Veerakumar et al., 2014). Las otras dianas terapéuticas de ECP eficaces para depresión mayor, como el NAc, el MFB y la habénula producirían una mejoría de los síntomas probablemente mediante la modulación de la misma red, por sus vías de conexión entre el núcleo dorsal del rafe, el ATV y la habénula (Veerakumar & Berton, 2015). Además, la latencia en los efectos terapéuticos de la ECP en la depresión (desde semanas a meses) sugerirían un componente de plasticidad neuronal implicado en la normalización de la actividad patológica en estas redes.

En conclusión, y por todo lo expuesto anteriormente, se considera actualmente que esta terapia consiste en una compleja técnica de neuromodulación multimodal de redes cerebrales, consistente en una excitación e inhibición del lugar de estimulación, así como en lugares de proyección, que produciría una sincronía de los circuitos cerebrales alterados. Además, la mayoría de autores coinciden en subrayar que al tratar de entender los mecanismos de acción de la ECP es importante tomar en consideración que existen múltiples mecanismos que pueden jugar un papel en los efectos terapéuticos observados, y que pueden variar para las diferentes patologías y dianas de estimulación (Agnesi et al., 2013; Ashkan et al., 2017).

## 1.2.2. Riesgos y limitaciones de la ECP

Las complicaciones asociadas al tratamiento con ECP suelen clasificarse en 3 grupos (Fenoy & Simpson, 2014; Patel et al., 2015; Zarzycki & Domitrz, 2020):

a) las relacionadas con la cirugía, siendo las más prevalentes la infección del dispositivo (1.7-6.1%), que en la mayoría de casos obliga a la retirada del mismo, y la hemorragia (0.78-1.1%);

b) las relacionadas con el dispositivo, como el fallo de batería o rotura/migración del cable (que a veces requerirán de una nueva intervención para solucionar el problema y un riesgo adicional);

c) las relacionadas con la estimulación que son diversas dependiendo del lugar de implantación del electrodo y el voltaje aplicado. Se ha descrito, por ejemplo, aparición de llanto/risa, síntomas maniformes, hipersexualidad/disminución de la líbido, síntomas depresivos/ideas de muerte, confusión, síntomas cognitivos, aumento/disminución de peso, apatía, fatiga, etc. Estas complicaciones se resuelven habitualmente con ajustes en los parámetros de estimulación.

## 1.2.3. Ética de la ECP en trastornos mentales

Dado que la ERT implica una elevada disfuncionalidad e impacto en la calidad de vida tanto de los pacientes como de sus familiares o cuidadores, según los principios éticos creados en el informe de Belmont esta población debería tener acceso a los potenciales beneficios de los avances neuro-quirúrgicos, al igual que el resto de la población. Siguiendo el modelo desarrollado para la aprobación del tratamiento con ECP para el TOC, previo a la implementación de la técnica, se debería (Gault et al., 2018; Mikell, Sinha, & Sheth, 2016):

- evaluar a los candidatos con unos criterios de gravedad, cronicidad, disfuncionalidad y resistencia al tratamiento predeterminados mediante la revisión de su historia clínica y con supervisión de un comité ético, así como la evaluación del paciente por un equipo multidisciplinar que incluyera a neurocirujanos experimentados en ECP y psiquiatras experimentados en el trastorno a intervenir;

- considerar una ratio riesgo/beneficio aceptable del procedimiento;

- valorar que los pacientes presentaran una adecuada capacidad para entender en qué consiste el ensayo clínico y el tratamiento, así como para firmar el consentimiento informado, excluyendo a aquéllos sin capacidad para consentir y permitiendo libremente la retirada del estudio;

- asegurar que la intervención se desarrolle en un centro de investigación clínico con experiencia;

- determinar que el tratamiento fuera llevado a cabo únicamente para el beneficio del paciente (con el objetivo de aliviar sufrimiento) y de ninguna manera por fuerza o propósitos políticos/sociales.

## 1.2.4. ECP en esquizofrenia

### 1.2.4.1. En busca de la diana terapéutica

La primera aplicación médica de la ECP en un escenario experimental se practicó en un paciente con esquizofrenia, aplicando la estimulación en el 'núcleo amigdaloide' (Heath, Monroe, & Mickle, 1955). Desde entonces, no se ha publicado ni se ha llevado a cabo ningún otro proyecto de investigación en pacientes con esquizofrenia hasta la realización del proyecto que es objeto de esta tesis.

Una de las mayores limitaciones para la implementación de la ECP en la esquizofrenia resistente ha consistido en la incertidumbre sobre la localización cerebral donde insertar los electrodos, ya que los mecanismos neurobiológicos y anatómicos que subyacen a la esquizofrenia, como se señaló anteriormente, todavía no están establecidos de forma precisa. A pesar de ello, en los últimos años ha existido un creciente interés en la aplicación de la ECP para la ERT, debido a las escasas opciones terapéuticas disponibles más allá de la clozapina.

Se han propuesto diversas dianas terapéuticas o 'targets' para la implantación de los electrodos, siendo la hipótesis principal que la esquizofrenia también sería un trastorno basado en un 'circuito alterado' y, por tanto, tributario de neuromodulación (Gault et al., 2018).

#### • Núcleo estriado

Una de las principales dianas terapéuticas propuestas para la implantación de los electrodos de ECP ha sido el núcleo estriado, por la robusta evidencia que implicaría a este núcleo como el foco de la alteración dopaminérgica que causaría la psicosis (ver apartado 1.1.1). Como ya se describió, el estriado es el input primario principal de los ganglios basales, pudiendo dividirse funcionalmente en el estriado ventral (VS, por sus siglas en inglés), el estriado central o asociativo (AS, por sus siglas en inglés) y el estriado dorso-lateral o sensorimotor (SMS, por sus siglas en inglés), en base a la topografía de los circuitos paralelos cortico-estriato-talámico-corticales ya descritos.

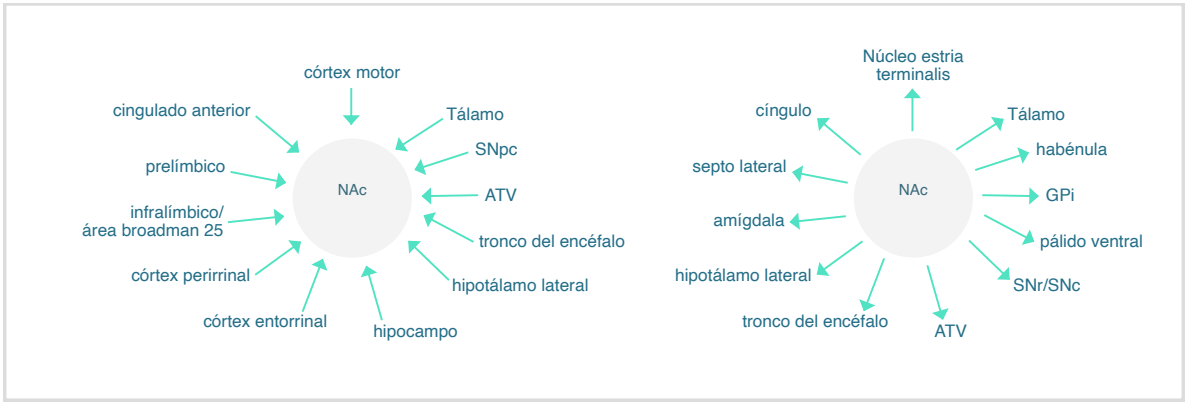


Figura 11. Representación esquemática de las conexiones aferentes (a) y eferentes (b) del NAc (adaptada de Salgado & Kapplitt, 2015).

## • Núcleo Accumbens

El NAc es la estructura principal del VS y la evidencia sugiere que es el input principal de los ganglios basales, ya que recibe aferencias indirectas de las proyecciones mesolímbicas dopaminérgicas desde el ATV y la sustancia negra (SN), así como proyecciones glutamatérgicas directas del subiculum y la amígdala, hipocampo, tálamo, córtex prelímbico y prefrontal (Salgado & Kaplitt, 2015). El resto de conexiones aferentes y las principales conexiones eferentes pueden observarse en la figura 11.

El NAc se divide en un core central, rodeado a nivel medial, ventral y lateral por una carcasa o cápsula. Se han descrito 2 circuitos DA distintos basados en la topografía del NAc. El core proyecta al pálido dorsolateral ventral, que a su vez proyecta al STN y la SN, formando parte de la vía nigroestriatal. Por otro lado, la cápsula proyecta a través del pálido ventromedial al TMD, el cual contiene una conexión recíproca con el ATV (formando la vía mesolímbica) y con el córtex prefrontal (CPF), enviando proyecciones DA a distintos lugares de la vía mesocortical (Salgado & Kaplitt, 2015). Se ha propuesto, por tanto, que la modulación del VS mediante ECP podría estabilizar la transmisión dopaminérgica aberrante presente en la esquizofrenia (Gault et al., 2018; Mikell et al., 2016).

## • Estriado asociativo

En el momento actual, el AS parece ser el locus principal de la disfunción de la neurotransmisión en la esquizofrenia, habiéndose localizado la liberación excesiva de dopamina en esta área estriatal. Además presenta extensas interconexiones con áreas cerebrales implicadas en la patogénesis de la esquizofrenia, como son el CPFDL, el córtex prefrontal orbital y medial y la SN (Mikell et al., 2016). Por tanto, se ha sugerido que mediante el control inhibitorio de la ECP podrían disminuir los niveles de DA en el estriado, así como modular la señal dopaminérgica en el CPFDL. Sin embargo, estudios recientes podrían poner en duda la evidencia del AS como lugar principal de la hiperdopaminergia en la esquizofrenia (Howes, Hird, Adams, Corlett, & McGuire, 2020; Jauhar et al., 2017; Katthagen, Kaminski, Heinz, Buchert, & Schlagenhauf, 2020). Además, la experiencia quirúrgica en la estimulación del AS es limitada (Mikell et al., 2016), hecho que dificultaría la intervención en esta diana terapéutica.

## • Hipocampo y área tegmental ventral

Otro de los modelos mecanísticos en la fisiopatología de la esquizofrenia implicaría al hipocampo, ya que se ha observado un volumen disminuido (Adriano, Caltagirone, & Spalletta, 2012) y una hipoactivación del mismo durante el estado de reposo observado con (BOLD)-fMR, junto a un estado hipermetabólico medido con el volumen de sangre cerebral en pacientes con esquizofrenia (Mikell et al., 2016). Este hipermetabolismo podría deberse a un aumento del glutamato extracelular que conduciría a una atrofia hipocampal (Schobel et al., 2013), seguida de un aumento de la DA presináptica en el estriado a través de la SN/ATV (Figura 12); conformando así una unión entre los hallazgos anatómicos, funcionales y de sistemas de neurotransmisión mediante las teorías glutamatérgicas y dopaminérgicas de la esquizofrenia (Howes et al., 2015; Mikell et al., 2016). En este sentido, se ha ensayado la estimulación del hipocampo con ECP en modelos animales, pudiendo revertir los cambios comportamentales relacionados con la hiperdopaminergia en el estriado (Mikell et al., 2016). Por tanto, la estimulación del hipocampo o de su principal es-

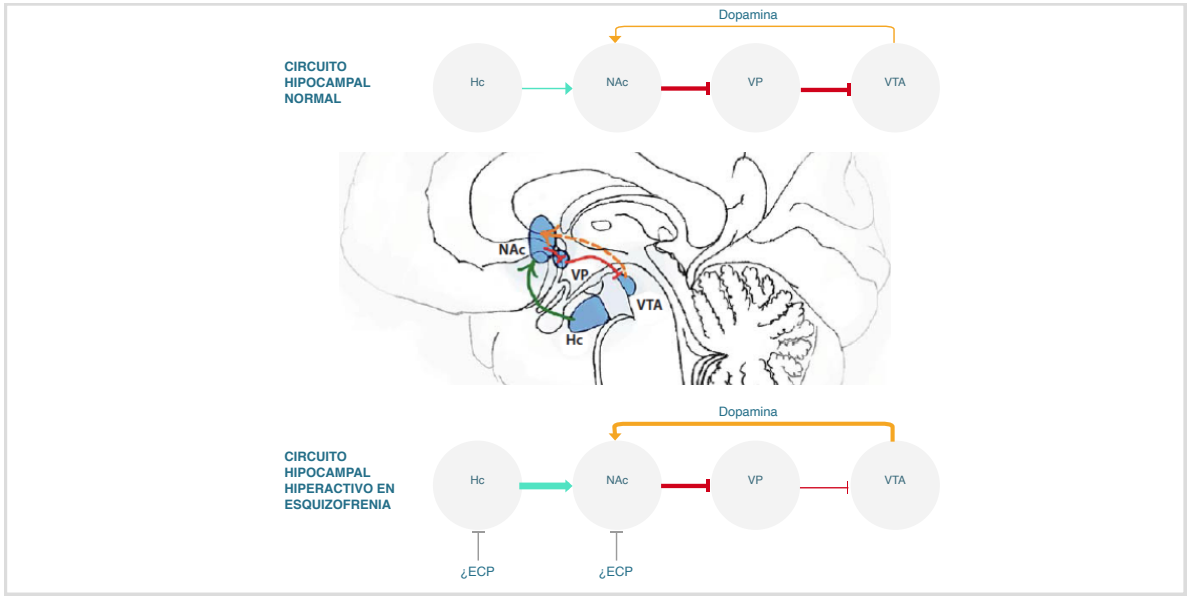


Figura 12. Modelo fisiopatológico que explicaría la alteración dopaminérgica observada en la esquizofrenia y que implicaría al circuito HC-NAc-VTA (adaptado de Mikell et al., 2009). Abreviaciones: HC: hicpocampo, NAc: Núcleo Accumbens, VP: Pálido Ventral, VTA: Área Tegmental Ventral

tructura de conexión, el núcleo septal medial (MSN), podría también modular el circuito estriatal. Además, el VS recibirá importantes proyecciones glutamatérgicas desde el subiculum, la estructura de salida del hipocampo. Se considera que esta proyección desarrollaría una función de sincronización en la liberación de DA mediante el ATV, por lo que se requerirían las señales hipocampales a través del VS para la liberación de DA frente a estímulos ambientales (Grace & Gomes, 2019). Por tanto, tanto el VS como el ATV serían estructuras clave integradas en el mismo circuito que implicaría al hipocampo (ver figura 12).

Hasta el momento, la estimulación del hipocampo y sus estructuras relacionadas se han aplicado discretamente para el tratamiento de la epilepsia (Zangiabadi et al., 2019), por lo que su uso en trastornos neuropsiquiátricos está todavía por explorar.

## • Sustancia negra *pars reticulata* y tálamo mediodorsal

La SNr es un núcleo principal de salida de los ganglios basales y se ha sugerido que su estimulación podría implicar también, mediante sus proyecciones aferentes, al TMD. Como ya se comentó, el núcleo mediodorsal talámico juega un papel integrativo en estructuras que modulan circuitos motores y cognitivos; así como en los ganglios basales y el cerebelo. Estudios post-mortem han evidenciado una disminución del volumen talámico, y en estudios de neuroimagen, una conectividad disminuida entre el TMD y el CPFDL, así como una hipo o hiperactividad de esta zona (dependiendo de la tarea utilizada) en pacientes con esquizofrenia (Ouhaz, Fleming, & Mitchell, 2018; Parnaudeau et al., 2013). Además, lesiones isquémicas del TMD se han asociado con la aparición de síntomas psicóticos (Santos, Alberti, Corbalán, & Cortina, 2009; Yoshida, Abe, & Yoshizawa, 2006). Por tanto, ambas estructuras serían también tributarias de neuromodulación.

A modo de resumen, y ligando estos conceptos con la esquizofrenia, podría decirse que el AS estaría conectado a la SN, al tálamo y al CPFDL, pudiendo así contribuir a los síntomas cognitivos, mientras que el VS formaría parte del circuito de recompensa junto al ATV, NAc, CPFm y CCA; sugiriendo una posible implicación en los síntomas negativos (Gault et al., 2018; Mikell et al., 2016). Además, tanto el VS como el AS también han sido indirecta, aunque fuertemente, implicados en la generación de síntomas psicóticos positivos de la esquizofrenia.

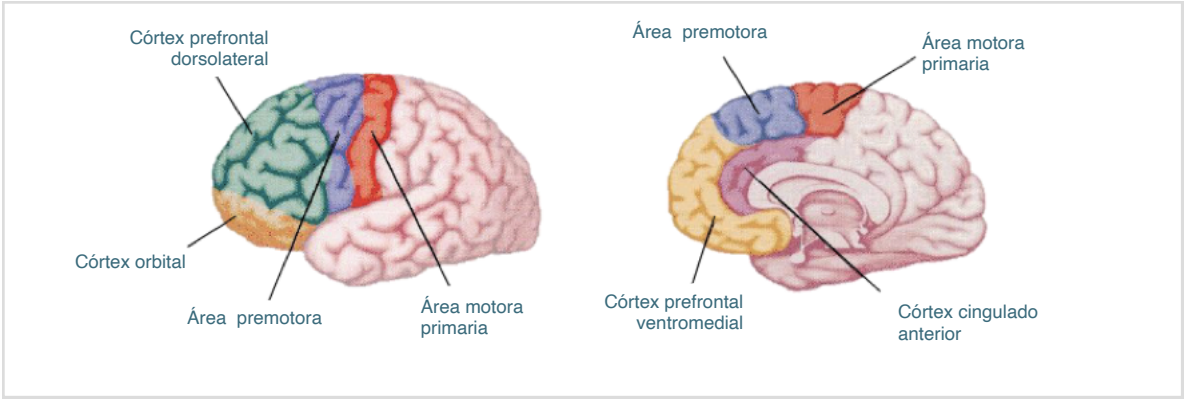


Figura 13. Representación esquemática de las principales subdivisiones del córtex frontal.

### • Conexiones cortico-estriatales y redes corticales asociativas

Como se comentó anteriormente, el córtex frontal puede dividirse en varias regiones funcionales generales: el córtex prefrontal orbital y medial, involucrado en emociones y motivación; el CPFDL, implicado en procesos cognitivos superiores o "funciones ejecutivas"; las áreas pre-motoras, implicadas en diferentes aspectos de la planificación motora; y el córtex motor, implicado en la ejecución de dichos planes (Figura 13). A pesar de que el estriado también recibe 'inputs' de otras áreas corticales, es el córtex frontal el que recibe los principales 'outputs' de los ganglios basales, a través del tálamo. Sin embargo, la aplicación de la ECP en estas regiones frontales parecería inaccesible, por la generalizada inervación dopaminérgica en todo el córtex.

A pesar de los patrones topográficos de conectividad entre el córtex frontal y los ganglios basales ya mencionados en el apartado 1.1.1, en los últimos años se ha demostrado mediante estudios de resonancia magnética cerebral que se requeriría una activación coordinada de las diferentes subregiones corticales para producir una actividad dirigida (Draganski et al., 2008). Existe cada vez más evidencia de la existencia de redes corticales asociativas amplias, que se concentrarían en nodos que integrarían y distribuirían la información a través de múltiples sistemas, y que estos nodos existirían tanto en áreas corticales como en el estriado. Hay autores que han hipotetizado que el malfuncionamiento en varias de estas redes neuronales (p. ej. la 'default mode network' (DMN), 'salience network' y 'central executive network') podrían estar implicadas en la generación de los síntomas psicóticos de la esquizofrenia (Menon, 2019; Nekovarova, Fajnerova, Horacek, & Spaniel, 2014; Peters, Dunlop, & Downar, 2016).

Específicamente, se ha observado en pacientes con esquizofrenia un fallo en la desactivación del área relacionada con el nodo anterior medial de la DMN durante la ejecución de diferentes tareas (Hu et al., 2017; Pomarol-Clotet et al., 2010). Esta red constituye un sistema de regiones cerebrales que normalmente están activas en reposo e inactivas durante la realización de diferentes tareas cognitivas que requieren atención. Además se ha sugerido la implicación de esta red en funciones de cognición social, recuperación de memoria autobiográfica y planificación de eventos futuros (Salgado-Pineda et al., 2011). Este nodo anterior incluye el córtex cingulado anterior subgenual (área de Brodmann Cg25) [sgACC (Cg25)], cuya alteración también ha sido consistentemente reportada en estudios de DTI en pacientes con esquizofrenia (Ellison-Wright & Bullmore, 2009), aunque también en otros trastornos psiquiátricos como la depresión mayor o el trastorno bipolar. Por tanto, esta región del córtex prefrontal medial también se ha contemplado como una diana potencial para la neuromodulación mediante ECP.

## 1.2.4.2. Estudios de ECP con modelos animales de esquizofrenia

Los escasos estudios publicados en modelos animales de esquizofrenia para el ensayo de la ECP se basan principalmente en la estimulación en tres localizaciones: el hipocampo (Ewing & Grace, 2013; Perez, Shah, Asher, & Lodge, 2013), el NAc (Bikovsky et al., 2016; Ma & Leung, 2014) y el CPFm (Bikovsky et al., 2016; Ravit Hadar et al., 2017; Klein et al., 2013). En uno de estos estudios (Klein et al., 2013) también se exploran diferentes áreas cerebrales para la aplicación de la estimulación, como el TMD, el núcleo entopedincular, el

globo pálido o el núcleo subtalámico. Mientras que la investigación en modelos animales de esquizofrenia se basaba inicialmente en alterar sistemas de transmisión dopaminérgicos (p.ej. con la inyección de agonistas DA como la ketamina) o glutamatérgicos (p.ej con antagonistas del receptor NMDA), en los últimos años ha habido un interés creciente en modelos consistentes en la llamada 'activación maternal inmune', en la que se administran agentes infecciosos a ratas embarazadas (p.ej. poly I:C o MAM). La descendencia de estas ratas alteradas desarrollan cambios neurofisiológicos y comportamentales que también se encuentran en la esquizofrenia, incluyendo déficits habitualmente llamados esquizofrenia-like, como el 'sensorimotor gating' (proceso neurológico consistente en la filtración de estímulos redundantes o innecesarios y que habitualmente se evalúa con la inhibición pre-pulso -PPI-), déficits atencionales selectivos, así como volúmenes disminuidos en hipocampo y CPF, y aumentados en ventrículos. Además, estas alteraciones emergen únicamente cuando la descendencia alcanza la adolescencia tardía o la adultez temprana, como ocurre en la esquizofrenia.

Los estudios en los que se aplica ECP al hipocampo de ratas 'naïve' (sin ser manipuladas para crear un modelo de esquizofrenia), han demostrado que la estimulación transitoria del subiculum ventral aumentaría el flujo DA en NAc, mejoraría la transmisión DA mesolímbica y produciría un aumento de la liberación de DA en el CPFm (Carreno et al., 2016; Lindenbach, Seamans, & Phillips, 2019). Consistentemente, un estudio en el que se aplicaba la ECP en la zona más ventral del hipocampo en modelos animales de esquizofrenia (ratas tratadas con MAM), observó que la estimulación normalizaba la actividad dopaminérgica neuronal aberrante y los comportamientos esquizofrenia-like (Perez et al., 2013). Otro estudio que evaluaba la ECP en la misma localización y con el mismo modelo animal observó que la estimulación revertía las alteraciones en potenciales evocados auditivos observadas previamente en este modelo animal, tanto en córtex infralímbico como en el TMD (Ewing & Grace, 2013).

Por otro lado, la estimulación de alta frecuencia en el CPFm y el TMD alivió los déficits de PPI en la descendencia adulta de ratas inyectadas con poly I:C (Klein et al., 2013). En un estudio posterior, tanto la estimulación de NAc como del CPFm mejoró el PPI en el mismo modelo animal, aunque en ratas controles la ECP de NAc redujo el PPI, mientras que la ECP en CPFm no obtuvo efecto (Bikovsky et al., 2016). Además, en este estudio se evaluó mediante PET de glucosa los efectos metabólicos cerebrales de la estimulación, sin hallar un patrón metabólico que pudiera explicar los efectos comportamentales de la ECP en estas dos dianas terapéuticas. El mismo grupo de investigación aplicó la ECP en CPFm durante la adolescencia de estas mismas ratas, alcanzando una normalización del PPI al llegar a la adultez, así como una mejoría en la atención selectiva y las funciones ejecutivas (Hadar et al., 2018).

En un trabajo en el que se estudiaba la ECP en NAc y el septo medial en un modelo animal de esquizofrenia con antagonistas de los receptores NMDA, se observó que ambas dianas normalizaban el déficit en PPI inducido por la ketamina (Ma & Leung, 2014), además de que la ECP del septo medial se acompañaba de una disminución de las oscilaciones gamma hipocampales, que se encuentran elevadas tras la inyección de ketamina.

También se han realizado diversos estudios en ratas naïve para poder estudiar los efectos de la estimulación del NAc a nivel cerebral. Un estudio en el que se aplicaba ECP en NAc para evaluar el papel de este núcleo sobre las neuronas dopaminérgicas, observó que la estimulación no afectaba significativamente la actividad del ATV o su patrón de descarga neuronal (vía mesolímbica), y sin embargo, la ECP causaba una potente disminución en el número de disparos neuronales dopaminérgicos espontáneos de la SNr (vía nigroestriatal) (Sesia, Bizup, & Grace, 2014). Para finalizar, un grupo de investigación publicó dos estudios a los que se aplicaba NAc-ECP en ratas naïve, sugiriendo en el primero que el mecanismo por el cual disminuye la actividad en un subgrupo de neuronas del OFC sería mediante la inhibición de la activación antidrómica de colaterales de axones cortico-estriatales (McCracken & Grace, 2007). En un estudio posterior, los mismos autores demuestran que la estimulación del NAc produciría un aumento de la sincronía (mediada por interneuronas) en diferentes áreas del circuito cortico-estriatal; como el CPFm, OFC lateral, TMD y el NAc (McCracken & Grace, 2009).

### 1.2.4.3. Estudios en humanos

Previo a la publicación del ensayo clínico presentado en esta tesis doctoral, existía 1 caso publicado de ECP en NAc (VC/VS) en una paciente diagnosticada de TOC y esquizofrenia residual (Plewnia et al., 2008). Con la estimulación unilateral de NAc se reportó una mejoría tanto de los síntomas TOC como del funcionamiento psicosocial, sin la reaparición de síntomas psicóticos.

Tras este caso aislado, se registraron 3 ensayos clínicos:

- https:// clinicaltrials. gov/ct2/ show/ NCT01725334:

  Este estudio planteado por la University Health Network en Toronto, proponía el NAc y la ATV como dianas donde implantar los electrodos, por la implicación del estriado y la vía mesolímbica en la regulación dopaminérgica y con el objetivo de mejorar tanto los síntomas positivos como negativos de la enfermedad. Sin embargo, este estudio ha sido cancelado por problemas relativos al reclutamiento.

- https://clinicaltrials.gov/ct2/show/NCT0236155:

  Este estudio impulsado por la Johns Hopkins University (JHU), plantea la SNr como diana terapéutica para la ECP. Se ha sugerido que la estimulación de SNr podría modular la actividad aberrante de los ganglios basales y del circuito que implica el TMD y el CPF, mejorando así tanto los síntomas positivos como cognitivos de la enfermedad.

- https:// clinicaltrials. gov/ ct2/ show/ NCT02377505:

  El tercer estudio llevado a cabo en el Hospital de Sant Pau, y con la colaboración de FIDMAG Germanes Hospitalàries, es el que se presenta en esta tesis. Se eligieron como dianas terapéuticas el NAc y el sgACC, con el objetivo de hallar mejoría en los síntomas positivos y negativos de la enfermedad. La justificación sobre la decisión en la elección de ambas dianas terapéuticas puede encontrarse en el artículo 5 del anexo.

### 1.2.4.4. Neuroimagen de la ECP en sgACC y NAc (o VC/VS)

A continuación se presenta una síntesis de los estudios de neuroimagen realizados en pacientes con diagnóstico de trastorno mental que han sido intervenidos de ECP en las mismas áreas que las utilizadas en los estudios presentados en esta tesis. Para un resumen de los hallazgos consultar la Tabla 3.

#### • SgACC

Los estudios en los que se ha utilizado el sgACC (Cg25) como diana terapéutica para la ECP se han llevado a cabo principalmente en pacientes diagnosticados de trastorno depresivo mayor resistente al tratamiento (TDR). El primer estudio publicado por Mayberg y cols. en 2005, mostró una disminución del flujo de sangre cerebral (CBF, por sus siglas en inglés) medido con PET en el Cg25 y en su vecino OFC tras aplicar ECP en el sgACC. Los respondedores a largo plazo también demostraron cambios en CBF en otras localizaciones implicadas en la depresión, como aumentos de flujo en el CPFDL o el córtex cingulado posterior y disminución en el hipotálamo (Mayberg et al., 2005).
También se ha estudiado mediante Fluorodesoxiglucosa (FDG)-PET, el efecto inmediato de la desconexión de la estimulación en pacientes con TDR a los que se le aplicó la ECP en el sgACC. Tras 48h de desconexión de la estimulación se observó una disminución del metabolismo en el córtex cingulado anterior dorsal, región premotora y el putamen (Martín-Blanco et al., 2015), sin observarse empeoramiento clínico de los pacientes.

Un reciente estudio piloto para el tratamiento de 16 pacientes con anorexia nerviosa intervenidas con sgACC-ECP, también mostró cambios en la actividad metabólica cerebral mediante FDG-PET. Los cambios más relevantes tras 12 meses de estimulación en comparación con el basal fueron: un aumento de la actividad metabólica en el lóbulo parietal (que se encuentra hiperactivada en pacientes con este trastorno), el giro parahipocampal y temporal; así como una actividad disminuida en el giro frontal medio y superior, el giro subcalloso y cingulado, ganglios basales (globo pálido, caudado, putamen), el tálamo y cerebelo (Lipsman et al., 2017).

Utilizando técnicas de neuroimagen con tractografía probabilística de todo el cerebro, también se ha des-

crito que aquellos pacientes con TDR respondedores a ECP en el sgACC presentaban conexiones bilaterales de fascículos de sustancia blanca entre el CPFm, córtex cingulado dorsal y rostral y núcleos subcorticales (NAc, caudado, putamen y tálamo anterior), en comparación con aquellos pacientes no respondedores, que no mostraban estos patrones de activación (Riva-Posse et al., 2014). Este estudio demuestra, por tanto, que la respuesta clínica de la ECP en sgACC para el TDR vendría mediada por la estimulación combinada de 3 haces de fibras de sustancia blanca que transitan a través del sgACC como son: 1) el fórceps minor bilateral del cuerpo calloso, que conecta con el CPFm; 2) los haces del cingulum bilateral conectando con el córtex cingulado subcalloso; y 3) la rama medial del fascículo uncinado bilateral que conectaría con el córtex cingulado subcalloso y el CPFm con el NAc, tálamo anterior y otras estructuras subcorticales. En un estudio posterior del mismo grupo se testaba la utilidad de utilizar esta técnica tractográfica para guiar de forma precisa la implantación de los electrodos en estos haces de sustancia blanca. Tras 1 año de estimulación el 81.8% de los pacientes habían respondido al tratamiento y el 54.5% alcanzaron la remisión clínica (Riva-Posse et al., 2018).

En esta misma línea, un estudio que utilizaba la tractografía para aplicar específicamente la ECP en la rama superolateral del MFB a cada sujeto de forma individual, encontró una rápida e importante respuesta antidepresiva que perduró a las 52 semanas en el 80% de los pacientes intervenidos (Fenoy et al., 2018, 2016). El MFB comprende fibras DA ascendentes y descendentes que conectarían el ATV con el NAc y el CPF, considerándose que jugaría un papel importante en procesos de motivación y recompensa. Sorprendentemente, los resultados de actividad metabólica con PET no mostraron cambios tras 12 meses de estimulación, en comparación con el estado basal (Fenoy et al., 2018).

### • NAc ó VC/VS

Utilizando la ECP en el NAc de pacientes con TDR, Bewernick y cols. (Bewernick et al., 2010) hallaron que la estimulación de alta frecuencia disminuía la actividad (medida con PET de glucosa) en el sgACC, aunque se asociaba con disminuciones de metabolismo en regiones prefrontales como el OFC y la amígdala en aquellos pacientes respondedores.

Tras la estimulación aguda de la VC/VS en pacientes con TOC se ha descrito mediante FDG-PET una disminución de la actividad metabólica en el OFC (Abelson et al., 2005; Nuttin et al., 2003), así como un aumento del flujo de sangre cerebral regional (rCBF, por sus siglas en inglés) en el ACC dorsal. Este aumento de actividad correlacionaba con la mejoría sintomatológica, sin embargo, la estimulación con el contacto del electrodo más dorsal en esta misma muestra, mostraba un cambio en la activación de la red, con aumentos de rCBF en tálamo, estriado y globo pálido (Dougherty et al., 2016). En otro estudio se han observado resultados similares, con aumentos de CBF (medido con 15O-PET) en el OFC, ACC, tálamo, estriado y globo pálido tras la estimulación aguda (Rauch et al., 2006).

La disminución de síntomas obsesivo-compulsivos tras la estimulación de la VC/VS también se ha relacionado con una normalización de la actividad del NAc, junto a una disminución de la hiperconectividad funcional fronto-estriatal medida con fMR (Figee et al., 2013). Este mismo grupo de investigación también mostró un aumento de la liberación de DA estriatal en 15 pacientes con TOC tanto en el tratamiento agudo como crónico del NAc con ECP (Figee et al., 2014). Esta asociación entre aumento de DA y eficacia de la ECP en el TOC parece contraintuitiva, dada la hipótesis hiperdopaminérgica del TOC en el circuito cortico-estriatal. Sin embargo, se ha sugerido que este estado hiperdopaminérgico en el TOC podría ser un mecanismo secundario para compensar los déficits serotoninérgicos que presenta el trastorno (Perani et al., 2008).

En resumen, se podría concluir mediante los estudios de neuroimagen realizados en pacientes con trastornos mentales a los que se aplica ECP, que se observan efectos fisiológicos relevantes en áreas distales al lugar de implantación de los electrodos. Además, que existen algunas coincidencias en la neuroimagen de aquellos pacientes con un mismo trastorno y diana terapéutica de estimulación, aunque en diferentes trastornos las coincidencias son limitadas. Por tanto, los últimos avances en la tractografía determinística individualizada para cada paciente podría ser una opción efectiva para la localización de los electrodos en la ECP de diferentes trastornos psiquiátricos.

| ÁREA DE ESTIMULACIÓN | ESTUDIO | TRASTORNO | TÉCNICA | EFECTOS |
|---|---|---|---|---|
| SgACC | Mayberg et al., 2005 | TDR | PET | ↓CBF en Cg25 y OFC<br>En respondedores a largo plazo: ↑ CBF en CPFDL, córtex cingulado posterior y ↓ en hipotálamo |
| | Martín-Blanco et al., 2015 | TDR | PET | Tras desconexión aguda de la ECP: ↓ metabolismo en córtex cingulado anterior dorsal, región premotora y el putamen |
| | Riva-Posse et al., 2014 | TDR | DTI | En pacientes respondedores vs. no respondedores: conexiones bilaterales de fascículos de sustancia blanca entre el CPFm, córtex cingulado dorsal y rostral y núcleos subcorticales (NAc, caudado, putamen y tálamo anterior) |
| | Lipsman et al., 2017 | Anorexia nerviosa | PET | ↑ actividad metabólica en lóbulo parietal, giro parahipocampal y temporal<br>↓ actividad en el giro frontal medio y superior, el giro subcalloso y cingulado, ganglios basales (pálido, caudado, putamen), así como el tálamo y cerebelo |
| NAc | Bewernick et al., 2010 | TDR | PET | ↓ metabolismo en SgACC, OFC y amígdala |
| | Figee et al., 2014 | TOC | | Liberación de DA estriatal |
| VC/VS | Abelson et al., 2005; Nuttin et al., 2003 | TOC | PET | ↓ actividad en OFC |
| | Dougherty et al., 2016 | TOC | PET | ↑ de rCBF en ACC dorsal<br>↑ de rCBF en tálamo, estriado y pálido (estimulación con electrodo dorsal) |
| | Rauch et al., 2016 | TOC | PET | ↑ de rCBF en OFC, ACC, tálamo, estriado y pálido |
| | Figee et al., 2013 | TOC | fMR | ↑ de rCBF en OFC, ACC, tálamo, estriado y pálido |

Tabla 3. Resumen de los principales hallazgos de neuroimagen con ECP en SgACC y NAc (VC/VS).

# 2. PLANTEAMIENTO, OBJETIVOS E HIPÓTESIS

## 2.1. **PLANTEAMIENTO**

Como se ha expuesto detalladamente en la introducción, la esquizofrenia es un trastorno psiquiátrico con un elevado porcentaje de pacientes que no responden a los tratamientos disponibles actualmente, hecho que conlleva una elevada carga humanística y del sistema de salud. Las técnicas de neuroimagen más recientes han sido capaces de avanzar en el conocimiento de la fisiopatología del trastorno, implicando el sistema dopaminérgico y glutamatérgico de diversas áreas del circuito que conecta el córtex con los ganglios basales. La evidencia más robusta apunta al núcleo estriado como el principal protagonista de la disregulación de estos sistemas de neurotransmisión que, por sus conexiones recíprocas con el córtex y el tronco del encéfalo, produciría una alteración de los diversos circuitos cortico-estriatales que podrían justificar los síntomas positivos, negativos y cognitivos en la esquizofrenia.  Otros trastornos neuropsiquiátricos resistentes al tratamiento convencional, principalmente el TOC y el TDR, que también han mostrado alteraciones en este circuito, han sido tributarios de beneficiarse de nuevas técnicas de neuromodulación, como la estimulación cerebral profunda. Los cada vez más estudios publicados en estos trastornos, han mostrado una eficacia considerable para estos pacientes resistentes, con una seguridad más que aceptable. Por tanto, se plantea que la ECP también sería una opción de tratamiento válida para aquellos pacientes que padecen una esquizofrenia resistente al tratamiento. Hasta la publicación de este estudio, no existe evidencia de la aplicación de esta técnica en pacientes con esquizofrenia; sin embargo, diversos estudios en modelos animales de esquizofrenia han demostrado eficacia para el tratamiento de síntomas esquizofrenia-like aplicando la ECP en diferentes lugares de estimulación. Además, las dos dianas terapéuticas seleccionadas para implantar los electrodos han sido utilizadas de manera segura en otros trastornos, principalmente en el TOC y el TDR, por lo que no debería suponer un riesgo en cuanto a la técnica llevada a cabo.

# 2.2. OBJETIVOS

Por todo lo expuesto anteriormente, en la presente tesis se plantean los siguientes objetivos:

## Objetivo principal

- Valorar la eficacia y seguridad de la ECP en el tratamiento de pacientes con esquizofrenia resistente al tratamiento en un estudio piloto, mediante un ensayo clínico aleatorizado, controlado y cruzado.

## Objetivos secundarios

- Comparar dos dianas terapéuticas de implantación de electrodos (NAc vs. SgACC) en cuanto a eficacia y seguridad.
- Evaluar si hay diferencias en cuanto a mejoría de síntomas positivos y/o síntomas negativos entre las dos dianas de implantación de los electrodos (NAc vs. SgACC).
- Comprobar los cambios en el metabolismo cerebral de los pacientes con esquizofrenia resistente antes y después de la intervención con ECP, medidos mediante 18-FDG-PET.

# 2.3. HIPÓTESIS

## Hipótesis principal

- El tratamiento continuado con estimulación profunda de alta frecuencia será eficaz para los pacientes con esquizofrenia resistente intervenidos con ECP [medida la respuesta al tratamiento como una disminución de la Escala para Síndrome Positivo y Negativos de la Esquizofrenia (PANSS, por sus siglas en inglés) basal-final ≥ 25%].

- La ECP será segura (no eventos secundarios mayores) para los pacientes incluidos. En caso de presentar efectos indeseados leves, serán modulables modificando los parámetros de estimulación.

## Hipótesis secundaria

- Ambos lugares de estimulación serán eficaces tanto para síntomas positivos como para síntomas negativos y presentarán perfiles de seguridad adecuados, sin diferencias destacables entre ellos.

- Los pacientes con esquizofrenia resistente intervenidos con ECP mostrarán un patrón de cambios metabólicos en áreas relacionadas con circuitos cortico-estriatales.

# 3. METODOLOGÍA

## 3.1. POBLACIÓN A ESTUDIO

Se incluyeron pacientes diagnosticados de esquizofrenia según criterios DSM-IV-TR, de entre 18 y 55 años, que cumplían criterios pre-establecidos de gravedad clínica, resistencia al tratamiento farmacológico y en los que estaba contraindicada la TEC, o en los que la mejoría obtenida con la misma no fuera mantenida. Los criterios de inclusión y exclusión detallados, así como los criterios de resistencia al tratamiento, se describen en la sección metodológica del estudio 1.

## 3.2. DISEÑO Y PROCEDIMIENTO

Se trata de un ensayo clínico aleatorizado y cruzado en el que se incluyeron ocho pacientes con esquizofrenia resistente al tratamiento, a los cuales se aleatorizó a uno de los dos 'targets' propuestos: córtex prefrontal medial, -área subgenual del córtex cingulado anterior Cg25 (sgACC)- o la estructura límbica que forma parte del estriado ventral, el NAc. Tras la implantación de los electrodos, se inició una primera fase de estabilización abierta (aunque ciega para los evaluadores) en la que se aplicaba la estimulación de alta frecuencia y se modificaban los parámetros de la misma en función de los cambios clínicos evaluados mediante entrevistas clínicas. Los pacientes recibieron tratamiento con ECP hasta la estabilización clínica (de al menos 6 meses de duración). Aquellos pacientes que en esta fase inicial respondieron al tratamiento, se incluyeron en un estudio doble-ciego y cruzado de 6 meses de duración en los cuales se mantuvo el estimulador conectado (fase on) durante tres meses y se desconectó los siguientes tres meses (fase off), o viceversa (Figura 14). En el caso de no respuesta al tratamiento, los pacientes fueron excluidos del estudio, aunque manteniendo el seguimiento clínico. A nivel basal, se evaluaron las variables socio-demográficas y escalas clínicas que se detallan en el siguiente apartado. Posteriormente a la intervención se realizó seguimiento quincenal de los pacientes, recogiendo durante este periodo las mismas escalas clínicas. Otras evaluaciones, como la exploración neuropsicológica y las pruebas de neuroimagen (PET y RM), se realizaron pre-tratamiento y al final de la fase de estabilización (pre-inicio de estudio cruzado), así como en la finalización del estudio.

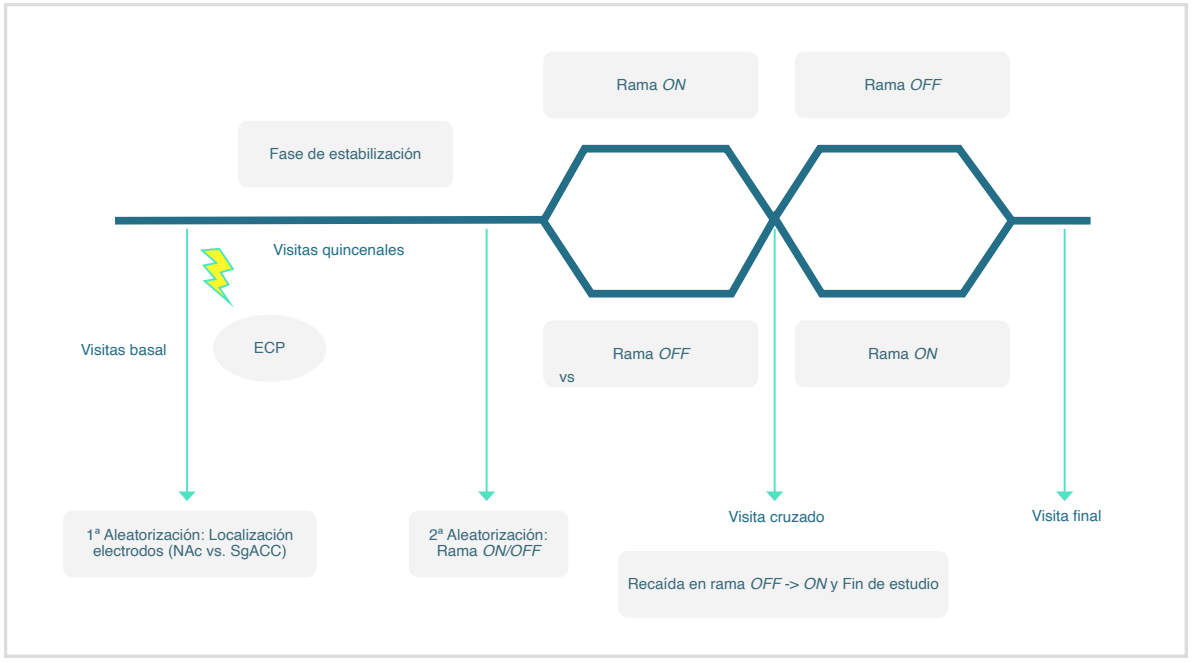


Figura 14. Esquema del diseño del estudio.

## 3.3. VARIABLES DE ESTUDIO

### 3.3.1. Variables clínicas

La variable de eficacia principal es la escala PANSS. También se valoraron:

- Cambios clínicos con la escala de Impresión Clínica Global (CGI, por sus siglas en inglés), la CGI de severidad (CGIs) y la CGI de mejoría global (CGIi), Escala para Síntomas Negativos de la Esquizofrenia (SANS) y la Escala Calgary para la Depresión (CDS).
- Escalas de funcionalidad: Social Functioning Scale (SFS), Personal and Social Performance (PSP) y la Escala de Evaluación de la Actividad Global (EEAG)
- Escalas de efectos secundarios: *Extrapyramidal Symptom Rating Scale* (ESRS) y *Udvalg für Kliniske Undersogelser* (UKU).
- Variables neuropsicológicas: estimación de Coeficiente Intelectual (CI) mediante el test de vocabulario de la Escala Wechsler de Inteligencia para Adultos (WAIS III). Se realizaron otros cinco subtests del WAIS III (dígitos, letras y números, semejanzas, matrices y cubos) para la valoración de memoria y función ejecutiva.

### 3.3.2. Variables de neuroimagen

- Se realizó una evaluación mediante PET con el radiofármaco 18F-FDG (molécula análoga de la glucosa), que determina la actividad metabólica cerebral, en un dispositivo Philips Gemini TF PET/TC .
- Se realizó una RM potenciada en T1 basal en un dispositivo Philips Achieva de 3-Tesla.

## 3.4. ANÁLISIS ESTADÍSTICOS

Los análisis estadísticos realizados en cada estudio se detallan en la sección metodológica de los artículos respectivos.

## 3.5. ASPECTOS ÉTICOS

Únicamente se consideraron para la inclusión en el estudio aquellos pacientes capaces de entender los potenciales beneficios y riesgos del tratamiento. El proceso de consentimiento para la inclusión fue riguroso, incluyendo varias entrevistas con el paciente y sus familiares/cuidadores. Además, se consideró la viabilidad de incluir a los pacientes en el estudio a través de un comité que incluía el psiquiatra habitual del paciente, un psiquiatra senior independiente y un neurocirujano experto en ECP.

Todos los pacientes incluidos (o sus tutores legales, en caso necesario) firmaron el consentimiento informado. El estudio seguía los principios de la Declaración de Helsinki, y fue aprobado por el Comité Ético del Hospital de la Santa Creu i Sant Pau, así como por la Agencia Española Reguladora de Medicamentos y Productos Sanitarios.

# 4. RESULTADOS

# 4.1. ESTUDIO 1

## Deep Brain Stimulation in Treatment Resistant Schizophrenia: A Pilot Randomized Cross-Over Clinical Trial.

Iluminada Corripio, Alexandra Roldán, Salvador Sarró, Peter J McKenna, Anna Alonso-Solís, Mireia Rabella, Anna Díaz, Dolors Puigdemont, Enric Álvarez, Antonio Arévalo, Pedro P. Padilla, Jesús M. Ruiz-Idiago, Rodrigo Rodríguez, Joan Molet, Edith Pomarol-Clotet, Maria J. Portella.

EBioMedicine. 2020 Jan;51:102568. doi:10.1016/j.ebiom.2019.11.029.

A B S T R A C T

*Background:* Up to 30% of patients with schizophrenia are resistant to antipsychotic drug treatment, with 60% of such cases also failing to respond to clozapine. Deep brain stimulation (DBS) has been used in treatment resistant patients with other psychiatric disorders, but there is a lack of trials in schizophrenia, partly due to uncertainties over where to site the electrodes. This trial aimed to examine the effectiveness of nucleus accumbens (NAcc) and subgenual anterior cingulate cortex (subgenual ACC) targeted DBS; the primary outcome measure was PANSS total score, as assessed fortnightly.

*Methods:* Eight patients with schizophrenia, who met criteria for treatment resistance and were also resistant to/intolerant of clozapine, were randomly assigned using central allocation to receive DBS in the NAcc or subgenual ACC. An open stabilization phase lasting at least six months was followed by a randomized double-blind crossover phase lasting 24 weeks in those who met symptomatic improvement criteria. The primary end-point was a 25% improvement in PANSS total score. (ClinicalTrials.gov Identifier: NCT02377505; trial completed).

*Findings:* One implanted patient did not receive DBS due to complications of surgery. Of the remaining 7 patients, 2/3 with NAcc and 2/4 with subgenual ACC electrode placements met the symptomatic improvement criteria (58% and 86%, and 37% and 68% improvement in PANSS total score, respectively). Three of these patients entered the crossover phase and all showed worsening when the stimulation was discontinued. The fourth patient worsened after the current was switched off accidentally without her or the investigators' knowledge. Physical adverse events were uncommon, but two patients developed persistent psychiatric adverse effects (negative symptoms/apathy and mood instability, respectively).

*Interpretation:* These preliminary findings point to the possibility of DBS having therapeutic effects in patients with schizophrenia who do not respond to any other treatment. Larger trials with careful attention to blinding will be necessary to establish the extent of the benefits and whether these can be achieved without psychiatric side-effects.

### 1. Introduction

Schizophrenia is a severe and disabling mental disorder characterized by positive, negative and cognitive symptoms, affecting around 1% of the population worldwide [1]. It is estimated that around

**Research in Context**

*Evidence before this study*

Poor response to antipsychotic drug treatment is a well-recognized problem in schizophrenia. Deep brain stimulation (DBS) has been used in treatment resistant major depression and obsessive-compulsive disorder, but trials are so far lacking in schizophrenia. Literature review to confirm the absence of existing trials included (a) searching PubMed using the terms deep brain stimulation and schizophrenia and checking the references of all relevant publications; (b) checking ClinicalTrials.gov; and (c) personal communication with the investigators of a currently recruiting American trial.

*Added value of this study*

This initial trial suggests that DBS might be beneficial in some patients with treatment resistant schizophrenia. Of particular note was the near-complete disappearance of positive symptoms (delusions and hallucinations) in two patients with nucleus accumbens electrode placements.

*Implications of all the available evidence*

The apparent positive effects of DBS in schizophrenia in this trial need to be treated with caution given the small numbers and mainly open label evaluation. It will also be important to determine whether and to what extent clinical improvement can be obtained without psychiatric adverse effects.

20–30% of patients are resistant to conventional antipsychotic drug treatment [2], and less than half of such patients (40.1%, 95% confidence interval 36.8%–43.4%) respond to the most effective of the second-generation or atypical antipsychotics, clozapine [3]. Other psychopharmacological strategies, in particular the use of a range of drugs with glutamatergic actions, have so far failed to fulfil their promise, either for negative symptoms [4] or for all symptoms [5].

Deep brain stimulation (DBS) is a well-established treatment for Parkinson's disease and other movement disorders, whose use has been extended in recent years to treatment resistant psychiatric illness [6]. The technique involves high frequency stimulation of deep brain areas through electrodes implanted under stereotactic surgery. It is believed to work primarily by producing functional inhibition in the region around the electrode, but excitatory effects on local axons and more distant excitatory effects may also play a part [7]. It has additionally been argued that the intervention may act in the longer term to correct pathological brain activity in brain networks with connections to the implantation site [8]. Importantly, unlike other forms of psychosurgery, DBS is reversible, i.e., the stimulation can be turned off (and if necessary the electrodes explanted) without any permanent loss of function.

To date, DBS has been employed principally in treatment resistant patients with two psychiatric disorders, obsessive-compulsive disorder and major depression, with broadly encouraging results in both cases [9,10]. The electrode placements most frequently employed have been in or around the nucleus accumbens (NAcc) in the former disorder [9], and in this site and the subgenual anterior cingulate cortex (subgenual ACC) in the latter [10]. The potential use of DBS in treatment resistant schizophrenia is currently a topic of considerable discussion [11,12], with much of the debate focusing on where to site the electrodes. Practical experience, in contrast, is virtually non-existent. Plewnia et al. [13] reported beneficial effects of DBS on obsessions and compulsions using an NAcc electrode placement in a patient with residual schizophrenia, but this patient had no psychotic symptoms. A trial in Toronto (Clinicaltrials.gov identifier NCT01725334) aimed to use electrode placements in the NAcc or the ventral tegmental area, with the aim of improving negative symptoms; however, this trial was abandoned due to lack of recruitment. A currently recruiting trial in Baltimore (Clinicaltrials.gov indentifier NCT02361554), targets the substantia nigra pars reticulata; its rationale is that local inhibitory effects will result in disinhibition of the mediodorsal thalamic nucleus and lead to improvement in positive and cognitive symptoms.

We report the outcome of the first completed trial of DBS in treatment resistant schizophrenia. Because of the uncertainties concerning electrode placement we decided to test the effectiveness of two targets. One was in the ventral striatum, specifically the NAcc, and the other was the subgenual ACC. Choice of these two sites was driven partly by the fact that both have been employed in obsessive-compulsive disorder and/or major depression, and partly because both sites can be considered to be in some sense characterized by neuronal overactivity in schizophrenia, and so potentially susceptible to the functional inhibitory effects of DBS. In the case of the NAcc there is longstanding circumstantial evidence for a functional dopamine excess in the disorder [14], with current findings pointing to increased dopamine synthesis capacity in the striatum [15]. At a theoretical level positive symptoms (in particular delusions and hallucinations) have also been linked to ventral striatal overactivity via Kapur's [16] influential 'aberrant salience' proposal, of increased and inappropriate dopamine activity giving rise to abnormal reward prediction error signals. Also relevant to the decision to employ a ventral striatal electrode placement is the fact that this part of the basal ganglia receives major afferent input from the hippocampus, which has been considered to play a role in the pathophysiology of schizophrenia and has been proposed as a target for DBS [11].

The choice of a subgenual ACC placement was based on the finding of failure of de-activation in the medial frontal cortex, described by ourselves [17] and others [18]. This failure is presumed to reflect dysfunction in the so-called default mode network, a set of brain regions that are normally active at rest but which de-activate during performance of a wide range of attention-demanding tasks; the medial frontal cortex – including the pregenual and subgenual portions of the anterior cingulate cortex, but also more rostral regions – forms one of two prominent midline 'nodes' or 'hubs' of this network [19]. On these grounds, the medial frontal cortex represents a more logical cortical target for the local inhibitory effects of DBS than the dorsolateral prefrontal cortex, which is also implicated in schizophrenia but where the abnormality takes the form of hypofunction [20].

In this paper we report clinical and functional outcomes from the trial. Neuropsychological and functional imaging findings will be reported in future communications.

## 2. Methods

### 2.1. Design

The trial had a combined open (6+ month) and double-blind crossover (24 weeks) design. The 24-week crossover phase length was based on previous experience by one of the two groups of investigators with DBS for depression [21]. The aim was to recruit 8 patients who would be randomly assigned 1:1 to electrode placements in either the NAcc or the subgenual ACC. This study is registered with ClinicalTrials.gov (identifier NCT02377505).

### 2.2. Participants

Patients were recruited from the outpatient, inpatient and residential facilities of two mental healthcare organizations in Barcelona: FIDMAG Germanes Hospitalàries and the Hospital de la Santa Creu i Sant Pau, plus referrals by other interested clinicians. Inclusion criteria were: age 18–55 years, having a diagnosis of schizophrenia according to

DSM-IV criteria, having a five-year minimum duration of illness and showing evidence of treatment resistance. For treatment resistance the following were required: (a) presence of continuing positive symptoms without remission for two years; (b) poor response to treatment with at least two different antipsychotics, including at least one atypical antipsychotic (not including clozapine) given in adequate doses for a period of at least 6 weeks; and (c) having been treated with clozapine with either no improvement at adequate dosage or poor tolerance. It was anticipated that most patients would also show negative symptoms, but presence of these was not an inclusion criteria. While not forming part of current definitions of treatment resistance, we added a requirement that the patients had been treated with ECT at some point without sustained improvement, unless this treatment was contra-indicated or not tolerated or had been refused. This was in the interests of focusing on patients in whom all other potentially effective treatment options had been tried [22].

At the time of study entry the patients were required to have a score of 4 (moderate) or greater on at least two of the Positive and Negative Symptoms Scale (PANSS) items, delusions, hallucinatory behaviour, suspiciousness, unusual thought content, or alternatively a score of 6 (severe) or greater on one symptom. They also had to score 6 or greater (severely ill) on the Clinical Global Impression (CGI) scale and to have been on stable doses of treatment for at least two months. Women of childbearing age had to have a negative pregnancy test within 72 h pre-study and had to be using contraception.

Exclusion criteria included: (a) contraindications to neurosurgery or DBS (e.g. pacemaker); (b) diagnosis of epilepsy or clozapine-induced seizures currently requiring treatment with anticonvulsants; (c) presence of suicidal or self-harming behaviour or ideation in the last two years; (d) significant cognitive impairment, as defined by WAIS III IQ $<70$, or performance in the severely impaired range on memory or executive function tests on more detailed neuropsychological testing; (e) presence of significant cardiovascular and/or cerebrovascular disease (defined as history of cerebrovascular events, clinical symptoms of cardiac or vascular disease, ischaemic changes on ECG, uncontrolled hypertension); (f) if female, breastfeeding; (g) history of drug or alcohol abuse/dependency in the previous two years.

Only patients who were able to fully understand the potential benefits and risks of treatment were considered for the trial. The consent process was rigorous, and included discussions with both the patient and his/her family if appropriate. Patients were also required to have a caregiver or identified responsible person (i.e., family member, social worker, case-worker, or nurse) who spent at least four hours/week with the patient and was able to provide advice and support concerning the study procedures. A committee including the patient's psychiatrist, an independent senior psychiatrist and a neurosurgeon further considered the feasibility of enrolling each patient into the study.

The patients were randomly assigned 1:1 to one of the two electrode placements using PROC PLAN of SAS (version 9). Randomization was carried out by central allocation using computer generated random numbers: an independent statistician from another department generated the list, assigned the target sequence and communicated it to one of the investigators in a sealed envelope. This investigator communicated the target to the neurosurgeons. A block randomization method was used. A similar procedure was followed for the randomization in the crossover phase (which also took into account the first randomization to ensure balanced allocation within the targets). After undergoing surgery to implant the electrodes, stimulation was started within 48–72 h and lasted until the patient was clinically stable, with a minimum period of 6 months. If the patient achieved symptomatic response (defined as an improvement $\geq 25\%$ in PANSS total score, calculated using the formula: [PANSS baseline score − PANSS post-scores] $\times$ 100/ [PANSS baseline score-30] [23], which was maintained in at least 50% of the subsequent PANSS ratings, he or she then entered the 24-week double-blind crossover phase, and was randomized to 12 weeks with the stimulation 'on' followed by 12 weeks 'off' or vice-versa. In case of worsening, the patient could be withdrawn from the study if necessary and the stimulation turned on again (if it was currently switched off). Pharmacological treatment could not be modified throughout the study period, except for prescription of benzodiazepines or hypnotics if required.

All patients gave written informed consent. The study was in line with the Declaration of Helsinki, and was approved by the hospital ethical committee and the Spanish regulatory drug agency (Agencia Española de Medicamentos y Productos Sanitarios).

### 2.3. Assessments

In addition to PANSS total score, which was the primary outcome measure, and its positive and negative subscales, assessments included the Psychotic Symptom Rating Scales (PSYRATS) [24], the Scale for the Assessment of Negative Symptoms (SANS) [25], the Calgary Depression Scale for Schizophrenia (CDSS) [26] and the Global Assessment of Functioning scale (GAF) [27]. Two social functioning scales were also used, the Personal and Social Performance (PSP) Scale [28] and the Social Functioning Scale [29].

Symptomatic changes were evaluated every two weeks with the PANSS until the end of the trial. The remaining clinical scales were administered at the main study points (i.e., baseline, immediately before the crossover phase and at termination). Adverse events were assessed in detail monthly by the member of the trial team performing the psychiatric and social evaluations. Following termination from the trial patients continued to be followed up by members of the trial team or their treating clinicians.

In the stabilization phase the assessors were blind to which electrode placement each patient had and to any changes in stimulation parameters that were made. Both the patients and the clinicians were unaware of the patients' stimulation status during the crossover phase. Measures to assess the success of blinding were not employed.

### 2.4. Surgical procedure

Electrode implantation was in the white matter adjacent to the Cg25 region (subgenual ACC) and in the NAcc. The DBS pulse-generating device was implanted abdominally. Prior to surgery, a Leksell G stereotactic frame (Elekta Instruments, Atlanta, GA, USA) was fitted to the patient's head. Using the StealthStation 7 (Medtronic Inc., Minneapolis, MN, USA) the CT scan with the stereotactic frame was fused to the MRI image to calculate the surgical targets. The target subgenual ACC white matter was delimited as follows: in a midline T2 sagittal image the cingulate gyrus inferior to the genu of the corpus callosum was identified; next, a line was traced from this point of the corpus callosum to the anterior commissure and the mid-point was identified; an image was then taken of the T2 coronal section corresponding to the plane of the mid-point and the definitive coordinates were calculated for the transition area between the white and grey matter for BA 25. The NAcc target was determined measuring the distances from the anterior commissure (AC) and the posterior commissure (PC) with the following coordinates: $x$ = 6–8 mm lateral to midpoint, $y$ = 1–3 mm anterior to the AC, $Z$ = 4 mm inferior to the AC line (see Fig. 1 for location of the NAc and subgenual ACC electrode implantations in subjects N5 and N7, respectively). In the operating room, with the patient under general anaesthesia, a burr hole was drilled in front of the coronal suture and laterally at a variable distance from the midline seeking to avoid the ventricles. DBS electrodes (Medtronic model 3387, Medtronic Inc., Minneapolis, MN, USA) were implanted bilaterally. Each of the four electrode contacts was tested intraoperatively at maximal voltage (9.0 V). During the same surgical procedure, a programmable internal pulse generator (Activa PC, Medtronic Inc., Minneapolis, MN, USA) was implanted

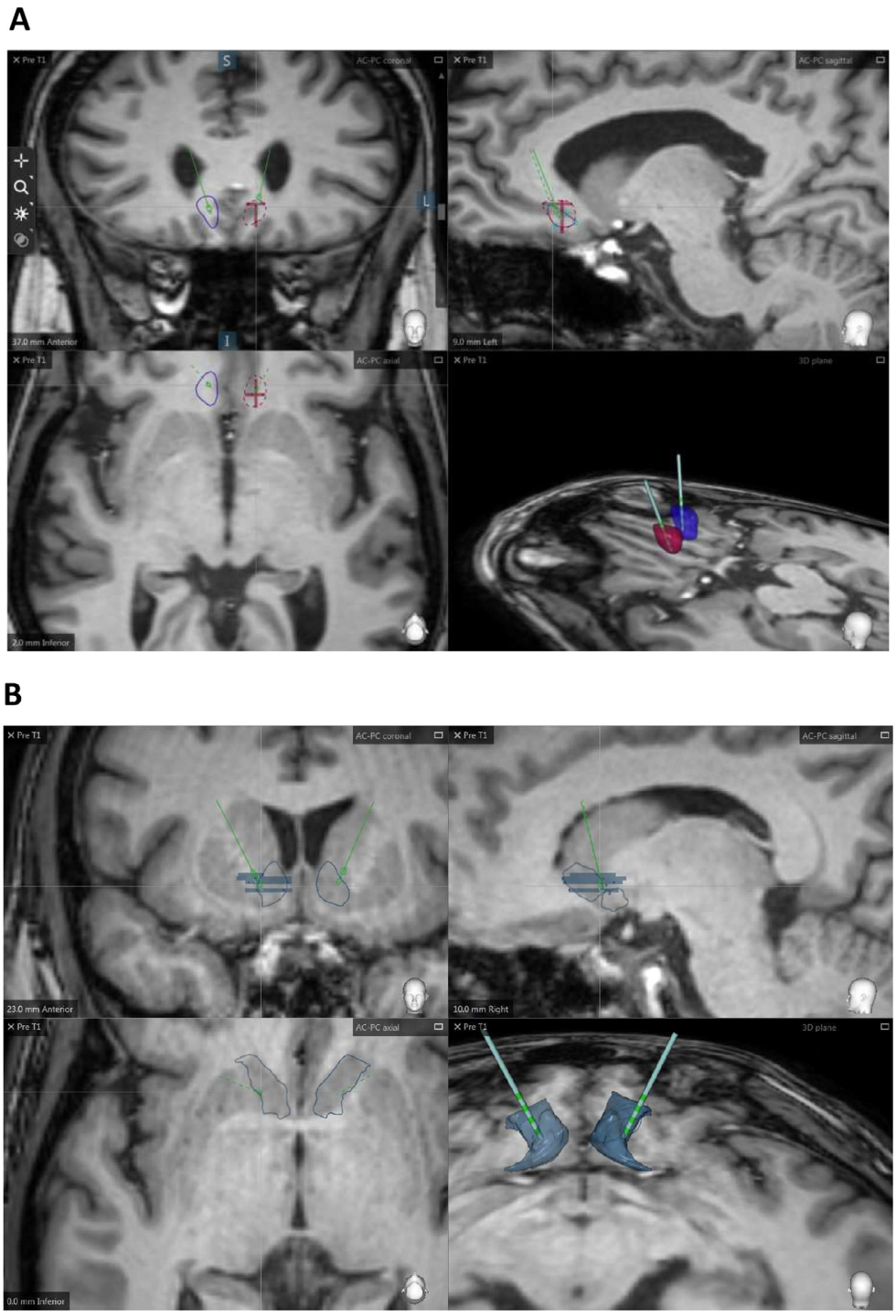


**Fig 1.** Location of the deep brain stimulation leads in the (A) nucleus accumbens (NAcc) and in the (B) subgenual anterior cingulate cortex (subgenual ACC) in right and left hemispheres. The upper row of images corresponds to coronal and sagittal slices; the lower images correspond to axial section in 2D and 3D views. The 3D plane shows a volumetric reconstruction of both targets (bilateral NAcc in metallic blue; left subgenual ACC in purple, right subgenual ACC in blue. Images were generated using the SureTune software (Medtronic Eindhoven Design centre, MEDC).

subcutaneously in abdominal wall tissue. The procedure was carried out under general anaesthesia.

Stimulation was started 48–72 h after surgery using unilateral left stimulation, (contact anode, case cathode), with the initial following parameters: 2.5 V, 60 microseconds ($\mu$s) pulse width and 130 Hertz (Hz) of frequency; these were chosen based on prior experience by our group (Sant Pau) with DBS in patients with major depression. Two contacts with good levels of impedance were selected taking into account the position of the electrode within the selected area (e.g., patient N1 showed had a contact outside the NAcc and so this was not used). After a week bilateral stimulation was begun, again based on previous clinical experience with DBS in psychiatric populations.

During the stabilization phase stimulation parameters were modified individually for each patient by an independent clinician depending on clinical state, and guided specifically by the presence and degree of positive symptoms. Patients were not informed about any changes. The sequence of changes to maximize the therapeutic effect was (1) increasing voltage up to 7.5 V, (2) increasing pulse width or frequency up to 210 $\mu$s/Hz, and (3) changing active contacts or mode.

### 2.5. Data analysis

Formal analysis of changes in PANSS and other ratings was considered to be of limited value due to the small sample size, and is also complicated by the fact that the endpoint criteria (i.e., progression to crossover phase or termination due to lack of effectiveness) depended on response to DBS. For completeness, however, statistical models were fitted to the PANSS data (PANSS total, PANSS positive, PANSS negative) for the sample as a whole (i.e., not separating by electrode placement), considering only the stabilization phase. Linear mixed models with repeated measures evaluated the effect of DBS by considering the PANSS scores in the visit previous to the surgical implant and all the subsequent assessments up till the end of the stabilization phase. This model also tested the effect of time (evolution of PANSS scores across time, discounting the DBS off-on effect) including also individual slopes and intercepts (i.e., the random effects part of the model). Paired t-tests were additionally carried out, considering individual PANSS scores at the baseline visit and at the last recorded visit in the stabilization phase. Statistical analyses were conducted with version 3.6.0 of the R software.

### 2.6. Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

## 3. Results

### 3.1. Patient characteristics

Slightly less than thirty patients were considered for the trial (Sant Pau $N$ = 14; FIDMAG $N$ = 13–15, exact numbers not recorded). The most common reason for exclusion was a lack of perceived need for treatment by the patient. Other reasons in individual cases included failure to meet diagnostic criteria, ongoing substance abuse, presence of comorbid psychiatric disorder (obsessive-compulsive disorder and autistic spectrum disorder) and failure to meet severity criteria.

Eight patients were enrolled in the study. The first patient was recruited on 28/11/2014 and the last on 20/04/2017. One patient (N3) did not proceed to stimulation; he suffered a right internal capsule haemorrhage immediately after surgery and subsequently developed infection in the device which threatened to spread to the electrodes. As a result the generator and electrodes were removed three months after surgery.

All but one of the seven remaining patients showed ultra-treatment resistant illness, according to Howes et al. [30]. In the remaining patient (N6) clozapine was not tolerated at doses higher than 100 mg/day (the dose she was taking at study entry). These seven patients' baseline characteristics and electrode placement after first randomization are shown in Table 1. Three patients were implanted in the NAcc (N1, N5, N6) and 4 patients in the subgenual ACC (N2, N4, N7, N8). All patients were receiving treatment with clozapine augmented with different antipsychotics. Highest stimulation parameters achieved during the study period in each patient are shown in supplementary Table S1.

### 3.2. Stabilization phase

The open stabilization phase lasted between 8 and 20 (average 13) months. Average scores over first eight months of treatment (the period during which all patients remained in the stabilization phase), separated according to electrode placement, are shown in Fig. 2. Individual scores for the patients over the entire stabilization phase are shown in Supplementary Figs. S1 and S2. It is noteworthy that two of the three patients with NAcc placements showed a nearly full remission (N1) and full remission apart from intermittent recurrences (N6) of positive symptoms (which took the form exclusively of delusions and hallucinations in both cases). One of these patients (N1) has been reported previously [31].

Given the limitations of applying statistical analysis to the data, detailed results are reported in the Supplementary material. Briefly, however, testing across the whole sample ($N$ = 7) revealed a significant effect of DBS on PANSS total, positive symptoms and negative symptoms scores (all $p<0.001$), when the baseline (i.e., DBS off) was compared to all remaining time points in the stabilization phase (i.e., DBS on) using a repeated measures linear mixed model. This result was replicated for PANSS total score and positive symptoms score, but not negative symptoms score, when a simpler paired $t$-test was performed, considering the baseline (DBS off) and last observation (DBS on) (PANSS total $p$ = 0.007; PANSS positive $p$ = 0.002; PANSS negative $p$ = 0.18).

### 3.3. Double-blind crossover phase

Four patients (N1, N2, N4 and N6) met the symptomatic response criteria, 2 with NAcc (N1 and N6) and 2 (N2 and N4) with subgenual ACC placements (for percentages of improvement see Supplementary Table S2). Three of these patients entered the crossover phase. Patient N1 (NAcc placement) entered in an 'on' phase. Six weeks after the stimulation was switched to 'off' a worsening in psychotic symptoms became evident, which took the form mainly of a worsening of negative symptoms [PANSS scores immediately before entering crossover and in the first switch-off visit where a worsening of symptoms was evident: total: 64 vs. 73, positive symptoms: 14 vs. 14, negative symptoms: 16 vs. 21]. This patient remained in the trial until the end of the crossover phase. Patient N2 (subgenual ACC placement) began in an 'off' phase. This was followed by a worsening of psychotic symptoms within a few days [PANSS scores: total: 79 vs. 98, positive symptoms: 17 vs. 23, negative symptoms: 18 vs. 24]. The patient was admitted with suicidal ideation, the stimulation was switched back on, and he was withdrawn from the study. Patient N4 (subgenual ACC placement) also began in an 'off' phase and also showed a worsening of psychotic symptoms, in this case two weeks later [PANSS scores: total: 47 vs. 93, positive symptoms: 16 vs. 25, negative symptoms: 13 vs. 29. The stimulation was switched back on, and the patient was withdrawn from the study. Details of the three patients' courses during the crossover phase are summarized in Fig. 3.

**Table 1**
Patients' baseline characteristics and electrode placement at baseline.

| Patient ID | Sex | Age | Illness duration (years) | Antipsychotic treatment (mg/d) | ECT | PANSS Total | PANSS Positive | PANSS Negative | PANSS General | GAF | CGI | Electrode Placement |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| N1 | F | 46 | 24 | Clozapine 350<br>Risperidone 6 | Refused | 97 | 27 | 24 | 46 | 40 | 6 | NAcc |
| N2 | M | 34 | 9 | Clozapine 500<br>Haloperidol 5 | Non-response | 108 | 26 | 28 | 54 | 25 | 6 | Subgenual ACC |
| N3 | M | 37 | 8 | Clozapine 600<br>Aripiprazole 45 | Non-response | 76 | 21 | 28 | 27 | 25 | 6 | NAcc |
| N4 | F | 53 | 23 | Clozapine 800<br>Olanzapine 10<br>Pimozide 10 | Yes | 84 | 22 | 23 | 39 | 30 | 6 | Subgenual ACC |
| N5 | M | 43 | 11 | Clozapine 400<br>Ziprasidone 160 | Intolerance (confusion) | 102 | 24 | 29 | 49 | 30 | 6 | NAcc |
| N6 | F | 35 | 10 | Clozapine 100<br>Paliperidone 3 | Refused | 65 | 17 | 12 | 36 | 30 | 6 | NAcc |
| N7 | F | 38 | 21 | Clozapine 450<br>Paliperidone depot 100/month | Refused | 85 | 27 | 21 | 37 | 31 | 6 | Subgenual ACC |
| N8 | M | 54 | 35 | Clozapine 500<br>Aripiprazole 20 | Refused | 87 | 22 | 32 | 33 | 31 | 6 | Subgenual ACC |

PANSS – Positive and Negative Symptoms Scale; GAF – Global Assessment of Functioning scale; CGI – Clinical Gobal Impression of severity of illness.

The fourth patient who met the symptomatic response criteria (N6, NAcc placement) achieved excellent remission of psychotic symptoms, although these intermittently returned, requiring frequent alterations of stimulus parameters. After 10 months in total, at a time when she had been symptom free for several weeks, the stimulation was turned off unknown to the patient and the investigators. (What happened is unclear but possibilities include either that the off button had been accidentally touched when her stimulus parameters were checked during a clinic visit, or that the stimulator function was interrupted when she passed through a security scanner at a tourist attraction the same day.) Her symptoms (delusions and auditory hallucinations) returned within 24 h and persisted until the switching off event was discovered a few days later. The patient reported subjective improvement 20 min after the current was turned back on. The next day she was symptom free. The patient was given the option of formally entering the crossover phase, but declined.

Two spontaneous disconnections also occurred in N5 (NAcc placement) at the beginning of treatment. These lasted less than a week on both occasions and were not obviously associated with clinical changes.

### 3.4. Secondary outcomes

Average PSYRATS and SANS scores from baseline to randomization or termination for all 7 patients are shown in Table 2. Mirroring the pattern with the PANSS, reductions were evident on both scales. Depression scores also decreased. Improvements were also seen on the GAF and CGI. There was evidence of improvement on one of the two social functioning scales used, the PSP (see Table 2), but not on the other, the SFS (see Supplementary Table S3).

### 3.5. Adverse events

DBS was generally well-tolerated in the 7 patients who proceeded to electrode activation. However, one patient with an NAcc placement (N1) developed akathisia after the stimulation was changed from unilateral to bilateral; this eventually responded when the stimulation was changed back to unilateral, maintaining the reduced parameters. As noted, during the crossover phase this patient developed worsening of negative symptoms from a previously mild level. This worsening has persisted, despite DBS being resumed and subsequent alterations in the stimulation parameters.

Patient N5 described an electrical sensation in his trunk and his head that occurred occasionally and depended on certain body movements. Examination, including neuroimaging, did not reveal evidence of device malfunction (e.g., damaged electrodes or wire connections to the internal pulse generator). Changing of the stimulation from unipolar to bipolar mode was followed by a resolution of the symptom.

After trial end, after 11 months of stimulation in total, patient N6 developed behavioural changes compatible with hypomania. Immediately prior to this she had taken a unilateral decision to stop taking antipsychotic medication. Stimulation parameters were initially lowered with a certain amount of improvement. However, six weeks later she was admitted in a mixed affective state, which responded to treatment with antipsychotics. Since then the patient's clinical state has been characterized by mood instability with fluctuations on a daily basis, impulsive behaviour and at times suicidal ideation. These symptoms initially proved difficult to control with mood stabilizers and changes to her DBS parameters, although her mood fluctuations improved after re-instatement of antipsychotic medication (aripiprazole). Currently she is free of prolonged periods of mood disturbance, although she continues to experience spells of depression lasting hours or days. Her psychotic symptoms (referential delusions accompanied by auditory hallucinations) have remained in remission most of the time, though they are prone to re-appear for periods of 12–36 h, often when she is under stress.

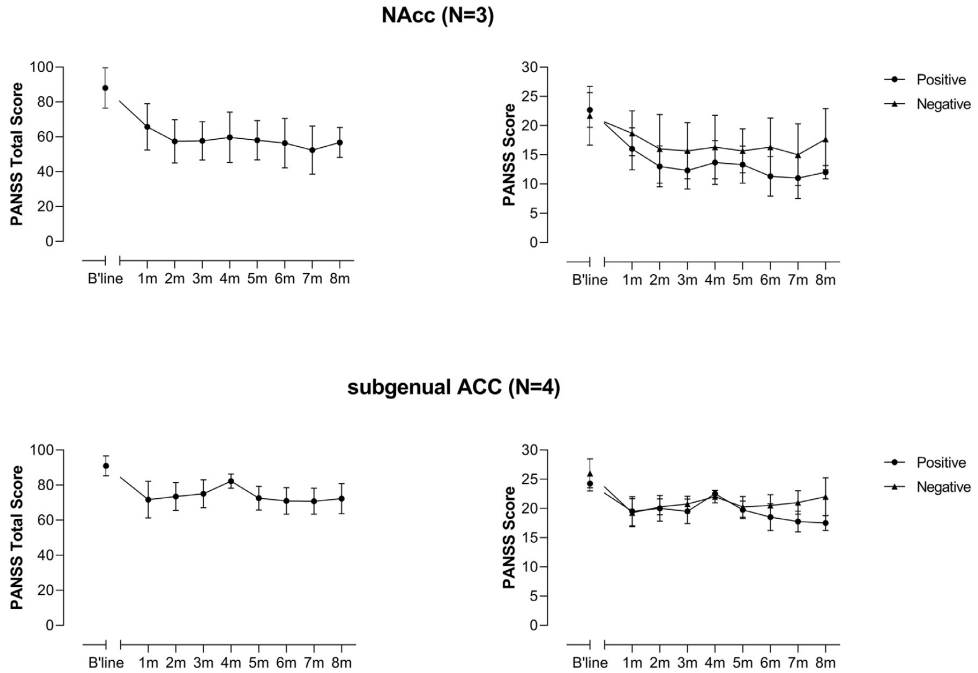


**Fig 2.** Symptomatic changes in the 7 DBS treated patients over the first 8 months of the stabilization phase.

*3.6. Post-operative course in the patient who did not receive DBS*

After suffering a right-sided peri-operative haemorrhage, patient N3 initially showed confusion which lasted four days. After this settled he was noted to show improvement in his previously severe active psychotic symptoms. This improvement remained evident for over seven months, but hallucinations and referential delusions ultimately re-appeared, although less severely than before the operation.

Six months after being withdrawn from the trial, the patient showed no neurological signs, though he had experienced seizures which were controlled with anticonvulsant medication. He shows a lesion in the anterior right internal capsule.

## 4. Discussion

To our knowledge, this is the first study reporting the effectiveness and safety of DBS in patients with treatment resistant schizophrenia, all but one of whom were also resistant to clozapine. Although the sample size was small and the variability in treatment response makes it difficult to generalize, there were indications of improvement, with the NAcc appearing to be the more promising of the two placements employed. Caution is necessary before accepting improvement observed under open conditions at face value. However, three of the four patients who showed significant improvement worsened when the current was switched off under double-blind conditions; the fourth patient also worsened abruptly when the device was accidentally switched off without her or her clinicians' knowledge.

Two out of the three patients with NAcc targeted DBS met the symptomatic improvement criterion. In these patients the improvement in their main symptoms, delusions and hallucinations, was marked, taking the form of a near complete disappearance (patient N1) and complete absence of these symptoms most of the time (patient N6). As noted in the Introduction, the NAcc and the ventral striatum of which it forms part is a plausible target for the local functional inhibitory effects of DBS, as it is strongly suspected of being a site of functional overactivity in schizophrenia, specifically increased dopaminergic activity. Nevertheless, it should be noted that functional imaging studies in schizophrenia have uniformly found that ventral striatal activation in response to reward predictive stimuli is reduced rather than increased as the salience theory predicts [32]. On this basis it is unclear why a functional inhibition produced by DBS would have an ameliorative effect on positive symptoms. Possible explanations for this inconsistency might be in terms of the local or more distant excitatory effects of DBS [7], or possibly in terms of modulatory effects on the mesolimbic and mesocortical components of the mesotelencephalic dopamine projection [11].

In the patients with electrode placements in the subgenual ACC, improvement appeared less marked and, in the two who went on to meet improvement criteria, was more gradual (see individual graphs in Supplementary Fig. S2). Why this should be so is unclear. However, as noted by Veerakumar and Berton [8], while the motor effects of DBS in neurological disorders are immediate, the response in psychiatric disorders such as major depression is typically of the order of weeks to months, suggesting that longer-term effects on brain networks of which the implantation site forms part may be relevant.

As noted in the Introduction, our choice of sites for electrode placements was guided by a combination of evidence from its use in other psychiatric disorders and pathophysiological findings from patients with the disorder itself. Relevant findings from animal studies have also recently become available and may potentially provide further insights into the mechanism of DBS in schizophrenia. Thus, Bikovsky et al. [33] examined the effects of DBS in an animal model of schizophrenia in which pregnant females were administered a viral mimic (polyinosinic-polycytidilic acid, poly I:C). The progeny of mothers administered these or other similar agents have been found to show a variety of behavioural and neuropathological changes

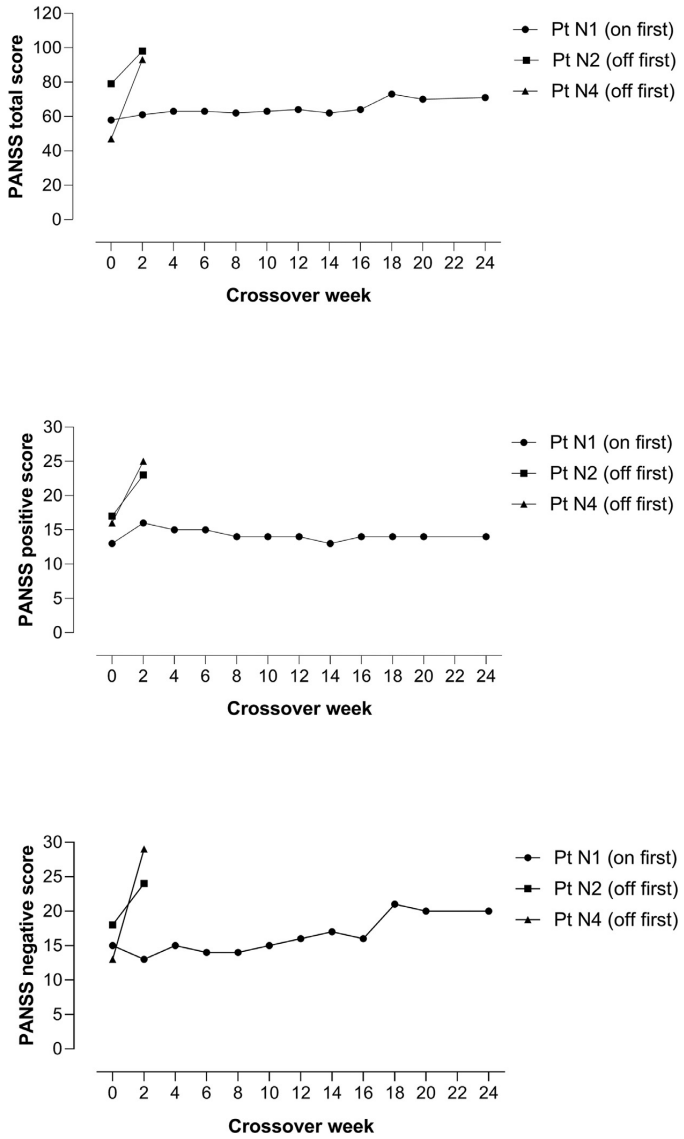


**Fig 3.** Changes in PANSS total, positive and negative scores in the three patients who entered the crossover phase.

reminiscent of schizophrenia, which only emerge in late adolescence or early adulthood; they also show decreased prepulse inhibition and disrupted latent inhibition. DBS administered in both the NAcc and the medial prefrontal cortex to such rats in adulthood was found to reduce abnormalities in both prepulse inhibition and latent inhibition.

DBS was physically well-tolerated in the seven patients who proceeded to electrode activation. The only major physical adverse event was akathisia in one patient with a NAcc placement which appeared after stimulation was changed from unilateral to bilateral; this improved when the stimulation was changed back to unilateral [31]. On the other hand, lasting psychiatric adverse effects were prominent in the two patients with NAcc placements whose positive symptoms improved. One (N1) developed an amotivational state during the crossover phase that has since proved resistant to all interventions. The features of this state are consistent with negative schizophrenic symptoms, but apathy is also a recognized side-effect of DBS in Parkinson's disease [34]. The other patient (N6) developed mood instability that has so far lasted over a year, though with a gradually improving course. Depression and mood elevation, which can sometimes be prolonged, are also recognized complications of DBS for Parkinson's disease with a variety of different electrode placements [34]. It may also be relevant that while this patient was given a diagnosis of schizophrenia before trial entry, lifetime structured psychiatric interview at that time revealed a previous one-month episode when, after her antipsychotic medication was changed, she developed erotomanic ideation and showed flight of ideas; psychotic symptoms remained present during this period. It

**Table 2**
Changes in other scales from baseline to randomization or termination.

| | Mean score at baseline (±SD) | Mean score at randomization/ termination (±SD) |
|---|---|---|
| PSYRATS (sum of delusion and hallucination subscales | 44.71±12.65 | 32.57±21.79 |
| SANS (total score) | 55.57±12.97 | 46.29±23.43 |
| CDSS | 7.29±6.21 | 3.71±4.79 |
| GAF | 31.14±4.49 | 47.14±17.07 |
| CGI | 6 ± 0.0 | 4.14±1.68 |
| Personal and Social Performance Scale* | 30.83±8.49 | 42.67±25.91 |

* Based on 6 patients, data missing at randomization/termination for 1 patient.
For scores on the Social Functioning Scale see Supplementary Table S3.
PSYRATS – Psychotic Symptom Rating Scales; SANS – Scale for the Assessment of Negative Symptoms; CDSS – Calgary Depression Scale for Schizophrenia; GAF – Global Assessment of Functioning scale; CGI – Clinical Global Impression of Severity.

seems possible, therefore that her diagnosis may actually be schizoaffective disorder.

In conclusion, this small initial trial of DBS in schizophrenia provides grounds for considering that it may be useful in some treatment resistant and ultra-treatment resistant patients. There were suggestions that the NAcc placement had greater beneficial effects than that in the subgenual ACC, though this finding could easily be overturned in a larger trial. NAcc-targeted DBS also seemed to be particularly effective in patients with a clinical picture characterized mainly by delusions and hallucinations. One of the eight patients implanted suffered a serious complication (internal capsule haemorrhage), though fortunately this was without serious long-term sequelae. This frequency has to be contrasted with experience from DBS in neurological disorders, where the risk of neurosurgical complications, including infection and haemorrhage, have been estimated to be 1–3% [35]. Additionally, in the two patients in whom marked improvement was seen, this came at a cost of significant psychiatric complications. The main limitation of this trial is its small sample size. Additionally, the 24 week duration of the crossover phase may have been insufficient to fully dissipate carryover effects. The fact that, out of the three patients who entered the double-blind crossover phase, the two randomized to 'off first' both received subgenual ACC DBS could cast doubt on the findings in this part of the study.

## 5. Disclosures

Dr. Corripio has received research grants and served as consultant, advisor or speaker for the companies Otsuka and Ferrer. Dr. Pérez has been a consultant to or has received honoraria or grants from AB·Biotics, AstraZeneca, Bristol-Myers-Squibb, CIBERSAM, ISCIII, Janssen Cilag, Lundbeck, Otsuka, Servier and Pfizer. Dr. Álvarez has received consulting and educational honoraria from Eli Lilly, Lundbeck, Pfizer, Sanofi-Aventis and Otsuka; has participated as principal local investigator in clinical trials sponsored by Eli Lilly, Bristol-Myrers Squibb, Sanofi-Aventis and AB·Biotics; and has served as national coordinator of clinical trials sponsored by Servier and Lundbeck. All these collaborations are not related to DBS project. All the other authors declare no competing interests.


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## Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.ebiom.2019.11.029.

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# 4.2. ESTUDIO 2

## Brain Metabolic Changes in Patients With Treatment Resistant Schizophrenia Treated With Deep Brain Stimulation: A Series of Cases

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A B S T R A C T

Deep brain stimulation (DBS) has been found to be effective in treatment resistant neurological and psychiatric disorders. So far there has been only one completed trial in schizophrenia, in which seven treatment resistant patients received DBS in the subgenual anterior cingulate cortex (sgACC, N = 4) or the nucleus accumbens (NAc, N = 3); four met symptomatic response criteria over the trial period. Six patients underwent 18 F-FDG PET at baseline and after at least 6 months of stimulation. Individual patient analysis indicated that DBS to both the sgACC and NAc was associated with local and distant changes in glucose metabolism. Increments and decrements of brain activity were observed in regions that included the medial prefrontal cortex, the dorsolateral prefrontal cortex, the anterior cingulate cortex, the caudate nucleus, the NAc, the hippocampus and the thalamus. Increased activity appeared to be associated with clinical improvement. These preliminary findings suggest that DBS acts by modulating cerebral activity in the cortico-basal-thalamic-cortical circuit in patients with schizophrenia who show improvement in psychotic symptoms.

### 1. Introduction

Schizophrenia is a highly incapacitating complex disorder, which affects about 1% of general population and commonly starts in late adolescence or early adulthood (Kahn et al., 2015). Although antipsychotic treatment is effective in controlling key symptoms, such as delusions and hallucinations, between 20 and 30% of patients do not respond or show only a minimal response (Siskind et al., 2017). For this reason, alternative therapies for such patients, which include deep brain stimulation (DBS), are under active consideration (Corripio et al., 2016).

DBS is a well-established treatment for Parkinson's disease and other movement disorders, whose use has been extended in recent years to treatment resistant psychiatric disorders, especially major depression and obsessive-compulsive disorder (Krack et al., 2010). The technique involves high frequency stimulation of deep brain areas through electrodes implanted under stereotactic surgery. On the basis that schizophrenia has been considered to reflect dysfunction in areas related to the cortico-striatal-thalamic-cortical circuit, DBS has been proposed as an intervention to modulate this circuitry (Gault et al., 2018; Mikell et al., 2016). Although the technique has shown evidence of potential effectiveness in animal models of schizophrenia (Bikovsky et al., 2016; Hadar et al., 2017; Klein et al., 2013; Ma and Leung, 2014), trial evidence in patients with schizophrenia is currently scarce. To date, three

trial protocols have been registered, one of which was abandoned (NCT01725334), one of which is underway (NCT02361554) and the third of which, carried out by our group, is now completed and published (NCT0237505). Corripio et al. (2020) treated 7 patients under open conditions for 6+ months, of whom 4 (2/3 with NAcc and 2/4 with SgACC electrode placements) met symptomatic improvement criteria and entered a double-blind cross-over phase lasting 24 weeks.

The effects of DBS on brain functioning are not completely understood, although the dominant theoretical model is that it exerts local inhibitory and distant activatory or more complex modulatory effects (Deniau et al., 2010; Veerakumar and Berton, 2015). The aim of this study was to describe changes in regional cerebral glucose metabolism in patients who received NAc and sgACC-DBS in the only completed trial, that of Corripio et al. (2020). We hypothesized that metabolism would be modified within the cortico-striatal-thalamic-cortical circuit, in parallel with changes in psychotic symptoms.

## 2. Material and methods

This study was carried out as part of a clinical trial designed to test the efficacy and safety of DBS for treatment resistant schizophrenia (TRS) (Corripio et al., 2020) (ClinicalTrials.gov Identifier: NCT02377505). In this, 8 patients with TRS who were also resistant to or intolerant of clozapine were randomly assigned to one of two electrode placements: the NAc or the sgACC. Four-pole electrodes were implanted bilaterally under stereotactic frame guidance. One patient did not proceed to stimulation due to complications from the implantation procedure (haemorrhage followed by infection), which eventually led to the electrodes being removed. In the remaining 7 patients stimulation was started unilaterally 48–72 h after implantation, and was later shifted to bilateral.

### 2.1. Subjects

From the entire sample of eight patients, six were included in the present study. One was withdrawn from the trial because of surgical complications as described above, and another was excluded due to technical issues with PET acquisition. Detailed inclusion and exclusion criteria are reported elsewhere (Corripio et al., 2020). All patients gave written informed consent. The study was designed following the latest version of the Declaration of Helsinky, was approved by the hospital ethical committee and the Spanish regulatory drug agency (Agencia Española de Medicamentos y Productos Sanitarios).

The patients were clinically assessed at baseline and regularly throughout the trial period using the Positive and Negative Symptom Scale (PANSS) (Kay et al., 1987). Symptomatic response to DBS was defined as having a sustained improvement ≥25% on PANSS total score (calculated using the formula: PANSS baseline score – PANSS endpoint score) x 100/(PANSS baseline score-30) (Leucht et al., 2009). Symptomatic changes were recorded during a 'stabilization' phase, which lasted minimum six months following surgery. Stimulation parameters were modified individually for each patient during the stabilization phase; pharmacological treatment, however, was not modified. Patients who achieved sustained symptomatic response at the end of the stabilization phase entered a 24-week cross-over trial phase, during which they received 12 weeks of stimulation followed by 12 weeks of no stimulation or vice versa under double-blind conditions.

### 2.2. PET scanning

PET scanning was carried out at baseline, ie before surgery, and at the end of the stabilization phase. Analyses of the images were performed at the end of the cross-over clinical trial phase. Clinical raters were blind to the DBS target and stimulation parameter changes.

Baseline (prior to surgery) and follow-up (end of stabilization phase) 18 F-FDG PET/CT scans were acquired on a Philips Gemini TF PET/CT following the EANM guidelines for PET brain imaging. Images were obtained 60 min after the intravenous injection of 277 MBq 18 F-FDG, during a 10-min acquisition time. The reconstruction method was iterative (LOR RAMLA, three iterations and 33 subsets) with a 128 × 128 matrix size included in a field of view (FOV) of 256 mm, resulting in 2 mm pixel size and 2 mm pixel slice thickness.

Baseline T1-weighted MRI scans were also acquired for each patient in a 3-T Philips Achieva using the following parameters: TR/TE 8.1/3.7 ms, flip angle = 8°, FOV 23 cm, with in-plane resolution of 256 × 256 and 1 mm slice thickness.

Native-space single-subject analysis was performed. The SPM12 software package [https://www.fil.ion.ucl.ac.uk/spm/] was used to examine changes in brain metabolism associated with DBS in each patient individually. First, baseline and follow-up PET scans were intensity-scaled with respect to the mean pons uptake to obtain SUVr images. Second, both PET scans were aligned and subsequently co-registered to the associated baseline T1-MRI scan. Next, a Gaussian smoothing of 8 mm FWHM was applied to the PET images in order to improve the signal-to-noise ratio. Finally, post-pre SUVr difference images were computed and overlaid on each patient's T1-MRI scan, in order to determine the precise anatomical location of changes. Only voxelwise SUVr changes > 5% were considered relevant for each patient.

## 3. Results

The six patient's baseline characteristics are shown in Table 1. All patients were receiving treatment with clozapine augmented with different antipsychotics, which was unchanged throughout the study. Three patients received DBS in the NAc (subjects 1, 2 and 3) and three in the sgACC (subjects 4, 5, 6). Stimulation parameters were modified according to the patients' clinical response within the following ranges: amplitude [2.5–7.5 V], pulse-width [60–210 μs] and frequency [120–210 Hz]. Five out of the six patients achieved symptomatic response with DBS treatment at the time of scanning: patient 3 achieved remission (85% of improvement on PANSS total score and 100% on positive symptom score); patient 2 showed clinical worsening soon after PET acquisition (non-sustained response) and subject 6 showed no change in clinical status. See Table 1 for detailed information on clinical changes.

Fig. 1 shows the set of brain scans displaying the most relevant regions for metabolic changes in each patient. Pre- and post-stimulation metabolic differences did not follow a specific pattern, although those individuals stimulated in the NAc seemed to show some commonalities in the pattern of cortical and subcortical increases.

Considering the findings individually, patients 1 and 2, both with NAc placements, showed areas of increased metabolic activity in the NAc, the hippocampus, the thalamus, and the medial and dorsolateral prefrontal cortex. In patient 3, who also had an NAc placement and achieved symptom remission after DBS, clinical improvement was associated with a widespread increase in cerebral metabolic activity.

Among the three patients with sgACC placements, one, patient 4, showed a decrease in metabolic activity was observed in the same areas that were increased in patients that received NAc-DBS: the NAc, the thalamus, the posterior cingulate cortex and the medial frontal cortex. By contrast, patient 5 showed increased cerebral activity in these regions. Psychotic symptoms improved in both subjects, but this was most marked in negative and general symptoms in patient 5. Patient 6 did not show any clinical improvement and post-stimulation metabolic changes were minor (see Table 2 for a detailed summary of the individual brain regions showing increases or decreases in brain glucose metabolism).

## 4. Discussion

This study found that high frequency DBS delivered to the sgACC

**Table 1**
Demographic and clinical data. Pre: PANSS scores before DBS intervention; Post: PANSS scores at time of the second scan; %: Percentage of improvement, calculated using the formula: PANSS baseline score – PANSS endpoint score) x 100/(PANSS baseline score - number of items of the scale or subscale).

| Patient ID | Gender | Age | Illness duration (years) | Antipsychotic treatment | mg/day | Time-lapse (months) | PANSS | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Total | | | Positive | | | Negative | | | General | | |
| | | | | | | | Pre | Post | % | Pre | Post | % | Pre | Post | % | Pre | Post | % |
| **1** | F | 46 | 24 | Clozapine<br>Risperidone | 350<br>6 | 8 | 97 | 50 | 70.1 | 27 | 9 | 90 | 24 | 18 | 35.3 | 46 | 23 | 76.7 |
| **2** | M | 43 | 11 | Clozapine<br>Ziprasidone | 400<br>160 | 9 | 102 | 71 | 43.0 | 24 | 14 | 58.8 | 29 | 26 | 13.6 | 49 | 31 | 54.5 |
| **3** | F | 35 | 10 | Clozapine<br>Paliperidone | 100<br>3 | 15 | 65 | 35 | 85.7 | 17 | 7 | 100 | 12 | 8 | 80.0 | 36 | 20 | 80.0 |
| **4** | M | 34 | 9 | Clozapine<br>Haloperidol | 500<br>5 | 12 | 108 | 79 | 37.2 | 26 | 17 | 47.4 | 28 | 18 | 47.6 | 54 | 44 | 26.3 |
| **5** | F | 53 | 23 | Clozapine<br>Olanzapine<br>Pimozide | 800<br>10<br>10 | 10 | 84 | 47 | 68.5 | 22 | 16 | 40.0 | 23 | 13 | 62.5 | 39 | 18 | 91.3 |
| **6** | F | 38 | 21 | Clozapine<br>Paliperidone | 450<br>100 mg/ month | 13 | 85 | 86 | 0.0 | 27 | 21 | 30.0 | 21 | 30 | 0.0 | 37 | 35 | 9.5 |

and NAc was associated with local and distant changes in glucose metabolism. In the six patients examined, these changes tended to be seen in areas related to the cortico-striatal-thalamic-cortical circuit (Haber, 2016), such as the medial frontal cortex, the orbitofrontal cortex (OFC), the dorsolateral prefrontal cortex, the ACC, the caudate, the NAc, the hippocampus and the thalamus, although with considerable individual variation. Broadly, there were suggestions that stimulation of the NAc led to increased metabolism within the key structures of the circuit, whereas stimulation of the sgACC was associated with decreases in metabolism in some of these areas.

Addtionally, there were suggestions of a relationship between clinical response and the changes exerted on brain functioning. Thus, patient 6 with a NAc placement achieved positive symptom remission with DBS, and this was associated with a widespread increase in cerebral metabolic activity. Conversely, another patient with an sgACC placement did not show any clinical improvement and metabolic changes were minimal. This finding may suggest that greater clinical improvement is associated with a general increment of metabolic activity across the brain, beyond the cortico-striatal-thalamic-cortical circuit.

As far as we know, there is no other evidence bearing on the brain functional effects of DBS in patients with schizophrenia. However, one study employing an animal model of schizophrenia could be considered to be in line with our findings. Thus, Bikovsky et al. (2016) examined the effects of DBS in an animal model of schizophrenia in which pregnant females were administered a viral mimic (polyinosinic-polycytidilic acid, poly I:C). The progeny of mothers administered these or other similar agents have been found to show a variety of behavioural and neuropathological changes reminiscent of schizophrenia, which only emerge in late adolescence or early adulthood; they also show

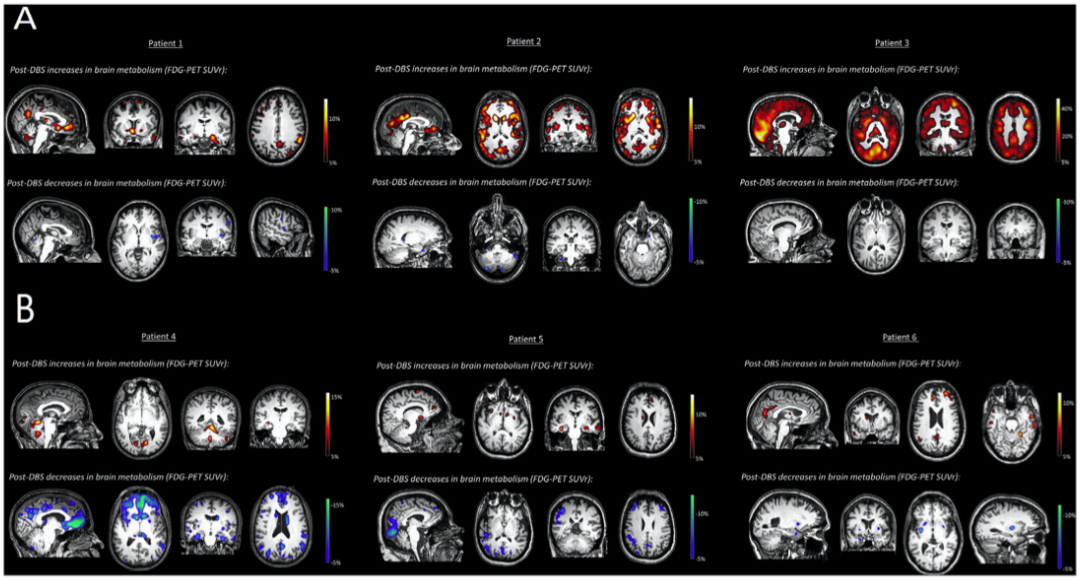


**Fig. 1.** A. Areas of increased (red-orange) and decreased (blue) metabolic activity in patients stimulated in NAc; B. Areas of increased (red-orange) and decreased (blue) metabolic activity in patients stimulated in SgACC. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

**Table 2**
Summary of brain areas showing increases and decreases in metabolic activity after DBS treatment.

| Patient ID | Electrode placement | Areas of post-DBS metabolic increase | Areas of post-DBS metabolic decrease |
|---|---|---|---|
| 1 | *NAc* | NAc (bilat), hippocampus (R), thalamus (bilat), Caudate (R), PCC (bilat), mPFC (bilat), DLPFC (L), anterior cingulate cortex (bilat). | Insula (R) |
| 2 | *NAc* | NAc (bilat), hippocampus (L), thalamus (R), Caudate (bilat), PCC (bilat), mPFC (bilat), DLPFC (bilat), OFC (bilat), insula (bilat). | Temporal pole (R), Cerebellum (bilat). |
| 3 | *NAc* | Diffuse bilateral cortical and subcortical increase in brain metabolism | |
| 4 | *sgACC* | Cerebellum (bilat) and occipital cortex (bilat) | NAc (bilat), thalamus (bilat), PCC (bilat), mPFC (bilat), and middle temporal cortex (bilat) |
| 5 | *sgACC* | NAc (bilat), hippocampus (bilat), thalamus (L), caudate (L), mPFC (R), cerebellum (bilat). | Calcarine (bilat), occipital cortex (bilat), DLPFC (bilat), Parietal (L) |
| 6 | *sgACC* | Caudate (L), DLPFC (R), PCC (bilat), medial temporal cortex (bilat). | Putamen (bilat) |

decreased prepulse inhibition and disrupted latent inhibition. Bikovsky et al. (2016) found that DBS at two sites, the medial frontal cortex and the NAc, both improved prepulse inhibition and latent inhibition deficits in such animals. Brain activity as measured using FDG-PET also increased, but only in the rats who received DBS in the medial frontal cortex; the increases were seen in the parietal cortex, the ventral hippocampus, the striatum and the NAc.

There is also relevant evidence from patients who have received DBS for other psychiatric disorders. An fMRI study by Figee et al. (2013) found that DBS targeted to the NAc in patients with obsessive-compulsive disorder acted to normalize NAc activity and reduce fronto-striatal hyperconnectivity. The pattern in DBS-treated patients with major depression appears to be more complicated, however. Mayberg and co-workers (Lozano et al., 2008; Mayberg et al., 2005) found that sgACC-DBS reduced activity in the sgACC itself, the OFC, the medial frontal cortex and the hypothalamus, and increased activity in the dorsolateral prefrontal cortex, the dorsal ACC and the posterior cingulate cortex, as well as in premotor and parietal regions. Using an NAc placement, Bewernick et al. (2010) found that DBS decreased activity in the sgACC, with additional decreases in prefrontal regions and the OFC, as well as in the amygdala in those who responded to the treatment. There is also a study applying sgACC-DBS in 16 patients with anorexia nervosa (Lipsman et al., 2017): following 12 months of stimulation there was evidence of increased activity in parietal and temporal regions, as well as areas of decreased activity in the superior and middle frontal gyrus, subcallosal and cingulate gyrus, basal ganglia regions including the globus palliudus, caudate, putamen, and the thalamus and the cerebellum.

To conclude, in this first series of cases examining metabolic changes after DBS treatment in patients with TRS, we observed metabolic increases NAc stimulation but less clearly so with SgACC stimulation, and indications that greater clinical improvement was associated with changes (increases in activity) in areas of the cortico-striatal-thalamic-cortical circuit. Several limitations should be mentioned. First, in keeping with the pilot nature of the trial from which the findings are derived, the sample size was small. For this reason the PET imaging analysis was performed using a native-space, single-subject approach. Studies with a larger sample size will be needed to properly understand the nature DBS-associated changes in schizophrenia. Secondly, differences in doses of antipsychotic medication and stimulation parameters may also have influenced metabolic activity, adding further variability to the individual findings.

## Contributors

Author Alexandra Roldán and Anna Alonso-Solís managed the Investigation, Data curation and writing of the original draft. Author Maria Portella contributed to the Methodology and writing of the original draft. Frederic Sampedro contributed to the Formal analyses and writing of the original draft. Author Salvador Sarró was involved in Data curation. Peter Mckenna greately contributed in the writing of the review. Authors Eva Grasa and Mireia Rabella managed project administration and methodology. Authors Enric Alvarez, Josefina Pérez and Víctor Pérez were involved in the conceptualization of the study, providing their expertise in schizophrenia and deep brain stimulation studies. Author Rodrigo Rodriguez contributed to the Methodology. Authors Valle Camacho, Alejandro Fernandez and Francisco Fuentes contributed to Data Curation, Software and provided their expertise in PET studies. Author Iluminada Corripio and Edith Pomarol-Clotet were involved in the conceptualization, Investigation and supervision. All authors contributed to the writing and validation of the final version of the manuscript and gave their approval to it.

## Declaration of competing interest

All authors report no biomedical financial interest or potential conflict of interest.

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# 5. DISCUSIÓN

En esta tesis se ha presentado el primer estudio de estimulación cerebral profunda en ocho pacientes diagnosticados de esquizofrenia resistente al tratamiento aplicada en dos regiones cerebrales diferentes, el NAc y el sgAcc, como dianas terapéuticas de la estimulación. Los resultados demuestran que el 50% de los pacientes intervenidos presentan una mejoría de la clínica psicótica tanto positiva, negativa como general, medida con la variable principal de eficacia PANSS. Cabe destacar que los porcentajes de mejoría obtenidos y medidos con dicha escala sobrepasan el 25%, cifra propuesta como mejoría suficiente para esta población de pacientes extremadamente graves (Leucht, Davis, Engel, Kissling & Kane, 2009); y que incluso dos pacientes intervenidas en el NAc presentaron una práctica remisión tanto de los síntomas positivos como negativos, hecho también relevante al considerar que no existen actualmente tratamientos eficaces para la mejoría de la sintomatología negativa.

Además, si valoramos únicamente los pacientes que pudieron ser evaluados de forma mantenida (un paciente tuvo que ser excluido poco después de la intervención por efectos secundarios de la cirugía), hallaríamos que cuatro de los siete pacientes alcanzaron esa mejoría, ascendiendo por tanto el porcentaje de respuesta al 57%, cifra significativa y en línea con las obtenidas en otros trastornos neuropsiquiátricos, como el TOC o el TDR (Alonso et al., 2015; Graat, Figee, & Denys, 2017).

En cuanto a la eficacia comparando ambos 'targets' ensayados, encontramos que 2/3 de los pacientes intervenidos en NAc y 2/4 de los pacientes estimulados en sgACC alcanzaron la respuesta al tratamiento, siendo la eficacia mayor para el NAc que para el sgACC. Estos resultados corresponderían a los obtenidos tras la exclusión del paciente intervenido en NAc que no pudo ser evaluado por lo comentado anteriormente. Cabe destacar, además, que este paciente excluido presentó una disminución importante de la clínica psicótica tras la intervención (justificable por el proceso inflamatorio y de gliosis reactiva post-quirúrgica), pero que se mantuvo a lo largo de la evolución y tras la recuperación del efecto secundario a la cirugía durante un año aproximadamente (datos no publicados). Además, el paciente estimulado en NAc no respondedor sí alcanzó la mejoría predeterminada (se puede observar en el estudio 2 la mejoría obtenida previo a la realización del PET), aunque de manera fluctuante y no mantenida. Poco después de la realización del PET, el paciente presentó un evento vital estresante (fallecimiento de un familiar cercano) que hizo que presentara un empeoramiento clínico importante, con sintomatología depresiva e ideación autolítica, que requirió ingreso hospitalario y, por tanto, la exclusión del estudio. Por todo ello, a pesar de que son datos no publicados, esto haría apuntar aún más hacia una eficacia superior del NAc frente al sgACC.

En cuanto a la mejoría sintomatológica, otro punto observado a destacar y que afianza los resultados obtenidos en este trabajo, sería que todos los pacientes respondedores han presentado empeoramientos francos de la sintomatología tras la desconexión del estimulador, ya sea en la inclusión del estudio cruzado (rama off), por desconexiones espontáneas o tras agotamiento de batería.

Sin embargo, recientemente se ha descrito también la aparición de sintomatología psicótica tras la implantación de NAc-ECP en un paciente de 31 años diagnosticado con un trastorno depresivo crónico (de 9 años de evolución), sin antecedentes de síntomas maníacos o psicóticos (Graat et al., 2019). La sintomatología delirante aparece al utilizar voltajes elevados (7.5V), desaparece inicialmente al disminuir la estimulación a 3.5V y reaparece por encima de 4.5V. Los autores también explican que, posteriormente, el paciente presentó sintomatología cognitiva y desorganización del pensamiento que se mantuvieron a pesar del tratamiento antipsicótico y la desconexión de la estimulación. Los autores justifican la aparición de esta sintomatología, además de por una predisposición del paciente, por la

posible liberación de DA inducida por la ECP en NAc, como fue descrito anteriormente por el mismo grupo de investigación (Figee et al., 2014). La descripción de este caso distaría de nuestros resultados, ya que la muestra de pacientes con esquizofrenia resistente ha requerido voltajes elevados (hasta 7V), presentando mejoría clínica y sin observarse empeoramiento de los síntomas psicóticos en ninguno de los sujetos. Además, ningún otro caso de TOC o TDR intervenido en NAc publicado hasta la fecha ha descrito la aparición de síntomas psicóticos con la estimulación. Cabría plantearse, por tanto, si la sintomatología depresiva crónica desde los 22 años y resistente a fármacos antidepresivos del paciente reportado, no pudiera estar enmarcada dentro de sintomatología negativa, y que la eclosión de síntomas positivos apareciera después, ya que no se ha descrito hasta el momento la aparición de síntomas de desorganización conceptual tras la implantación de ECP, como ocurre en este caso particular (Graat et al., 2019).

En cuanto a la mejoría obtenida en los pacientes estimulados en sgACC, sería importante destacar también que los síntomas observados que presentaron una mejor respuesta fueron las alucinaciones auditivas. Un paciente, por ejemplo, presentó una remisión de las mismas, aunque manteniéndose los fenómenos de difusión del pensamiento. Otra paciente mostró una disminución muy importante en cuanto a la intensidad, frecuencia e invasión de los fenómenos alucinatorios, permitiendo ser desinstitucionalizada tras varios meses de estimulación. Aun así, los otros dos pacientes no respondedores estimulados en esta misma localización, también presentaban alucinaciones, sin haber observado una clara mejoría. Desde nuestro punto de vista, no es posible explicar esta variabilidad interindividual, ya que otros factores como el tiempo de evolución de la enfermedad o el tratamiento antipsicótico recibido no parecerían justificar las diferencias. Un aspecto a considerar sería quizás las posibles mínimas variaciones en la localización de los electrodos entre un paciente y otro, que podrían traducirse en una variabilidad en cuanto a eficacia. Como demuestra el estudio piloto en el que participan 11 pacientes con TDR publicado por Riva-Posse & cols. (Riva-Posse et al., 2018; Riva-Posse et al., 2014), la tasa de respuesta puede aumentar considerablemente (hasta alcanzar el 81% en dicho estudio) si se utiliza la neuroimagen con tractografía probabilística individualizada para guiar la implantación de los electrodos y seleccionar los contactos de estimulación adecuados en función de la localización de los haces de sustancia blanca de interés.

Desde un punto de vista teórico, se podría esperar que la estimulación del sgACC mostrase una eficacia superior (o al menos similar) en pacientes con una esquizofrenia resistente, ya que las últimas publicaciones en pacientes con ERT han evidenciado un aumento de glutamato en esta área, en contra de un aumento de dopamina en el estriado (Demjaha et al., 2014, 2012; Mouchlianitis, Bloomfield, et al., 2016). Además, los estudios publicados en modelos animales de esquizofrenia también han demostrado mejoría de los síntomas esquizofrenia-like con la aplicación de la ECP tanto en NAc como en sgACC (Bikovsky et al., 2016; Klein et al., 2013; Ma & Leung, 2014)

Para afianzar estos hallazgos, realizamos un estudio en pacientes diagnosticados de esquizofrenia, resistentes al tratamiento y con alucinaciones auditivas persistentes (ver trabajo 6 en el anexo), en el que se estudian las diferencias en la estructura cerebral a dos niveles: los cambios macroestructurales en la sustancia gris cerebral mediante 'adelgazamiento cortical' y diferencias microestructurales utilizando la difusividad media sub- e intracortical (relacionándose el aumento de difusividad con procesos degenerativos de pérdida neuronal). Los resultados destacan que, al comparar pacientes con alucinaciones persistentes versus pacientes diagnosticados de esquizofrenia respondedores al tratamiento, se observan diferencias a nivel macrocortical en el giro temporal medio/fusiforme derecho (área cerebral que se ha relacionado con las alucinaciones auditivas) (Cui et al., 2018; Huang, Zhuo, Xu, & Lin, 2019) y a nivel microestructural en el ACC ventral/OFC, asociándose además esta última región con la edad y con el ítem 'interrupción de vida' en la escala PSYRATS (que evaluaría el grado de interferencia o invasión de las alucinaciones en la vida del paciente). A nivel subcortical, en los pacientes resistentes con alucinaciones persistentes se observa un aumento de volúmenes del caudado izquierdo y pálido, así como un aumento de la difusividad en el putamen, NAc e hipocampo. También se estudiaron los cambios longitudinales un año tras el basal, observándose un aumento del adelgazamiento cortical en regiones parahipocampales, así como un aumento de difusividad en el cingulado posterior/paracentral, en comparación con pacientes diagnosticados de esquizofrenia no alucinadores y controles sanos. Este último hallazgo podría hacer pensar en un proceso de pérdida neuronal temprana a nivel del cingulado en pacientes resistentes con alucinaciones persistentes que, junto a los hallazgos de un aumento de niveles de glutamato en esta misma región (Mouchlianitis, Bloomfield, et al., 2016), sugerirían una pérdida neuronal temprana debida a este posible efecto neurotóxico del exceso de glutamato en regiones corticales como el ACC. El hecho de que también se observen

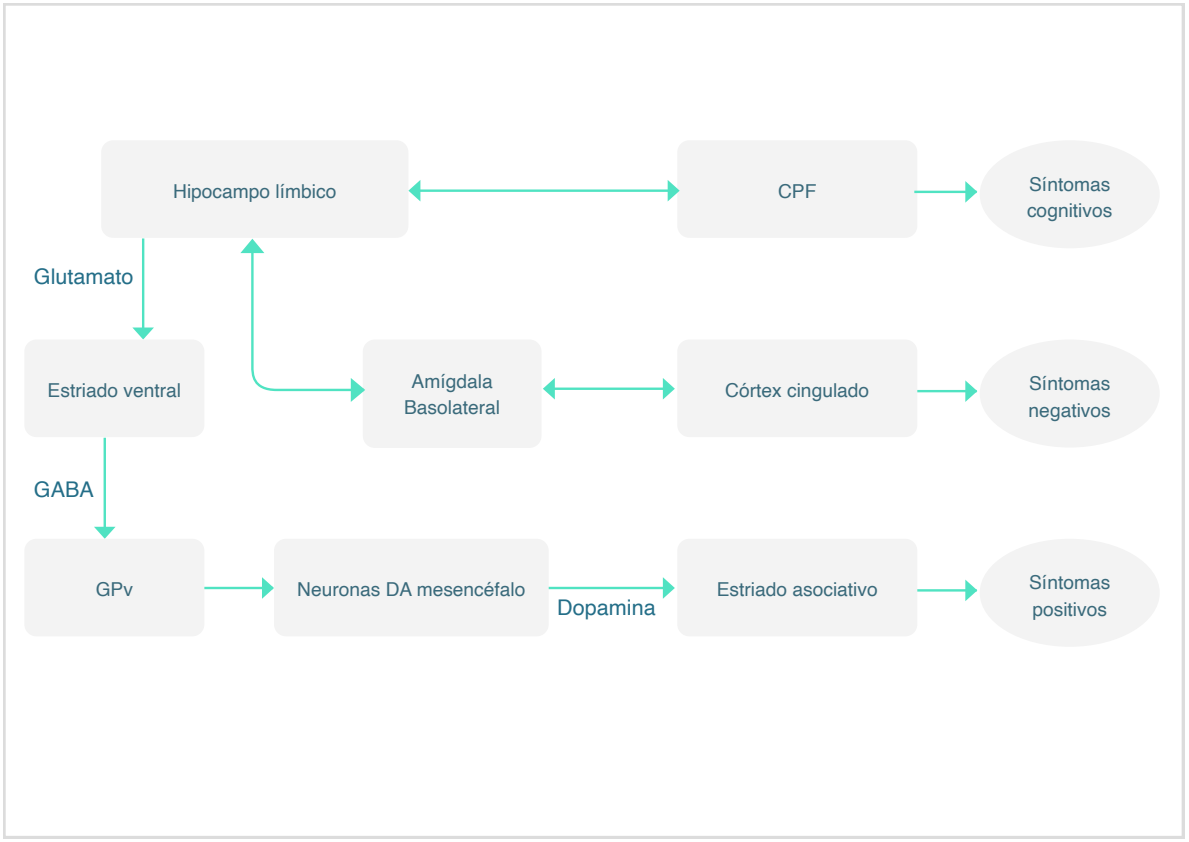


Figura 15. Alteraciones hipocampales podrían producir una disrupción de diversos circuitos y contribuirían a la generación de los síntomas positivos, negativos y cognitivos de la esquizofrenia (adaptada de Grace & Gomes, 2019).

diferencias microestructurales en el NAc e hipocampo de pacientes resistentes al comparar ambos grupos con diagnóstico de esquizofrenia, reforzaría la idea de que ambas estructuras, que forman parte del circuito cortico-estriatal (Haber, 2016), también estarían implicadas en la neurobiología de las alucinaciones persistentes (Grace & Gomes, 2019).

En este sentido, la hipótesis más reciente sobre la fisiopatología de la esquizofrenia apuntaría a que la disregulación dopaminérgica del trastorno podría ser secundaria a una disfunción glutamatérgica, y se ha sugerido que el CPF y el hipocampo estarían implicados en dicha disfunción, ya que ambos regulan las neuronas DA del mesencéfalo a través de proyecciones glutamatérgicas (Figura 15) (Grace & Gomes, 2019; Howes et al., 2015; Stone et al., 2010; Stone, Morrison, & Pilowsky, 2007).

En esta misma línea, los resultados obtenidos en el segundo trabajo presentado en esta tesis, donde se estudian los cambios de metabolismo cerebral observados con 18F-PET tras la estimulación, muestran, por un lado, que aquellos pacientes estimulados en NAc presentan un patrón de activación metabólica similar, implicando múltiples áreas del circuito cortico-estriatal-tálamo-cortical, y por otro lado, que los pacientes estimulados en el sgACC no presentarían este mismo patrón, a pesar de que en algunos pacientes se observa un decrecimiento de la actividad metabólica en estas mismas áreas.

Estos hallazgos confirmarían que la estimulación localizada de un núcleo o área cerebral determinada cerebral actuaría no sólo en el lugar de la estimulación, sino también en áreas más distales del mismo y, en el caso del NAc, probablemente en vías excitatorias del circuito con el que se halla relacionado. En pacientes con TOC estimulados en este mismo núcleo, se ha demostrado mediante fMR que la ECP podría normalizar la actividad del NAc y reducir la hiperconectividad fronto-estriatal (Figee et al., 2013). En particular, el hipocampo ventral y el NAc reciben inputs directos del CPFm (Haber, 2016) y se ha sugerido que el NAc juega un rol en la modulación del sistema dopaminérgico tras la activación hipocampal (Floresco, Todd, & Grace, 2001; Grace & Gomes, 2019; Mikell et al., 2009). La teoría más consistente que explicaría los mecanismos neurobiológicos de la esquizofrenia, como se comentó en la introducción, se basa princi-

palmente un estado dopaminérgico aberrante en la vía mesolímbica, con una señal dopaminérgica excesiva en el estriado. Esta hiperdopaminergia estriatal se ha asociado a síntomas positivos de la esquizofrenia a través de la misatribución de estímulos irrelevantes por la red de salience (Howes & Kapur, 2009; Kapur et al., 2005). Además, varios estudios de fMR en individuos con esquizofrenia han mostrado una hiperconectividad entre el córtex y el núcleo estriado, y estudios con DTI han hallado una conectividad anatómica disminuida entre el CPFDL y el estriado (para revisión ver McCutcheon et al., 2019). Por tanto, se podría hipotetizar que la mejoría de síntomas psicóticos observados con la ECP del NAc en pacientes diagnosticados de ERT podría justificarse por una estabilización del tono dopaminérgico en el NAc, hipocampo y áreas prefrontales.

Sin embargo, un estudio piloto publicado recientemente por un grupo de investigación de la universidad de Shangai (Wang et al., 2020) ha explorado también el tratamiento con ECP en dos pacientes con esquizofrenia, implantando los electrodos en la habénula. Los autores justifican de forma discreta que este núcleo estaría implicado en la regulación de la función dopaminérgica del mesencéfalo y de la actividad serotoninérgica del núcleo del rafe, y que aportaría un papel importante en el control del sueño y los estímulos aversivos. Los autores concluyen que los resultados son mixtos, pues uno de los casos no presentó mejoría de la sintomatología y tuvo que ser retirado del estudio a los 10 meses de tratamiento por un empeoramiento franco de la clínica (empeoramiento del 69% de los síntomas positivos) que requirió ingreso hospitalario. El segundo caso descrito, sí presentó una mejoría de los síntomas (37% de mejoría en PANSS general a los 12 meses de seguimiento); sin embargo, cabe destacar que el paciente no parecía cumplir criterios de esquizofrenia resistente y, además, los autores informan de un aumento del tratamiento antipsicótico a los cuatro meses de seguimiento por empeoramiento de la psicopatología general, lo que podría conllevar un sesgo en los resultados.

En cuanto a los efectos secundarios presentados, se debería tener muy presente los efectos secundarios derivados de la cirugía, como ocurrió en uno de los pacientes incluidos en el estudio. En este caso, hematomas intraparenquimatosos a nivel cortico-subcortical frontales bilaterales y del caudado derecho, y una posterior infección por una Pseudomona aeruginosa resistente implicó que fuera necesario retirar el dispositivo de ECP. El paciente presentó clínica confusional durante varias semanas, apareciendo finalmente como secuela lesiones necróticas en el parénquima superficial y profundo frontal bilateral, así como una lesión en la cabeza del caudado derecho y una epilepsia consecuente a las lesiones. Este tipo de complicaciones graves están descritas en la literatura y, aunque en general son poco frecuentes [infección del dispositivo (1.7-6.1%) y hemorragia (0.78-1.1%)], su gravedad implica tenerlas muy en consideración a la hora de explicar los potenciales riesgos de la intervención en la inclusión de los pacientes.

Otro efecto secundario a destacar es el de una paciente intervenida en NAc que presentó alteraciones conductuales compatibles con síntomas hipomaníacos tras 11 meses de estimulación desde la intervención y después de haber decidido unilateralmente abandonar el tratamiento antipsicótico. Como se comenta en el artículo 1, la paciente requirió ingreso hospitalario y reiniciar el tratamiento antipsicótico, así como una disminución de los parámetros de estimulación. Sin embargo, los cambios comportamentales han persistido hasta la fecha, en forma de inestabilidad anímica, impulsividad, ideación autolítica fluctuante, comportamiento pueril y demandas de atención…, por lo que estas alteraciones serían compatibles en el momento actual con rasgos de personalidad disfuncionales. Estos rasgos parecían estar presentes previamente al debut de la esquizofrenia, aunque estaban atenuados en el momento de la inclusión en el estudio y no suponían una limitación mayor que el de la propia enfermedad psicótica. Sin embargo, todo parece indicar que se habrían agravado con la estimulación y a lo largo de la evolución sí ha supuesto tanto una alteración en la evolución clínica de la paciente (con múltiples ingresos en contexto de ideación autolítica), como en su calidad de vida. Estos cambios conductuales han sido descritos previamente en pacientes intervenidos de ECP (Pham et al., 2015) y se deberían tener en cuenta a la hora de decidir la inclusión en los estudios, ya que puede suponer un dilema ético el considerar cómo la inducción o empeoramiento de estos rasgos de personalidad disfuncionales pueden modificar la calidad de vida de los pacientes (Pugh, 2020).
El resto de efectos indeseados presentes en nuestros pacientes han sido leves y se resolvieron con ajustes en los parámetros de estimulación, por lo que podríamos considerar que la ECP es una técnica segura más allá de las complicaciones quirúrgicas.

Por todo lo expuesto anteriormente, consideramos que los objetivos planteados en la presente tesis doctoral se han podido responder en los estudios 1 y 2, con determinadas limitaciones que comentaremos en el siguiente apartado.

# 6. LIMITACIONES

Las limitaciones que implican unos estudios como los presentados en esta tesis doctoral son diversas. Se debe tener en cuenta que se trata de un proyecto piloto, no habiéndose realizado ningún otro estudio previo a nivel mundial de ECP en pacientes con esquizofrenia, con las precauciones que deben estimarse en cuanto a nivel de desconocimiento de resultados y de potenciales efectos secundarios. Por este motivo, la primera y principal limitación del estudio es el reducido tamaño muestral. Aun así, consideramos que haber reclutado un mayor número de pacientes, sin conocer los potenciales beneficios y/o riesgos, y tratándose de una técnica invasiva, habría supuesto un dilema ético importante.

Por otro lado, esta limitación aún se potencia más al haber elegido dos áreas cerebrales diferentes para la implantación de los electrodos, disminuyendo así aún más las posibles comparaciones a nivel de eficacia y seguridad entre individuos y entre los diferentes 'targets'. En este sentido, dado el gran debate que existe aún sobre la neurobiología que subyace a la esquizofrenia (y más aún a la ERT), consideramos que era necesario ensayar diferentes lugares de estimulación para tratar de aportar resultados en diferentes dianas terapéuticas relacionadas con el trastorno, y que posteriormente al inicio del diseño de nuestro estudio también se han mostrado eficaces en modelos animales.

Una tercera limitación vendría dada por el mismo diseño del ensayo clínico, no siendo posible realizar un análisis adecuado de las modificaciones en los parámetros de estimulación. Esto se debe a que las modificaciones se realizaban en función de los cambios clínicos durante la fase de estabilización abierta, en momentos diferentes y sin un protocolo estandarizado. Además, al requerirse voltajes de estimulación elevados para alcanzar la mejoría clínica, la duración de la batería del generador de impulsos fue excesivamente corta en comparación con los trastornos neurológicos, lo que conllevó que algunos pacientes presentaran un agotamiento de batería relativamente súbito. Esto provocó en todos los casos un empeoramiento clínico de los síntomas psicóticos y un malestar significativo para los pacientes, que aumentó al comprobar que, tras el recambio quirúrgico de la batería, algunos de ellos no alcanzaron la mejoría previa observada. Por ello, se podría considerar la implantación de generadores recargables desde el inicio del estudio; aunque, de nuevo, la eficiencia de este proceso en un estudio de investigación piloto probablemente no hubiese sido viable. Otro aspecto por el que no se consideró la utilización de este tipo de generadores desde el inicio de la intervención fue por las potenciales dificultades de manejo que pudieran presentar los pacientes diagnosticados de ERT con la recarga del estimulador. Éstos son pacientes graves, con síntomas persistentes y en muchos casos con sintomatología cognitiva, lo que conlleva elevadas dificultades a nivel ejecutivo, psicosocial y en las tareas del día a día. Sin embargo, en lo referente a la recarga del estimulador, la experiencia en este estudio nos ha hecho comprobar que no ha sido así, ya que a los pacientes respondedores a la ECP se les implantó dicho dispositivo, pudiendo realizar las recargas del estimulador de manera correcta tras una sesión explicativa. En cuanto a la viabilidad de análisis de los parámetros de estimulación, en próximos estudios convendría fijar un protocolo de modificación de estos parámetros, estableciendo los momentos determinados durante el seguimiento y en función de unos criterios clínicos predeterminados, con el objetivo de poder realizar comparaciones entre pacientes.

Otra de las limitaciones inherente en los estudios de neuroimagen vendría dada por la elevada duración de enfermedad en los pacientes y las elevadas dosis de tratamiento, al ser pacientes resistentes. Sin embargo, se trata de una limitación presente en todos los trabajos de neuroimagen que tratan poblaciones con diagnóstico de ERT como la presentada en esta tesis. Cabe destacar que en el estudio número 2 se subsana esta limitación realizando comparaciones intra-individuo.

Por último, otra de las limitaciones podría venir dada por la variabilidad individual en la localización de un mismo 'target', ya que se ha descrito en estudios de ECP en otras patologías psiquiátricas que mínimas desigualdades en la localización de implantación del electrodo pueden provocar diferencias sustanciales en cuanto a la respuesta al tratamiento, como ya comentamos anteriormente. La manera de subsanar esta limitación en estudios futuros, podría venir dada por la utilización individualizada de nuevas técnicas de tractografía para la implantación de los electrodos, con el objetivo de neuromodular aquellos haces de sustancia blanca que realmente interesan para el tratamiento de esta patología.

# 7. CONCLUSIONES

- La ECP es eficaz para el tratamiento de síntomas psicóticos positivos y negativos de la enfermedad en el 50% de los pacientes diagnosticados de esquizofrenia resistente al tratamiento incluidos en nuestro estudio. Las mejorías alcanzadas y medidas con la escala PANSS fueron generalmente superiores al 25%, que es el porcentaje establecido en la literatura como una mejoría suficiente para estos pacientes resistentes.

- Los resultados apuntarían a una mayor eficacia de aquellos pacientes estimulados en NAc que en sgACC.

- La ECP es una técnica globalmente segura para estos pacientes, a pesar de que se deben tener muy presentes las complicaciones quirúrgicas, que ya habían sido descritas previamente para otros trastornos neurológicos. Además, los posibles cambios comportamentales inducidos por la estimulación también podrían suponer un dilema ético a la hora de plantear este tratamiento. Se podría concluir que, al margen de estas complicaciones quirúrgicas, el resto de efectos secundarios se han podido subsanar con modificaciones de los parámetros de estimulación.

- La estimulación con ECP de pacientes con esquizofrenia resistente al tratamiento conlleva cambios en la actividad metabólica cerebral, tanto en el mismo lugar de estimulación como en lugares alejados de la inserción de los electrodos.

- Los cambios metabólicos observados tras la ECP no responden a un patrón homogéneo, ni siquiera en aquellos pacientes intervenidos en la misma diana de inserción del electrodo. Aun así, habría una tendencia en aquellos pacientes estimulados en NAc, que muestra un patrón de activación metabólica en zonas determinadas del circuito cortico-estriatal-tálamo-cortical. Esto confirmaría su implicación en la fisiopatología de la enfermedad y su potencial capacidad de neuromodulación con ECP.

# 8. IMPLICACIONES Y LÍNEAS FUTURAS

- Los resultados presentados en esta tesis doctoral abren un nuevo horizonte de tratamiento para algunos de aquellos pacientes diagnosticados de esquizofrenia que no han encontrado beneficio con los tratamientos disponibles actualmente. Sin embargo, todavía existen aspectos para avanzar en esta nueva línea de tratamiento. En el caso de nuestro estudio piloto, se deberían analizar otras variables que podrían aportar información adicional a la presentada en este trabajo, como los datos de electrofisiología o neuropsicología, con el objetivo, por ejemplo, de evaluar cambios o efectos secundarios a nivel cognitivo tras la estimulación. Por otro lado, sería de interés analizar los cambios de neuroimagen funcional, incluyendo la tractografía, para poder salvar limitaciones comentadas anteriormente y aumentar la tasa de respuesta con la ECP, así como para continuar avanzando en el conocimiento de la fisiopatología de la esquizofrenia, y más concretamente, de la ERT.

- Con la experiencia adquirida en los trabajos incluidos en esta tesis, se podría considerar en futuros estudios de ECP en esquizofrenia resistente el evaluar los cambios subjetivos tanto por parte del paciente como de sus familiares, en cuanto a mejoría clínica y de efectos secundarios sutiles. Estos cambios, a menudo, son difíciles de capturar en escalas de evaluación clínica, pero pueden apreciarse en una entrevista clínica o en la interacción diaria de los pacientes con sus familiares. Por otro lado, algo aprendido con los pacientes que sí han respondido al tratamiento con ECP es que se presenta una nueva realidad socio-funcional y familiar tras largos años de enfermedad incapacitante, y la adaptación a esta nueva situación de mejoría implica un proceso adaptativo y de reconstrucción de aspectos psicosociales, que pueden generar malestar si no se acompañan de un apoyo psicológico en el proceso de recuperación [entendido en el sentido amplio del término conocido como 'recovery' (Warner, 2009)], así como de aceptación y manejo del cambio de rol. Por tanto, para nuevos proyectos de ECP en esquizofrenia nos planteamos la necesidad de realizar intervenciones psicológicas familiares con el objetivo de trabajar la reinserción al ámbito familiar, así como de implementar un programa de atención integrada centrado en la recuperación funcional, que pensamos debería acompañar a un estudio de estas características. Asimismo, aquellos pacientes que no han respondido a la ECP o que han presentado una respuesta muy parcial, también plantean una dificultad añadida, ya que, como se comentó anteriormente, son pacientes graves, con sintomatología persistente y en la mayoría de los casos, de difícil manejo tanto en el seguimiento clínico como en el ámbito socio-funcional y familiar. La necesidad de incluir también a estos pacientes en programas de atención psicológica o recursos rehabilitadores tipo hospitales o centros de día, también debería contemplarse en próximos estudios. Además, todo ello hace pensar en la viabilidad de la intervención con ECP en pacientes con esquizofrenia. Si los resultados de próximos estudios van en la línea de nuestros resultados preliminares, debería plantearse si este tratamiento se podría considerar como un tratamiento de uso compasivo a nivel hospitalario para pacientes con ERT. Quizá se deberían establecer unos criterios de inclusión por parte de un grupo de expertos y se debería tener en cuenta también el coste-beneficio que supondría y si sería viable para los presupuestos de salud, así como si se podría disponer de recursos humanos para el seguimiento más estrecho que requieren este tipo de pacientes.

Por último, otros aspectos que, según se han planteado en la literatura, podrían tener un impacto en futuros estudios de ECP en esquizofrenia resistente consistirían en:

- El ensayo de diferentes dianas cerebrales implicadas en la fisiopatología de la esquizofrenia donde implantar los electrodos, como el hipocampo o el estriado asociativo.

- El uso de técnicas novedosas que se están empezando a implementar en modelos animales, como la optogenética (utilización de proteínas microbiales reguladoras de conductancia y sensibles a la luz, para modular la actividad neuronal a nivel molecular de conexiones específicas entre núcleos cerebrales, que permite a los investigadores limitar la estimulación a sub-redes cerebrales) y que se han propuesto como una posible intervención para la reorganización de la complejidad neural presente en la esquizofrenia (Peled, 2011).

- El uso de closed loop stimulation (Beuter, Lefaucheur, & Modolo, 2014), que se basaría en la utilización de biomarcadores neurales para guiar la estimulación como el registro de los local field potentials a través de los electrodos en el lugar de estimulación, con el objetivo de ajustar los parámetros de estimulación mediante algoritmos predictivos para alcanzar los cambios neurofisiológicos deseados (Bilge, Gosai, & Widge, 2018).

- El uso de nuevos modelos de dispositivos de ECP que permitan dirigir el lugar de estimulación mediante sus electrodos segmentados, multicontacto o direccionables, así como modelos gráficos 3D para la visualización del volumen de tejido específico activado en cada paciente (Kühn & Volkmann, 2017).

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# 10. ANEXO

# 10.1. ESTUDIO 3

## Response to antipsychotic drugs in treatment-resistant schizophrenia: Conclusions based on systematic review

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Schizophrenia affects 1% of general population and one of its features is the heterogeneity of response to treatment. 20–30% of individuals with schizophrenia have treatment-resistant schizophrenia (TRS) (Lieberman, 1999). Correctly identifying these patients could contribute to reduce burden in patients themselves, in society and in economy. In fact, TRS constitutes about 60–70% of schizophrenia's cost burden (Kennedy et al., 2014).

TRS definition was coined by Kane and colleagues in 1988 (Kane et al., 1988). In this groundbreaking trial, they demonstrated superiority in response rate of clozapine over chlorpromazine (30% vs 4%) in well-defined cohort of patients who did not respond to three well documented antipsychotic trials and one prospective trial with high doses of haloperidol. After that, TRS and treatment response concepts have experienced several variations, as analyzed in the review by Suzuki and colleagues (Suzuki et al., 2012), underlining heterogeneity of definitions and proposing consensus definition.

For these reasons, meta-analyses in this field (Samara et al., 2016; Chakos et al., 2001) could include heterogeneous samples, in part due to unclear or lax TRS definitions. Hence, they are less helpful when searching for evidence based treatment recommendations for TRS (Miyamoto et al., 2015). Another important factors that contribute to this heterogeneity among studies are: dosage differences, investigator bias combined with the difficulty of blinding clozapine treatment assignment, and the effect of prior antipsychotic treatment (Kane and Correll, 2016).

We performed a systematic and critical review of current literature about efficacy of drugs in well-defined TRS. We analyzed key aspects of methodology and quality, definitions of resistance and response, efficacy variables (response rate and mean improvement) and safety outcomes. Here, in this letter, our aim is to present our conclusions about the antipsychotics efficacy and the problems affecting the interpretation of studies on TRS.

Double-blinded randomized trials (DBRT) on TRS were searched by: 1. a systematic search in April 2015 by the following search strategy: schizophrenia[Title]) AND ("ultra-resistant"[Title] OR "treatment-refractory"[Title]) OR "treatment-resistant"[Title]) AND "English"[Language]) from Scopus, PubMed and CINAHL (EBSCO) databases, 2. manual search. We included only studies on treatment efficacy in a clear-defined TRS population according to criteria proposed by Suzuki et al. (2012):

1. History of treatment failure with two or more antipsychotics with different binding profile, clearly documented or prospective validation.
2. Requirement in dose and duration: each treatment with an antipsychotic has continued for six consecutive weeks at chlorpromazine-equivalent doses of ≥600 mg/day.
3. Requirement in rating scales: each treatment has resulted in a failure defined with both Clinical Global Impression (CGI) ≥4 and Functional Assessment for Comprehensive Treatment of Schizophrenia (FACT-Sz) ≤49 or Global Assessment of Functioning (GAF) ≤50 or Positive and Negative Syndrome Scale (PANSS) ≥75/Brief Psychiatric Rating Scale (BPRS) ≥45.

**Table 1**
Double blinded randomized trials about antipsychotic efficacy in treatment-resistant schizophrenia.

| Trial | Study description | Compared drugs (mg/d) | Response rate | Completion rate | Improvement of symptoms from baseline | Commentaries |
|---|---|---|---|---|---|---|
| **FGA vs FGA** | | | | | | |
| Lal et al., 2006 (1) | n = 31<br>15 weeks<br>ITT<br>Inpatients | Levomepromazine (810)/chlorpromazine (760) | 53%/42% | 90%/73% | −10/−7 | – No differences in efficacy.<br>– Industry sponsored. |
| **SGA vs FGA** | | | | | | |
| Kane et al., 2007 (2) | n = 300<br>6 weeks<br>PP | Aripiprazole (30)/perphenazine (40) | 27%/25% | 71%/79% | −10/−10 | – No differences in efficacy.<br>– Missing 116 patients between open-trial and BRDT.<br>– TRS definition was incomplete.<br>– Industry sponsored. |
| Kane et al., 2006 (3) | n = 306<br>12 weeks<br>ITT | Ziprasidone (155)/chlorpromazine (740) | 58%/55% | 90%/88% | NR | – No differences in efficacy.<br>– Unclear results, not reported baseline severity.<br>– Trial conducted in India.<br>– TRS definition was incomplete.<br>– Industry sponsored. |
| Wirshing et al., 1999 (4) | n = 67<br>8 weeks<br>PP | Risperidone (7,5)/haloperidol (19) | 32%/14% | 85%/87% | −10/−12 | – No differences in efficacy.<br>– Mix TRS and intolerant patients.<br>– Industry sponsored |
| Conley et al., 1998 (5) | n = 84<br>8 weeks<br>ITT and CA<br>Inpatients | Olanzapine (25)/chlorpromazine (1173) + BZT | 7%/0% | 71%/69% | −1/+2 | – No differences in efficacy.<br>– No industry sponsored. |
| **SGA vs SGA** | | | | | | |
| Meltzer et al., 2014 (6) | n = 160<br>24 weeks | RLAI 50/RLAI 100 (biweekly) | 45%/45% | 72%/70% | −18/−18 | – No significant differences in efficacy.<br>– Mix TRS patients and poor responders.<br>– Mix SAD and SCZ.<br>– Industry sponsored. |
| Kane et al., 2011 (7) | n = 321<br>12 weeks<br>ITT | Risperidone (9)/sertindole (18) | 58%/45% | 71%/68% | −21/−19 | – Risperidone had more responders.<br>– Modified version of PANSS.<br>– Lax TRS criteria, unclear selection of participants.<br>– Industry sponsored. |
| **Clozapine vs FGA** | | | | | | |
| Kane et al., 2001 (8) | n = 71<br>6 months<br>ITT<br>In- and outpatient | Clozapine (520)/haloperidol (19) + BZT | 57%/25% | 65%/33% | −10/−5 | – Clozapine had more efficacy.<br>– Favorable discontinuation rate in clozapine.<br>– Lax response definition.<br>– Industry sponsored. |
| Hong et al., 1997 (9) | n = 40<br>12 weeks<br>CA<br>Inpatients | Clozapine (543)/chlorpromazine (1163) | 29%/0% | 90%/89% | −8/−1 | – Clozapine had more efficacy.<br>– Conducted in China.<br>– No industry sponsored. |
| Rosenheck et al., 1997 (10) | n = 423<br>1 year<br>ITT<br>Inpatients | Clozapine (552)/haloperidol (28) + BZT | 37%/32% | 57%/28% | −12/−8 | – No differences in response rate, but favorable discontinuation rate and total improvement in clozapine.<br>– No industry sponsored. |
| Kane et al., 1988 (11) | n = 268<br>6 weeks<br>ITT<br>Inpatients | Clozapine (450)/chlorpromazine (900) + BZT | 30%/4% | 88%/87% | −16/−5 | – Clozapine had more efficacy.<br>– Industry sponsored. |
| **Clozapine vs SGA** | | | | | | |
| Sacchetti et al., 2010 (12) | n = 147<br>18 weeks<br>ITT | Clozapine (365)/ziprasidone (137) | 55%/68% | 62%/62% | −24.5/−25 | – Non-inferiority of ziprasidone.<br>– No differences in EPS.<br>– Mix TRS patients and intolerants.<br>– Non-inferiority trial.<br>– Industry sponsored. |
| Meltzer et al., 2008 (13) | n = 40<br>24 weeks<br>PP<br>Outpatients | Clozapine (564)/olanzapine (34) | 60%/50% | 48%/74% | −20/−21 | – No differences in efficacy.<br>– Mix SAD and SCZ.<br>– High-doses of olanzapine were used.<br>– Industry sponsored. |
| Tollefson et al., 2001 (14) | n = 180<br>18 weeks<br>PP<br>In- and outpatients | Clozapine (304)/olanzapine (20,5) | 34%/38% | 59%/60% | −14/−15 | – Non-inferiority of olanzapine.<br>– Non-inferiority trial.<br>– Industry sponsored. |
| Azorin et al., 2001 (15) | n = 273<br>12 weeks<br>PP<br>In- and outpatients | Clozapine (642)/risperidone (9) | 48%/43% | 72%/74% | −23/−18 | – No differences in response rate but clozapine improved more BPRS and CGI.<br>– Industry sponsored. |

*(continued on next page)*

**Table 1** (*continued*)

| Trial | Study description | Compared drugs (mg/d) | Response rate | Completion rate | Improvement of symptoms from baseline | Commentaries |
|---|---|---|---|---|---|---|
| Bondolfi et al., 1998 (16) | n = 86 8 weeks ITT Inpatients | Clozapine (300)/Risperidone (6) | 65%/67% | 79%/79% | −23/−27 | – No differences in efficacy.<br>– Mix TRS patients and intolerants.<br>– Industry sponsored. |

ITT intention to treat analysis, PP per-protocol analysis, CA completers analysis, BZT benzotropine, SAD schizoaffective disorder, SCZ schizophrenia patients, EPS extra-pyramidal symptoms, TRS treatment-resistant schizophrenia, FGA first-generation antipsychotics, SGA second-generation antipsychotics, RLAI risperidone long-acting injection, NR not reported.

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We found sixteen efficacy DBRT in TRS (Table 1), that is notably smaller number compared to the last meta-analysis (Samara et al., 2016). Nine compared clozapine versus non-clozapine antipsychotics and seven compared antipsychotics other than clozapine among themselves.

Among the seven non-clozapine trials, there were only two well-designed studies with applicable results:

- Conley et al. (1998): showing no advantage in efficacy of olanzapine over chlorpromazine at 8 weeks (7% and 0% respectively).
- Lal et al. (2006): showing how high-doses of FGAs produce more neurological adverse events and they can be difficult to distinguish from symptoms associated with psychosis. The improvement in participants' psychopathology could be, at least in part, secondary to dose reduction.

The other five trials had many flaws which may lead to erroneous conclusions (i.e. lax TRS criteria, inclusion of intolerants or schizoaffective patients, unclear results presentation).

Results showed clozapine superiority over first-generation antipsychotics (FGA) in three of four well-designed trials with clear TRS definitions. However, clozapine did not demonstrate superiority over second-generation antipsychotics (SGA): in our meta-analytic calculation there was no statistically significant advantage for clozapine in terms of response (OR 0.94 [95% CI: 0.69–1.27]. The analysis included five studies, including in total 339 clozapine and 347 SGA treated patients. There were no sign of heterogeneity ($chi^2 = 3.57$, $I2 = 0.0\%$, $p = 0.47$) and no indication of publication bias (Egger's test, $z = -0.24$, $p = 0.999$). Our results may be true finding, or be partly explained by 1) unclear eligibility criteria (i.e. mixing schizophrenia and schizoaffective patients), 2) unclear results presentation, 3) broad TRS definitions mixing intolerant patients. In fact, clozapine vs SGA trials achieved higher response rates compared to clozapine vs FGA trials (see Table 1). Another important issue was the lower clozapine doses in clozapine vs SGA trials. Regarding this, conclusions of meta-analysis by Samara and colleagues are very clear: "the underdosing in industry-funded trials could constitute a serious problem that could have affected the results". In addition, only few SGA have been compared with clozapine (i.e. ziprasidone, olanzapine, risperidone) and therefore, the efficacy in TRS-population of another SGAs remains unknown (e.g. amisulpride, aripiprazole, sertindole, quetiapine).

Non-clozapine polypharmacy and high-dose treatment in TRS are not supported by evidence. To our knowledge there are no studies in TRS population that compare clozapine monotherapy with non-clozapine polypharmacy, however there are two small open-trials (Kotler et al., 2004; Suzuki et al., 2008) offering discordant results.

Regarding high-dose treatment, there is only one DBRT (Meltzer et al., 2008) comparing high-dose of olanzapine (35 mg/d) versus clozapine (550 mg/d), showing similar response rates at 6 months (50% and 60% respectively). However, this industry supported study excluded patients who did not respond previously to olanzapine. This reveals another problem about inclusion of samples with different severity of treatment-resistance, since the TRS definition does not state exactly how effective antipsychotics should have been tried before clozapine. I.e. the samples with exclusion of patients who had failed trials of olanzapine may be considered less treatment-resistant than samples that have included non-responders to, for example, both olanzapine and risperidone. Underlining this issue, there is NIMH-sponsored study comparing high-dose of olanzapine (50 mg/d) versus clozapine (450 mg/d), that we did not include in the revision because it had a

cross-over design and originally was a safety trial, showing better tolerability and response rate in clozapine (0% vs 30%) (Conley et al., 2003).

In the review we did not include pragmatic studies because usually they applied a more liberal definition of treatment-resistance or they are not double-blinded (e.g. observational studies, population-based register studies, cost-effectiveness trials or open-label effectiveness trials). However, they may provide longitudinal results beyond acute response, they focus in other important outcomes (e.g. quality of life, social functions, discontinuation rate) and they also contribute to enhance our clinical practice. In fact, in many of these studies clozapine was superior to FGA and to SGA (McEvoy et al., 2006).

To summarize, we know surprisingly little about optimal antipsychotic treatment of TRS. However, clozapine remains as the first-line treatment after a failure of two antipsychotic trials according to treatment guidelines (Gaebel et al., 2005; NICE, 2014) and the results of major pragmatic studies. Varying, and broad definitions of TRS and other issues in methodology mentioned earlier in this Letter may cause problems affecting the interpretation of studies. Indeed, meta-analyses of original studies with low quality methods lead to flawed conclusions. Future efforts must ideally focus on 1. well-characterized TRS samples (e.g. description of symptoms that predominate, onset of resistance, earlier used antipsychotics), 2. consensus definition of TRS to facilitate global interpretation and replication of results (e.g. WHO has produced with an expert panel consensus definition for severe asthma and this is something we need for TRS as well), 3. sample sizes even above 300 participants "to have power to clearly show a difference of 20% between groups for binary outcomes" (Sinclair and Adams, 2014), and 4. studies without industry-sponsorship.

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**Contributors**

C.M. wrote the first draft of the manuscript. E.J. and A.S. managed the literature searches. All authors contributed to and have approved the final manuscript.

**Conflict of interest**

There are no conflicts of interests to declare.

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# 10.2. ESTUDIO 4

## Antipsychotic Augmentation vs. Monotherapy in Schizophrenia: Systematic Review, Meta-Analysis and Meta-Regression Analysis

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*Antipsychotic polypharmacy in schizophrenia is much debated, since it is common and costly with unclear evidence for its efficacy and safety. We conducted a systematic literature search and a random effects meta-analysis of randomized trials comparing augmentation with a second antipsychotic vs. continued antipsychotic monotherapy in schizophrenia. Co-primary outcomes were total symptom reduction and study-defined response. Antipsychotic augmentation was superior to monotherapy regarding total symptom reduction (16 studies, N=694, standardized mean difference, SMD=–0.53, 95% CI: −0.87 to −0.19, p=0.002). However, superiority was only apparent in open-label and low-quality trials (both p<0.001), but not in double-blind and high-quality ones (p=0.120 and 0.226, respectively). Study-defined response was similar between antipsychotic augmentation and monotherapy (14 studies, N=938, risk ratio = 1.19, 95% CI: 0.99 to 1.42, p=0.061), being clearly non-significant in double-blind and high-quality studies (both p=0.990). Findings were replicated in clozapine and non-clozapine augmentation studies. No differences emerged regarding all-cause/specific-cause discontinuation, global clinical impression, as well as positive, general and depressive symptoms. Negative symptoms improved more with augmentation treatment (18 studies, N=931, SMD=–0.38, 95% CI: −0.63 to −0.13, p<0.003), but only in studies augmenting with aripiprazole (8 studies, N=532, SMD=–0.41, 95% CI: −0.79 to −0.03, p=0.036). Few adverse effect differences emerged: D2 antagonist augmentation was associated with less insomnia (p=0.028), but more prolactin elevation (p=0.015), while aripiprazole augmentation was associated with reduced prolactin levels (p<0.001) and body weight (p=0.030). These data suggest that the common practice of antipsychotic augmentation in schizophrenia lacks double-blind/high-quality evidence for efficacy, except for negative symptom reduction with aripiprazole augmentation.*

**Key words:** Antipsychotics, polypharmacy, augmentation, monotherapy, schizophrenia, clozapine, aripiprazole

Management options for patients with schizophrenia remain suboptimal, as indicated by insufficient symptom control in a sizable subgroup of patients and low response rates, frequently leading to functional impairment[1-5]. Recommendations after inadequate antipsychotic response include waiting for a delayed response, dose adjustment, switching to another antipsychotic, and – in case of treatment resistance to at least two adequate antipsychotic trials – clozapine treatment[6-11].

Another adopted strategy is antipsychotic polypharmacy[12]. Limited data on clinicians' reasoning suggest various motivations for this strategy, including attempts to increase/speed up efficacy, treat residual positive symptoms, or reduce adverse effects allowing dose reduction of the first antipsychotic[13]. Antipsychotic polypharmacy has been reported as a common clinical practice[12,14,15], sometimes implemented by clinicians before or instead of trying clozapine[13,16]. Although the frequency of antipsychotic polypharmacy varies according to patient, illness, setting and provider variables[17], rates in schizophrenia commonly range between 10 and 30%[12,14,17-19].

Despite common use, the evidence for the efficacy and tolerability of antipsychotic polypharmacy is weak[20-22]. In fact, guidelines reserve augmentation with a second antipsychotic as a last-stage treatment option after clozapine failure, intolerability or rejection[6-10]. Additionally, concerns about antipsychotic polypharmacy include the potential for drug-drug interactions, decreased adherence due to complex drug regimes, higher cost[23-25], and increased adverse effects[10,22,26-29].

Meta-analyses aggregate the information of conceptually similar studies and consolidate their quantitative outcomes using statistics. The derived pooled estimates of treatment efficacy and safety are more robust compared to primary study results. Moreover, meta-analyses enable researchers to contrast results from multiple studies and to identify patterns of common effects across studies, or reasons for outcome variability. However, to facilitate informative results and meaningful subgroup and meta-regression analyses, the study methodology should be as homogeneous as possible; study quality should be taken into account; and the total population studied should be sufficiently large (≥1000 subjects)[30].

Although four meta-analyses examined the efficacy of antipsychotic polypharmacy, either irrespective of the antipsychotics used[20] or restricted to clozapine-treated patients[21,31,32], their results remained somewhat inconclusive, possibly influenced by: a) mixing together antipsychotic augmentation (adding a second antipsychotic after non-response to the first) and co-initiation (combination of two antipsychotics from the

beginning) strategies[20]; b) lack of separating lower from higher quality studies[20], and c) the relatively low number of available studies and patients treated in an augmentation paradigm[20,21,31,32].

In one of those meta-analyses, polypharmacy was associated with significantly greater response than monotherapy, with a number-needed-to-treat of 7[20]. However, the improved response was moderated by studies lasting at least ten weeks, conducted in China, examining co-initiation and involving clozapine. Further, that meta-analysis only included six studies of antipsychotic augmentation (N=197), and did not assess symptom reduction due to lacking data.

The three remaining meta-analyses focused on combination treatments with clozapine, either mixing co-initiation and augmentation studies together[21], or focusing on augmentation studies but analyzing only individual drug combinations[32], or focusing only on symptom reduction and not response rates[31]. One meta-analysis found clozapine co-treatment to be superior to clozapine monotherapy, but this finding was only apparent in open-label studies[21]. In one other meta-analysis, augmentation of clozapine with a second antipsychotic was associated with a small benefit (effect size = 0.239, p=0.028), but only 14 trials and 714 patients provided data, and higher versus lower quality studies were not analyzed separately[31].

Due to the limitations of those prior meta-analyses, the frequent use of antipsychotic polypharmacy in ordinary practice, and the recent publication of many additional studies, we conducted a new systematic review and meta-analysis comparing the efficacy and adverse effects of antipsychotic augmentation vs. monotherapy. Based on the prior literature[20,21,31-34], we hypothesized that antipsychotic augmentation would not be superior to monotherapy regarding efficacy (measured as total and specific symptom reduction as well as response/remission/relapse) when focusing on augmentation trials and those with higher quality, but that antipsychotic augmentation might confer a higher risk of adverse effects (except for reduction of specific adverse effects when adding a partial D2 agonist to D2 antagonists).

## METHODS

The systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standard[35,36]. At least two independent authors searched PubMed/MEDLINE, PsycINFO, Chinese Journal Net, Wangfan, and China Biology Medicine databases from inception until May 25, 2015, without language restrictions, supplemented by a manual review of reference lists from eligible publications and relevant reviews. Authors were contacted for additional information if needed.

We included randomized controlled trials with samples consisting of at least 20 adults with a diagnosis of schizophrenia or schizoaffective disorder; in which patients were assigned to augmentation of the current antipsychotic with a different antipsychotic versus augmentation with placebo (in blinded studies) or continuation of existing antipsychotic monotherapy; and in which meta-analyzable data were reported, including symptomatic/functional or adverse effect outcomes. We excluded studies comparing antipsychotic monotherapy versus two antipsychotics started concurrently, as well as those comparing antipsychotic augmentation with antipsychotic switch instead of continuation of the original antipsychotic monotherapy.

Co-primary outcomes were total symptom reduction, as assessed by the Positive and Negative Syndrome Scale (PANSS)[37] or the Brief Psychiatric Rating Scale (BPRS)[38], and study-defined treatment response. Secondary outcomes were all-cause and specific-cause discontinuation (inefficacy, intolerability); reduction of positive symptoms (as assessed by the PANSS positive, the BPRS positive, or the Scale for the Assessment of Positive Symptoms, SAPS[39]), of negative symptoms (as assessed by the PANSS negative, the BPRS negative, or the Scale for the Assessment of Negative Symptoms, SANS[40]), and of general symptoms (as assessed by the PANSS general); reduction of global illness severity (as assessed by the Clinical Global Impression Scale - Improvement, CGI-I[41]); reduction of depressive symptoms (as assessed by the PANSS/BPRS anxiety/depression, the Hamilton Scale for Depression, HAM-D[42], or the Calgary Depression Scale for Schizophrenia, CDSS[43]); improvement of functioning (as evaluated by the Global Assessment of Functioning Scale, GAF[44]); and frequency and severity of adverse effects.

Data of each study were independently identified, checked and extracted by at least two authors, including information relevant for the Cochrane risk-of-bias tool[45]. Inconsistencies were resolved by consensus/involvement of a third reviewer.

We conducted a random effects[46] meta-analysis of outcomes using Comprehensive Meta-Analysis V3 (www.meta-analysis.com). Study heterogeneity was explored using $I^2$ statistics and chi-square test of homogeneity, with $I^2$>50% and p<0.05 indicating significant heterogeneity. All analyses were two-tailed with alpha=0.05, without adjustments for multiple comparisons.

For "total" and "specific" psychopathology (except depression and negative symptoms) and for inefficacy-related discontinuation, all studies except those focusing on the amelioration of adverse effects were analyzed. The reason for using this restricted data set was that studies focusing on the amelioration of adverse effects could have included treatment responders, leaving little or no room for improvement. In contrast, for depression and negative symptoms and for individual adverse effects, all-cause discontinuation and intolerability-related discontinuation, all available data were analyzed, including studies focusing on the reduction of adverse effects.

Group differences in continuous outcomes were analyzed as the pooled standardized mean difference (SMD) in either change from baseline to endpoint (preferred) or endpoint scores (only preferred if change score results were skewed, i.e., SD > twice the mean). Additionally, weighted mean difference (WMD) was calculated for weight change in kilograms. Dichotomous data were analyzed calculating the pooled risk ratio (RR). Intention-to-treat (ITT) data were always preferred, but observed cases (OC) data were also allowed.

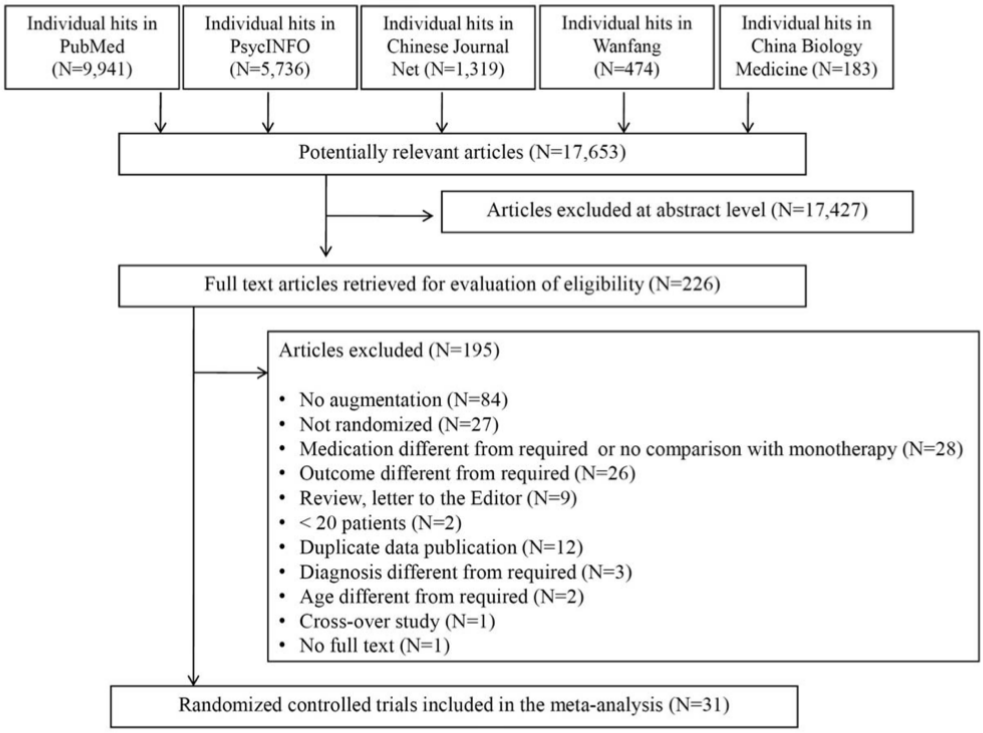


**Figure 1** PRISMA diagram of the literature search

All outcomes were analyzed for the pooled sample and for high-quality studies separately. The latter were defined *a priori* as double-blind studies using ITT/last-observation-carried-forward (LOCF) analyses, as opposed to open-label studies and those using OC data. In two studies with more than one active augmentation arm[47,48], the number of patients in the monotherapy group was divided by the number of active study arms to avoid double-counting of control subjects.

For meta-regression analyses, the baseline BPRS total scores were converted to PANSS total scores using equipercentile linking[49]. Exploratory subgroup and meta-regression analyses were added *post-hoc* for negative symptom change (the only overall significant outcome in both low- and high-quality studies) in studies using partial D2 agonists.

We inspected funnel plots, used Egger's regression test[50] and the Duval and Tweedie's trim and fill method[51] to quantify whether publication bias could have influenced the results.

## RESULTS

The initial search resulted in 17,653 hits. Altogether, 17,427 studies were excluded at the title/abstract level. Of the remaining 226 references, 195 were excluded after full text review, yielding 31 studies that were included in the meta-analysis (Figure 1).

### Efficacy of antipsychotic monotherapy vs. augmentation (efficacy data set)

Details on the 22 meta-analyzed studies with efficacy as the primary outcome (N=1,342) are provided in Table 1. They included 13 double-blind and ITT/LOCF "high-quality" studies and 9 open-label and/or OC "low quality" ones.

Antipsychotic augmentation was superior to monotherapy regarding total symptom reduction (16 studies, N=694, SMD =–0.53, 95% CI: −0.87 to −0.19, p=0.002), but only in open-label (n=6, N=285, SMD=–0.81, 95% CI: −1.18 to −0.43, p<0.001) and low-quality (n=7, N=316, SMD=–0.83, 95% CI: −1.16 to −0.50, p<0.001) studies, not in double-blind (n=10, N=409, SMD=–0.37, 95% CI: −0.83 to 0.10, p=0.120) and high-quality (n=9, N=378, SMD=–0.30, 95% CI: −0.78 to 0.19, p=0.226) ones (Figures 2 and 3). The funnel plots and Egger's test did not indicate publication bias (p=0.320).

In subgroup analyses, antipsychotic augmentation was superior in certain settings (only inpatients: n=6, N=316, SMD=–0.82, 95% CI: −1.22 to −0.43, p<0.001; only outpatients: n=5, N=247, SMD=–0.76, 95% CI: −1.49 to −0.03, p=0.042) and regions

**Table 1** Study, patient and treatment characteristics

| Study | Agents | No. patients | Risk of bias* | Blinding | Primary outcome | Analysis | Trial duration (weeks) | Setting | Monotherapy dose, mg/d: mean (range) | Augmentation group dose, mg/d: mean (range) | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| ***Clozapine + first-generation antipsychotic*** | | | | | | | | | | | |
| Liu et al[52] (China) | CLZ + FLU | T: 60<br>M: 30<br>A: 30 | 1 | OL | Efficacy | ITT | 24 | Inpatients | CLZ:<br>NR (375-500) | CLZ:<br>NR (375-500) | FLU:<br>NR (25-50) |
| Friedman et al[53] (US) | CLZ + PIM | T: 53<br>M: 28<br>A: 25 | 3 | DB | Efficacy | ITT | 12 | Inpatients (64.2%) and outpatients (35.8%) | CLZ:<br>478.1 (NR) | CLZ:<br>518.8 (NR) | PIM:<br>6.48 (2.0-8.9) |
| Gunduz-Bruce et al[54] (US) | CLZ + PIM | T: 28<br>M: 14<br>A: 14 | 4 | DB | Efficacy | ITT | 12 | Outpatients | CLZ:<br>NR (NR) | CLZ:<br>NR (NR) | PIM:<br>4 (fixed) |
| ***Clozapine + second-generation antipsychotic*** | | | | | | | | | | | |
| Chang et al[55] (Korea) | CLZ + ARI | T: 61<br>M: 32<br>A: 29 | 5 | DB | Efficacy | ITT | 8 | Inpatients and outpatients (% NR) | CLZ:<br>290.6 (NR) | CLZ:<br>304.3 (NR) | ARI:<br>15.5 (5-30) |
| Fan et al[56] (US) | CLZ + ARI | T: 38<br>M: 18<br>A: 20 | 2 | DB | Adverse effects | OC | 8 | Outpatients | CLZ:<br>400 (NR) | CLZ:<br>397 (NR) | ARI:<br>15 (fixed) |
| Fleischhacker et al[57] (Europe, South Africa) | CLZ + ARI | T: 207<br>M: 99<br>A: 108 | 4 | DB | Adverse effects | ITT | 16 | Outpatients | CLZ:<br>363 (163-900) | CLZ:<br>384 (200-900) | ARI:<br>11.1 (5-15) |
| Guan[58] (China) | CLZ + ARI | T: 60<br>M: 30<br>A: 30 | 1 | OL | Efficacy | ITT | 16 | Inpatients | CLZ:<br>NR (300-500) | CLZ:<br>NR (200-300) | ARI:<br>NR (20-30) |
| Muscatello et al[59] (Italy) | CLZ + ARI | T: 40<br>M: 20<br>A: 20 | 5 | DB | Efficacy | OC | 24 | Outpatients | CLZ:<br>341.2 (200-450) | CLZ:<br>310.7 (200-450) | ARI:<br>12.5 (10-15) |
| Sun et al[60] (China) | CLZ + ARI | T: 62<br>M: 30<br>A: 32 | 1 | OL | Efficacy | ITT | 6 | Inpatients | CLZ:<br>368.2 (200-450) | CLZ:<br>168 (75-300) | ARI:<br>21.6 (10-30) |
| Lin et al[61] (China) | CLZ + PAL | T: 70<br>M: 35<br>A: 35 | 3 | DB | Efficacy | ITT | 12 | Inpatients | CLZ:<br>217.9 (NR) | CLZ:<br>231.7 (NR) | PAL:<br>8.2 (6-12) |
| Freudenreich et al[62] (US) | CLZ + RIS | T: 24<br>M: 11<br>A: 13 | 2 | DB | Efficacy | ITT | 6 | Outpatients | CLZ:<br>456 (200-700) | CLZ:<br>456 (200-700) | RIS:<br>4 (NR) |
| Anil Yagcioglu et al[63] (Turkey) | CLZ + RIS | T: 30<br>M: 14<br>A: 16 | 6 | DB | Efficacy | ITT | 6 | Inpatients (20.0%) and outpatients (80.0%) | CLZ:<br>414.3 (300-900) | CLZ:<br>515.6 (300-900) | RIS:<br>5.1 (NR) |

**Table 1** Study, patient and treatment characteristics *(continued)*

| Study | Agents | No. patients | Risk of bias* | Blinding | Primary outcome | Analysis | Trial duration (weeks) | Setting | Monotherapy dose, mg/d: mean (range) | Augmentation group dose, mg/d: mean (range) | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Honer et al[64] (International) | CLZ + RIS | T: 68<br>M: 34<br>A: 34 | 6 | DB | Efficacy | ITT | 8 | Inpatients (38.2%) and outpatients (61.8%) | CLZ: 487 (NR) | CLZ: 494 (NR) | RIS: 3 (NR) |
| Josiassen et al[65] (US) | CLZ + RIS | T: 40<br>M: 20<br>A: 20 | 3 | DB | Efficacy | ITT | 12 | Inpatients (26.1%) and outpatients (73.9%) | CLZ: 403 (NR) | CLZ: 529 (NR) | RIS: 4.4 (NR) |
| Hu[66] (China) | CLZ + RIS | T: 60<br>M: 30<br>A: 30 | 1 | OL | Efficacy | ITT | 12 | Inpatients | CLZ: 253.6 (NR) | CLZ: 126.3 (NR) | RIS: 2.9 (2-6) |
| Weiner et al[67] (US) | CLZ + RIS | T: 69<br>M: 36<br>A: 33 | 2 | DB | Efficacy | ITT | 16 | Inpatients (26.1%) and outpatients (73.9%) | CLZ: NR (NR) | CLZ: NR (NR) | RIS: 4 (fixed) |
| Nielsen et al[68] (Denmark) | CLZ + SER | T: 50<br>M: 25<br>A: 25 | 6 | DB | Efficacy | ITT | 12 | Outpatients | CLZ: 435 (NR) | CLZ: 394 (NR) | SER: 16 (fixed) |
| Shiloh et al[69] (Israel) | CLZ + SUL | T: 28<br>M: 12<br>A: 16 | 5 | DB | Efficacy | ITT | 10 | Inpatients | CLZ: 446 (NR) | CLZ: 403 (NR) | SUL: NR (100-600) |
| Jiang et al[70] (China) | CLZ + ZIP | T: 24<br>M: 12<br>A: 12 | 2 | OL | Efficacy | ITT | 12 | NR | CLZ: 597.2 (75-600) | CLZ: 489.7 (75-600) | ZIP: NR (20-160) |
| Muscatello et al[71] (Italy) | CLZ + ZIP | T: 40<br>M: 20<br>A: 20 | 6 | DB | Efficacy | ITT | 16 | Outpatients | CLZ: 462.5 (350-600) | CLZ: 428.7 (350-600) | ZIP: 80.0 (fixed) |
| ***First-generation + second-generation antipsychotic*** | | | | | | | | | | | |
| Shim et al[72] (US, Korea) | HAL + ARI | T: 54<br>M: 28<br>A: 26 | 2 | DB | Adverse effects | ITT | 8 | NR | HAL: 24.8 (NR) | HAL: 20.7 (NR) | ARI: 22.5 (15-30) |
| ***Second-generation + second-generation antipsychotic*** | | | | | | | | | | | |
| Chen et al[47] (China) | RIS + ARI | T: 119<br>M: 30<br>A: 89 | 3 | DB | Adverse effects | ITT | 8 | Inpatients and outpatients (% NR) | RIS: 4.93 (NR) | RIS: 4.63 (NR)<br>RIS: 4.79 (NR) | ARI: 5 (fixed)<br>ARI: 10 (fixed) |

**Table 1** Study, patient and treatment characteristics *(continued)*

| Study | Agents | No. patients | Risk of bias* | Blinding | Primary outcome | Analysis | Trial duration (weeks) | Setting | Monotherapy dose, mg/d: mean (range) | Augmentation group dose, mg/d: mean (range) | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | RIS: 5.07 (NR) | ARI: 20 (fixed) |
| Kane et al[73] (US) | QTP/RIS + ARI | T: 323<br>M: 155<br>A: 158 | 1 | DB | Efficacy | ITT | 16 | Outpatients | QTP/RIS: 516/4.8 (400-800/4-8) | QTP/RIS: 513/4.6 (400-800/4-8) | ARI: 10.3 (2-15) |
| Lee et al[74] (Korea) | RIS + ARI | T: 35<br>M: 18<br>A: 17 | 2 | DB | Adverse effects | ITT | 12 | Inpatients | RIS: 3 (NR) | RIS: 3 (NR) | ARI: 10 (fixed) |
| Liu et al[48] (China) | RIS + ARI | T: 86<br>M: 27<br>A: 59 | 1 | DB | Adverse effects | ITT | 4 | Inpatients | RIS: NR (>4) | RIS: NR (>4) | ARI: 5 (fixed)<br>ARI: 10 (fixed) |
| Ou et al[75] (China) | OLZ + ARI | T: 70<br>M: 35<br>A: 35 | 1 | OL | Efficacy | OC | 8 | Inpatients | OLZ: 18.2 (NR) | OLZ: 17.8 (NR) | ARI: 10 (fixed) |
| Yasui-Furukori et al[76] (Japan) | RIS/OLZ + ARI | T: 36<br>M: 18<br>A: 18 | 1 | DB | Adverse effects | OC | 12 | Outpatients | RIS/OLZ: 5.0/12.5 (3-8/5-20) | RIS/OLZ: 5.9/12.1 (2-12/2.5-20 | ARI: 15.2 (6-30) |
| Zhao[77] (China) | RIS + ARI | T: 56<br>M: 28<br>A: 28 | 1 | OL | Adverse effects | NR | 12 | Inpatients and outpatients (% NR) | RIS: NR (3-8) | RIS: NR (3-8) | ARI: 10 (fixed) |
| Zhou et al[78] (China) | RIS + ARI | T: 100<br>M: 50<br>A: 50 | 0 | OL | Adverse effects | NR | 24 | Inpatients | RIS: NR (4-6) | RIS: NR (4-6) | ARI: 5 (fixed) |
| Liang & Liu[79] (China) | ARI + CLZ | T: 65<br>M: 33<br>A: 32 | 1 | OL | Efficacy | ITT | 8 | NR | ARI: NR (20-30) | ARI: NR (20-30) | CLZ: NR (25-100) |
| Kotler et al[80] (Israel) | OLZ + SUL | T: 17<br>M: 8<br>A: 9 | 2 | OL | Efficacy | ITT | 8 | Inpatients | OLZ: 22.5 (20-30) | OLZ: 22.2 (20-30) | SUL: 600 (fixed) |

*number of low risk judgements, T – total, M – monotherapy, A – augmentation, OL – open label, DB – double blind, ITT – intent to treat, OC – observed cases, CLZ – clozapine, FLU – fluphenazine, PIM – pimozide, ARI – aripiprazole, PAL – paliperidone, RIS – risperidone, SER – sertindole, SUL – sulpiride, ZIP – ziprasidone, HAL – haloperidol, QTP – quetiapine, OLZ – olanzapine, NR – not reported

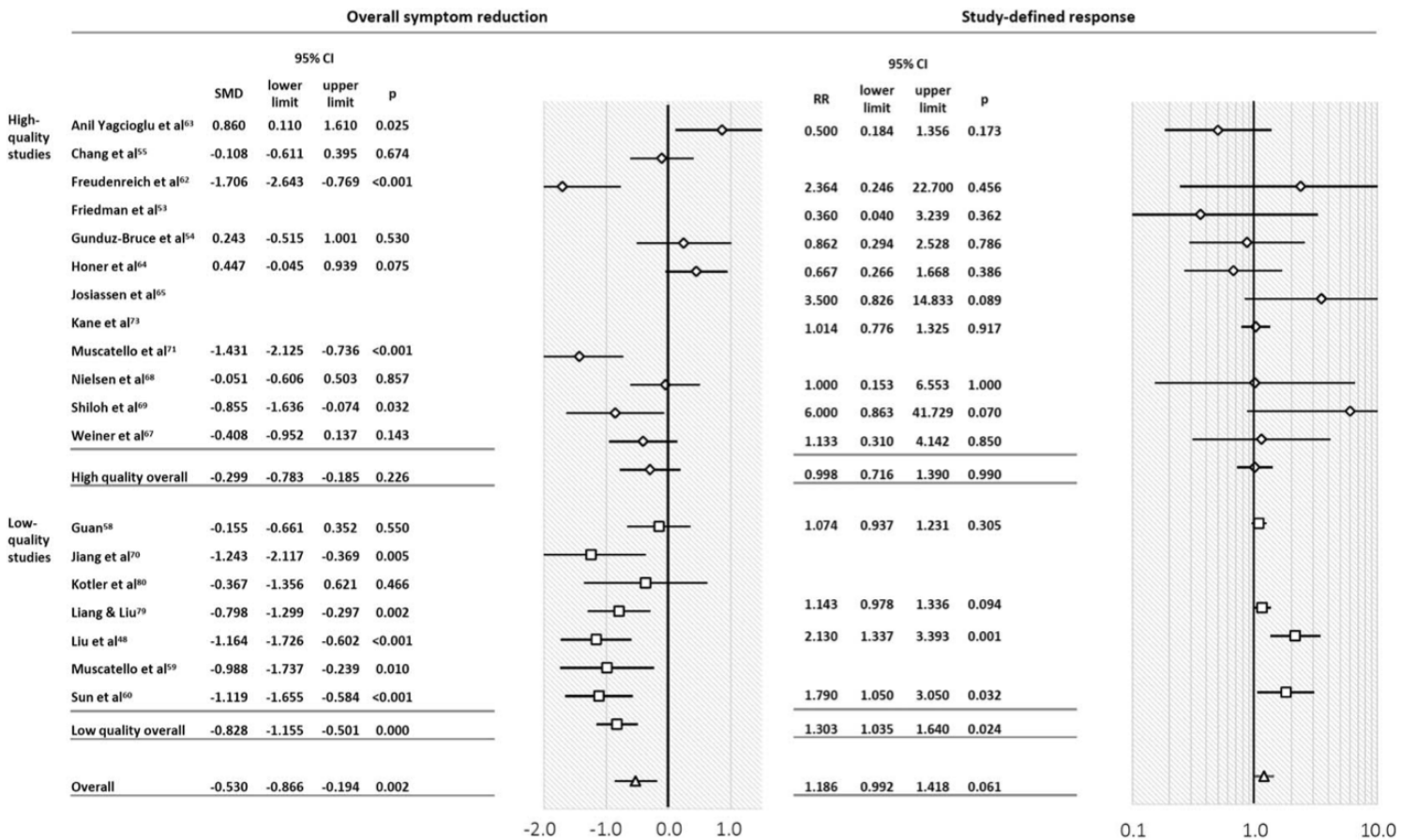


**Figure 2** Forest plots of overall symptom reduction and study-defined response. SMD – standardized mean difference, RR – risk ratio

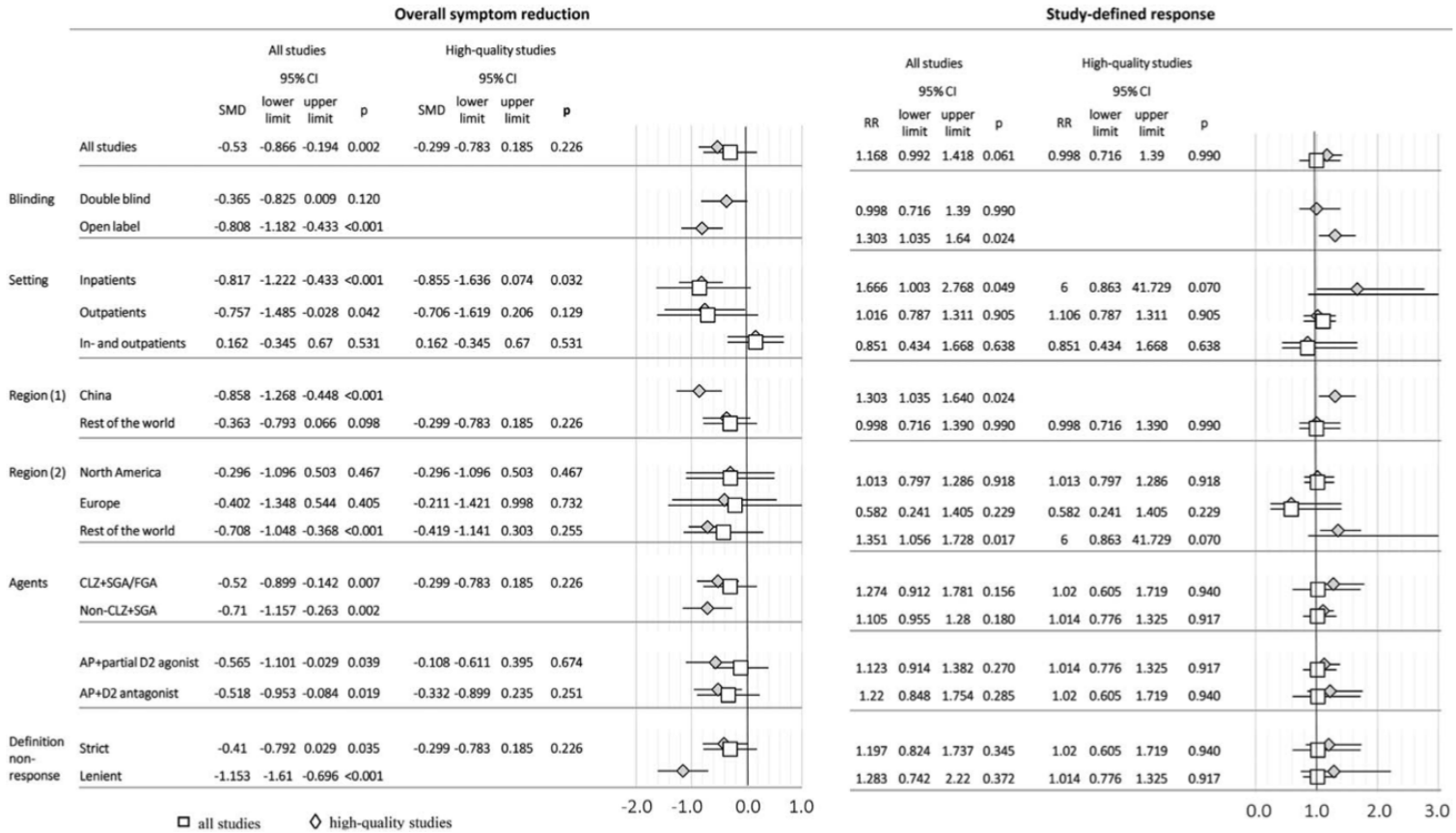


**Figure 3** Primary outcomes, subgroup analyses and meta-regression in studies with efficacy as primary outcome. SMD – standardized mean difference, RR – risk ratio, CLZ – clozapine, SGA – second generation antipsychotic, FGA – first generation antipsychotic, AP – antipsychotic

(China: n=5, N=269, SMD=−0.86, 95% CI: −1.27 to −0.45, p<0.001; non-North American/European countries: n=8, N=374, SMD=–0.71, 95% CI: −1.05 to −0.37, p<0.001). However, superiority in these subgroups was not apparent in high-quality studies (Figure 3).

Findings regarding symptom reduction were replicated in augmentation studies of clozapine with a second generation antipsychotic (SGA) or a first generation antipsychotic (FGA) (n=14, N=612, SMD=–0.52, 95% CI: −0.90 to −0.14, p=0.007), clozapine with a SGA (n=12, N=528, SMD=–0.52, 95% CI: −0.93 to −0.11, p=0.012), and non-clozapine SGA with a SGA (n=2, N=82, SMD=–0.71, 95% CI: −1.16 to −0.26, p=0.002); studies augmenting with a partial D2 agonist (n=4, N=214, SMD=–0.57, 95% CI: −1.10 to −0.03, p=0.039), and those augmenting with D2 antagonists (n=12, N=480, SMD=–0.52, 95% CI: −0.95 to −0.08, p=0.019). Results persisted independent of the non-response definition (strict, ≥2 adequate trial failures vs. lenient, ≥1 adequate trial failure): respectively, n=13, N=542, SMD=–0.41, 95% CI: −0.79 to 0.03, p=0.035; and n=2, N=86, SMD=–1.15, 95% CI: −1.61 to −0.70, p<0.001). However, again, differences were non-significant when analyzing only high-quality studies (Figure 3).

In meta-regression analyses, a higher augmentation-to-monotherapy ratio of chlorpromazine equivalent dose (p=0.019) and higher baseline PANSS/converted BPRS scores (p=0.011) were associated with less symptom improvement, while studies with high risk of bias near-significantly moderated greater improvement with antipsychotic augmentation (p=0.050). The influence of the PANSS/converted BPRS scores was replicated in high-quality studies (p=0.033), whereas the other factors were non-significant.

Response, as defined by ≥20% PANSS/BPRS reduction (n=10), ≥25% PANSS reduction (n=3), and ≥20% PANSS reduction or CGI-I of 1 or 2 (n=1), did not differ between antipsychotic augmentation and monotherapy (n=14, N=938, RR=1.19, 95% CI: 0.99 to 1.42, p=0.061). In subgroup analyses, antipsychotic augmentation was superior in open-label/low-quality studies (n=4, N=245, RR=1.30, 95% CI: 1.04 to 1.64, p=0.024), but not in double-blind/high-quality ones (n=10, N=693, RR=1.00, 95% CI: 0.72 to 1.39, p=0.990) (Figure 2). The funnel plots and Egger's test did not indicate publication bias (p=0.508).

Antipsychotic augmentation was again superior in inpatient only studies (n=4, N=207, RR=1.67, 95% CI: 1.00 to 2.77, p=0.049), Chinese studies (n=4, N=245, RR=1.30, 95% CI: 1.04 to 1.64, p=0.024) and non-North American/European studies (n=5, N=273, RR=1.35, 95% CI: 1.06 to 1.73, p=0.017) (Figure 3). In these subgroups, the number of high-quality studies was ≤1, not allowing for separate analyses. There was no advantage of any specific antipsychotic combination, or depending on non-response definition. No significant moderator of treatment response emerged. No between-group differences were observed regarding inefficacy-related discontinuation (n=6, N=596, RR=1.08, 95% CI: 0.44 to 2.67, p=0.870), global clinical impression (n=8, N=403, SMD=–0.01, 95% CI: −0.32 to 0.30, p=0.947), positive symptoms (n=14, N=604, SMD=–0.25, 95% CI: −0.66 to 0.16, p=0.230), general symptoms (n=4, N=144, SMD=–0.73, 95% CI: −1.91 to 0.46, p=0.229), and functioning (n=2, N=80, SMD=–0.36, 95% CI: −1.19 to 0.47, p=0.389).

### Efficacy and tolerability of antipsychotic monotherapy vs. augmentation (complete data set)

The complete data set (efficacy-focused plus adverse effect-focused studies) included 31 trials (N=2,073) (see Table 1). The mean PANSS/converted BPRS score was higher in efficacy-focused studies (total sample = 79.7 ± 10.8, clozapine studies = 79.3 ± 9.6, non-clozapine studies = 81.7 ± 15.9) than in adverse-effect focused ones (total sample = 67.4 ± 9.2, clozapine studies = 71.5, non-clozapine studies = 66.6 ± 9.9).

All-cause discontinuation (n=22, N=1,482, RR=1.13, 95% CI: 0.90 to 1.42, p=0.284), and intolerability-related discontinuation (n=11, N=949, RR=0.87, 95% CI: 0.50 to 1.50, p=0.611) did not differ between antipsychotic augmentation and monotherapy.

Negative symptoms improved with antipsychotic augmentation (n=18, N=931, SMD=–0.38, 95% CI: −0.63 to −0.13, p=0.003), but in subgroup analyses this effect was only significant in studies augmenting D2 antagonists with a partial D2 agonist (n=8, N=532, SMD=–0.41, 95% CI: −0.79 to −0.03, p=0.036), not when combining two D2 antagonists (n=10, N=399, SMD=–0.36, 95% CI: −0.72 to 0.01, p=0.055). These findings were replicated in high-quality studies (4 trials augmenting D2 antagonists with a partial D2 agonist, N=355, SMD=–0.28, 95% CI: −0.55 to −0.009, p=0.043). In exploratory subgroup and meta-regression analyses, no relevant moderator of negative symptom improvement with a partial D2 agonist emerged.

Antipsychotic augmentation and monotherapy did not differ regarding depressive symptoms (n=10, N=351, SMD=−0.69, 95% CI: −1.42 to 0.05, p=0.066).

Few differences in adverse effects emerged. D2 antagonist augmentation was associated with less insomnia (n=3, N=169, RR=0.26, 95% CI: 0.08 to 0.86, p=0.028), but more prolactin elevation (n=2, each representing augmentation with risperidone, N=74, SMD=2.20, 95% CI: 0.43 to 3.96, p=0.015), while aripiprazole augmentation of D2 antagonists was associated with reduced prolactin levels (n=9, N=450, SMD=–1.60, 95% CI: −2.19 to −1.01, p<0.001) and body weight (n=6, N=260, WMD=–0.93, 95% CI= −1.77 to −0.09, p=0.030).

## DISCUSSION

While some prior meta-analyses have examined the efficacy of combination or "polypharmacy" strategies in schizophrenia[20,21,31,32], this is the first meta-analysis of randomized controlled trials focusing exclusively on augmentation strategies (i.e., the addition of a second antipsychotic after non-response to the first) versus continued treatment with one antipsychotic (with addition of placebo in the blinded studies), irrespective of the baseline antipsychotic.

Although our prior meta-analysis, published in 2009[20], included 19 studies and 1,229 patients, merely 6 studies with only 197 patients were "augmentation" studies, which are the ones that are truly relevant, as they clinically reflect the management of refractory/non-responsive patients. In the current study, we increased the meta-analyzed data from 6 to 31 studies and 197 to 2,073 patients. This greater number of studies allowed for an evaluation of various symptom domains beyond study-defined response, plus the assessment of adverse effects and subgroup and meta-regression analyses, including examination of the effect of open versus blinded trials.

In contrast to that prior meta-analysis[20], in which response rates had been significantly greater in the antipsychotic polypharmacy group that mixed co-initiation and augmentation trials (number-needed-to-treat = 7), the current meta-analysis did not provide any evidence for enhanced efficacy of antipsychotic augmentation in high-quality, blinded studies for either antipsychotic response or symptom reduction. This finding suggests that expectation and salience biases, also present in clinical care, may underlie observed improvements and decision making when augmenting one antipsychotic with a second one.

Although in efficacy-focused studies total symptoms decreased significantly more in the augmentation group, this effect was driven by open-label studies and those using OC analyses. Notably, the non-significance regarding total symptom reduction in high-quality studies was not driven by fewer studies and widening of the confidence intervals. Rather, more high-quality than low-quality studies were included (nine vs. seven), and the confidence intervals remained almost identical, whereas the between-group effect size was much smaller in high-quality studies. Furthermore, in efficacy-focused studies, no difference between antipsychotic augmentation and monotherapy was found regarding response rate, but, again, in the subgroup of low-quality studies superiority of the augmentation arm was observed.

Evidence regarding symptom improvement and treatment response was lacking for augmentation of either clozapine or non-clozapine antipsychotics (with the latter studies being surprisingly uncommon). The previously identified benefit regarding augmentation of clozapine with a second antipsychotic[31] could not be confirmed in blinded trials and those using ITT data. Prior meta-analyses that focused on antipsychotic co-treatment strategies involving clozapine[21,31,32] had much fewer studies (augmentation studies: 5-14 vs. 20 in our meta-analysis; patients: 187-734 vs. 1,112 in our meta-analysis) and in one instance[21] combined antipsychotic augmentation and co-initiation trials.

Despite the overall unfavorable results in high-quality studies for total, positive and general symptoms, global clinical impression, depression, treatment response and study discontinuation, augmentation of D2 antagonists with a partial D2 agonist was associated with significantly reduced negative symptoms, a finding that was confirmed in high-quality studies. Since the treatment of negative symptoms remains a big challenge in schizophrenia[81,82], these findings, based on eight studies (including four high-quality trials) clearly require further investigation, especially comparing augmentation with a partial D2 agonist versus switching to a partial D2 agonist. Since two new partial D2 agonists, brexpiprazole[83] and cariprazine[84], were recently approved for schizophrenia, it will be of interest to see if the potential benefits for negative symptoms extend to these other agents.

Different from the generally held notion that antipsychotic polypharmacy carries a greater risk of adverse effects[22], this was only found regarding greater prolactin elevation when combining two D2 antagonists. Rather, combination of two D2 antagonists was associated with less insomnia, whereas augmentation with the partial D2 agonist aripiprazole resulted in lower prolactin levels and reduced body weight.

The lack of superior efficacy of antipsychotic augmentation in high-quality studies is in contrast to common clinical belief and practice, where antipsychotic co-treatment is often implemented for non-response to antipsychotic monotherapy[12]. However, the clinical evaluation of improvement with antipsychotic augmentation mirrors the findings from open-label studies, suggesting that in clinical settings the expectations of patients and clinicians may translate into perceived favorable outcomes. Large pragmatic randomized controlled trials of antipsychotic augmentation strategies conducted in generalizable settings and samples are needed to confirm the lack of efficacy advantages of antipsychotic augmentation, as we cannot fully rule out a selection bias of less severely ill patients agreeing to participate in blinded trials. However, this possibility seems relatively low, since mean baseline PANSS/converted BPRS total symptom severity was around 80 in these pretreated individuals, and PANSS/converted BPRS total symptom severity did not significantly moderate the results.

In meta-regression analyses, less symptom improvement was associated with a higher chlorpromazine equivalent dose in the augmentation versus monotherapy arms, and a greater baseline symptom severity, with the latter relationship remaining significant in high-quality studies. These findings suggest that antipsychotic augmentation is even less effective in the sicker patients and those requiring higher antipsychotic doses. Alternatively, the higher total antipsychotic doses in the combination groups may be a reflection of lack of initial improvement, prompting dose escalation. This relationship might also be due to greater dopamine blockade resulting in less improvement due to secondary negative symptoms or other unfavorable effects.

Although the moderation of less efficacy by higher baseline symptom severity contradicts a recent meta-analysis[85], those results pertained to acutely exacerbated patients in whom greater baseline symptom severity created more room for improvement. Conversely, in our meta-analysis, a substantial number of patients had likely benefitted to some degree from antipsychotic monotherapy in the past, so that higher residual symptom severity is probably a marker of less treatment responsiveness.

The results of this study need to be interpreted within some limitations. These include: a) the still relatively small number

of double-blind studies comparing antipsychotic augmentation with monotherapy in schizophrenia, particularly for augmentation of non-clozapine antipsychotics and for specific antipsychotic co-treatment pairs; b) the heterogeneous study origin, design, definition and degree of insufficient response to monotherapy, measurements and outcomes; c) the limited number of studies reporting negative and depressive symptoms as well as adverse effects, which were often not comprehensively assessed or reported; d) the potential influence of cultural or ethnic differences (although we addressed regional effects in pre-planned subgroup analyses, yet the effect of studies from China overlapped almost 100% with an efficacy signal only detected in open-label/low-quality studies); e) the exclusion of studies focusing on adverse effects from the efficacy analyses to reduce heterogeneity (supported by a >10-point lower mean PANSS/converted BPRS symptom severity in side effect-focused versus efficacy-focused studies); f) the combination of studies augmenting clozapine and non-clozapine antipsychotics, potentially representing different patient subgroups (although mean baseline PANSS/converted BPRS total scores were comparable, and subgroup analyses replicated results in both clozapine and non-clozapine studies); g) the restriction of the distinction between high-quality and low-quality to blinding and data analysis (although risk-of-bias tool clearly confirmed quality differences without having a significant influence in the meta-regression analysis, suggesting that major influencing biases were captured through blinding/ITT categorization); h) the lack of adjustment for multiple comparisons (yet, adjustment for multiple comparisons would only have increased the level of non-significance of differences between groups); i) the potential effect of non-adherence, and j) the lack of detailed data to determine whether the effect of partial agonist augmentation was mainly on primary or secondary negative symptoms.

In summary, data from this study suggest that high-quality evidence is lacking for antipsychotic augmentation in patients with schizophrenia, which applies also to patients with inadequate response to clozapine. The clinical relevance of the negative symptom advantage of adjunctive partial D2 agonist treatment needs to be further assessed. Additionally, effects of augmentation with a partial D2 agonist versus a switch to a partial D2 agonist on negative symptoms need to be compared before these results can be considered for clinical care. Antipsychotic augmentation treatment should also be compared with high-dose antipsychotic monotherapy or augmentation with psychosocial interventions. Furthermore, non-clozapine antipsychotic augmentation strategies should be compared against a switch to clozapine or to improving adherence, including monotherapy with a long-acting injectable antipsychotic, which are each more rational choices for addressing antipsychotic non-response. Another gap is the systematic assessment of adverse effects of antipsychotic augmentation, extending also to cognition, functioning and subjective well-being. Finally, more high-quality trials are needed that examine antipsychotic augmentation in non-clozapine-treated patients across relevant outcome domains, including patients with carefully defined insufficient response to antipsychotic monotherapy.

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# 10.3. ESTUDIO 5

## Target selection for deep brain stimulation in treatment resistant schizophrenia

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### Abstract

**Background:** The use of deep brain stimulation (DBS) in treatment-resistant schizophrenia is a topic of considerable current interest, but where to place the electrodes placement presents a significant challenge.

**Objective:** This paper reviews pragmatic and theoretical rationales for DBS electrode placement in schizophrenia.

**Methods:** Literature review of a) experience with use of DBS in other psychiatric disorders, specifically obsessive-compulsive disorder (OCD) and major depression; and b) evidence of brain abnormality in schizophrenia, with its localizability. Also reviewed are the three trials of DBS in schizophrenia launched/carried out to date.

**Results:** Two sites, the nucleus accumbens and the subgenual anterior cingulate cortex, emerge as being of particular interest, having been successfully employed in other psychiatric disorders, and representing areas of potential functional overactivity in schizophrenia. The ventral tegmental area and substantia nigra pars reticulata have also been proposed as targets based on theoretical considerations alone. Electrode placement has been considered in the hippocampus, though functional imaging evidence for hyperactivity (or hypoactivity) in the disorder is limited and inconsistent.

**Conclusions:** On current evidence, the nucleus accumbens may represent the strongest candidate for DBS electrode placement in schizophrenia, with the ventral tegmental area also being of potential interest. The subgenual anterior cingulate cortex is also a credible site. The hippocampus and DLPFC lack a clear theoretical rationale for utilization. Evidence from case reports concerning psychotic symptoms in patients treated with DBS for other indications represent another potentially valuable but currently scarce source of evidence.

## Introduction

Schizophrenia is a common and frequently disabling psychiatric disorder characterized by psychotic symptoms ('positive symptoms'), such as delusions, hallucinations and formal thought disorder (incoherence of speech). Many patients follow a deteriorating course, with so-called negative symptoms – lack of volition, poverty of speech and emotional flattening – progressively developing [1, 2]. Both sets of symptoms, but especially the latter, interfere with social and occupational functioning and not infrequently lead to patients being unable to live independently.

The treatment of schizophrenia is currently unsatisfactory. The mainstay is antipsychotic drugs, which act by blocking the D2 family of post-synaptic dopamine receptors [3]. However, active psychotic symptoms are often not completely controlled by these drugs, and 20-30% of patients show no or minimal improvement [4]. Approximately thirty years ago one antipsychotic drug, clozapine, was shown to bring about improvement in some treatment-resistant patients [5], but even so around 60% still fail to respond to this drug [6]. Otherwise, therapeutic options are limited. A number of other 'atypical' or 'second-generation' antipsychotics have been introduced in the wake of clozapine, but these have either no or only small therapeutic advantages over conventional drugs [7]. Based on the glutamate hypothesis of schizophrenia (see below), several drugs with glutamate agonist, or in one case with complex effects at glutamatergic presynaptic autoreceptors, have been developed. To date, all these drugs have failed in large, well-controlled trials [8-11].

Deep brain stimulation (DBS) is used in growing numbers of patients with treatment-resistant psychiatric disorders, especially obsessive-compulsive disorder (OCD) and major depression, where it has had broadly encouraging results in both cases [12-14]. In the case of schizophrenia, while its use is under active consideration [15-17], actual clinical experience is very limited; a major reason for this appears to be uncertainty about where to site the electrodes [15, 16]. So far, only three trials have been attempted: one in Toronto [18] which was abandoned due to lack of recruitment; another in Baltimore [19] which is currently recruiting; and a third by our group in Barcelona [20], which was completed in 2019 with results now published [21].

In this article, we describe rationales for electrode placements for DBS, in the light of its use in other psychiatric disorders and the evidence for brain pathology in schizophrenia, especially whether and to what extent this can be considered to be localized. We take as a point of departure the established view that DBS works by producing a 'functional lesion', ie a zone of inhibition in a spherical region around the stimulating electrode, which is achieved by a mechanism akin to 'jamming' [22] or synaptic depletion [23]. However, it is important to note that this may be an oversimplification, and that both local and distant excitatory effects may also play a role [23, 24]. The intervention is also recognized to produce wider changes in brain networks of which the stimulation site forms part [25-27].

## Electrode placement in OCD and major depression

In neurological disorders electrode placement for DBS can be guided by knowledge about their underlying pathophysiology, which typically derives from multiple sources, including but not limited to pathological anatomy, animal models and brain imaging. Results from an earlier generation of ablative neurosurgical procedures may also be available, such as pallidotomy for Parkinson's disease and thalamotomy for essential tremor. Such information is largely unavailable for psychiatric disorders: their biological mechanisms are largely unknown, none of a range of animal models have gained wide acceptance, and the main conclusion from 40 years of brain imaging research is that structural changes are minor.

In these circumstances selection of electrode placements in psychiatric disorders has had to fall back on other strategies. In the case of OCD, two factors appear to have played a decisive role. One of these is the long history of clinical observations of compulsive behaviours and sometime obsessional thinking in basal ganglia disease states ranging from post-encephalitic Parkinsonism [28, 29], to Gilles de la Tourette's syndrome and Sydenham's chorea [30, 31]. This link was further strengthened in the 1990s by PET and SPECT studies which found evidence of functional abnormality in the basal ganglia in samples of OCD patients [32, 33; see also 34].

At least as important, if not more so, has been the history of use of ablative surgical treatments in the OCD, particularly one of the two main procedures employed, anterior capsulotomy [35, 36]. In what appears to have been a direct consequence of this, the earliest trials of DBS in OCD used electrode placements in the anterior limb of the internal capsule [37-39]. Later, electrode placements were tried in the nucleus accumbens or impinging on this structure [40-44; see also 45]. The reasoning here (presumably also influenced by the above clinical observations linking OCD to the basal ganglia) was that the nucleus accumbens was the crucial structure affected by lesions and/or stimulation in the anterior limb of the internal capsule [35, 46]. Another basal ganglia location, the subthalamic nucleus, has also been targeted for DBS [47, 48]. Placements outside the basal ganglia (eg the inferior thalamic peduncle [49]), however, have been unusual in the disorder.

A major impetus for the use of DBS in major depression was once again clinical observations, but this time of an altogether more modern kind – the occurrence of mood changes in patients receiving DBS [36, 50]. Thus, patients with Parkinson's disease were noted to sometimes develop transient euphoria with electrode placements in sites such as the subthalamic nucleus [51] and the substantia nigra [52]. Periods of frank hypomania lasting a few days, a few weeks or sometimes longer have also been documented with stimulation in these and other basal ganglia regions, including the subthalamic nucleus [51, 53-57], the pallidum [58] and the substantia nigra [59]. Another relevant finding was that OCD patients treated with DBS often showed improvement in accompanying depression [41, 43, 60; see also 17]; in one trial this was seen even in the absence of improvement in obsessive-compulsive symptoms [60]. Taken together, these clinical observations formed the basis for the use of targets in treatment resistant major depression

such as the anterior limb of the internal capsule [61, 62], the nucleus accumbens [63-65] and the inferior thalamic peduncle [49].

Functional imaging also looms large in the history of the application of DBS to major depression. Mayberg and co-workers [66, 67], based both on their own [68, 69] and other's [70] PET findings, argued that there is a characteristic functional imaging change associated with depressed mood, increased activity in parts of the inferior medial frontal cortex and orbitofrontal cortex, which tends to normalize after different modalities of antidepressant treatment. This group accordingly went on to employ an electrode placement in the subgenual anterior cingulate cortex in a series of trials of DBS in treatment resistant major depression [66, 71, 72]. Other centres have also used this target [73-78].

## Localization of the disease process in schizophrenia

Selection of a target for DBS in treatment resistant schizophrenia is hampered by the same issues as in other psychiatric disorders, namely that knowledge about the biological basis or bases of the disorder are severely limited. Certainly schizophrenia is a disorder with no established neuropathology: most of the claims for histopathological changes at post-mortem – from signs of neuronal degeneration [79], to hippocampal pyramidal cell disarray [80] to disordered embryonic migration of cortical subplate neurons [81, 82] – have not stood the test of time [83]. Currently, the only replicated findings are reduced cell volume in the hippocampus and dorsolateral prefrontal cortex and, less robustly, reduced cell numbers in the dorsal thalamus [83].

Microscopic pathology may be elusive but structural imaging has established the presence of macroscopic changes beyond any doubt. These take the form of lateral ventricular enlargement, of approximately 25% by volume, coupled with a reduction of grey matter volume of approximately 4%; white matter volume reductions are smaller at around 2% [84]. The volume reductions are widespread, affecting almost all cortical and subcortical regions examined, but it is clear that they are not uniform – as shown in Table 1, they are greatest in the frontal and temporal lobe cortex and the insula; subcortically, the hippocampus one of the areas of largest reduction in the brain [84]. Lack of reduction or in some cases volume increases in basal ganglia structures are believed to be a consequence of antipsychotic drug treatment [85].

The strongest evidence for localized brain changes in schizophrenia comes from functional imaging. The original finding here was hypofrontality, reduced activity in the dorsolateral and other lateral frontal regions first reported in the 1970s and 1980s [86, 87]. Despite having been somewhat inconsistently found in later studies, hypofrontality is now supported by meta-analysis, both at rest and during performance of cognitive tasks [88, 89].

From 2000 onwards studies carried out during performance of cognitive tasks identified another functional imaging abnormality, increased activation in the prefrontal cortex – especially medially but also affecting some lateral regions –

during performance of working memory and other tasks [90-92; for a meta-analysis see 89]. The leading explanation for this 'hyperfrontality' has been that it represents a dysfunctional prefrontal cortex 'working harder to keep up' with task demands [93].

Table 1. Meta-analysis of volume reductions in selected brain regions in schizophrenia (from Haijma et al, [84])

| | Samples | Effect size (d) | % volume reduction |
|---|---|---|---|
| *Main cortical divisions* | | | |
| Frontal lobe grey matter | 17 | -0.49 (-0.64/-0.34) | 4.8 |
| Temporal lobe grey matter | 19 | -0.43 (-0.60/-0.26 | 4.1 |
| Parietal lobe grey matter | 9 | -0.31 (-0.54/-0.08) | 2.5 |
| Occipital lobe grey matter | 9 | -0.22 (-0.37/-0.07) | 2.7 |
| | | | |
| *Other cortical regions* | | | |
| Prefrontal grey matter | 16 | -0.44 (-0.48/-0.31 | 6.1 |
| Orbitofrontal cortex | 19 | -0.21 (-0.37/-0.05) | 3.0 |
| Superior temporal gyrus grey matter | 16 | -0.58 (-0.75/-0.41) | 8.2 |
| Parahippocampal gyrus | 20 | -0.24 (-0.39/-0.09) | 4.5 |
| Anterior cingulate gyrus | 29 | -0.34 (-0.46/-0.22) | 5.8 |
| Posterior cingulate gyrus | 10 | -0.32 (-0.56/-0.09) | 6.1 |
| | | | |
| *Subcortical structures* | | | |
| Hippocampus | 87 | -0.52 (-0.60/-0.44) | -6.3 |
| Amygdala | 40 | -0.31 (-0.43/-0.19) | -4.8 |
| Thalamus | 35 | -0.31 (-0.40/-0.22) | -3.4 |
| Caudate nucleus | 35 | -0.03 (-0.14/+0.07) | n/a |
| Putamen | 28 | +0.10 (-0.07/+0.26) | n/a |
| Globus pallidus | 15 | +0.26 (+0.02/+0.50) | +5.2 |
| | | | |
| Cerebellum | 20 | -0.15 (-0.30/-0.01) | 1.5 |

Recently, a third functional imaging abnormality has been documented in schizophrenia, failure of de-activation in the medial frontal cortex. First reported by Pomarol-Clotet et al [94] (see Figure 1) and Whitfield-Gabrieli et al [95], it has been found during performance of a range of tasks and appears to be a robust finding [96]. It is also possible that this finding accounts for some of the apparent hyperfrontality seen in the disorder, since both hyperactivation and failure of de-activation give the same appearance in the subtractive designs that are typically employed in fMRI studies [97]. This abnormality is presumed to reflect dysfunction in the so-called default mode network, a set of regions that are normally active at rest but which de-activate during performance of a wide range of attention-demanding tasks [98]. The medial frontal cortex (including the pregenual and subgenual portions of the anterior cingulate cortex, but also more rostral regions), along with the posterior cingulate cortex/precuneus form two prominent 'nodes' or 'hubs' of this network.

Figure 1. Failure of de-activation in the medial frontal cortex in 32 patients with schizophrenia compared to 32 healthy controls (data from Pomarol-Clotet et al [94]).

The concept of neurochemical abnormality has always been central to biological thinking in schizophrenia. Accumulating evidence that antipsychotic drugs exerted their therapeutic effects by blocking post-synaptic dopamine D2- family receptors [3], plus the fact that amphetamine and other drugs with dopamine agonist actions could induce psychosis [99], led to the dopamine hypothesis – the proposal that a functional excess of dopamine underlies the positive symptoms of the disorder, especially delusions and hallucinations. On the basis of both theoretical and practical considerations the excess of is widely considered to affect the ventral striatum [100-103].

Direct support for the dopamine hypothesis is currently strong, based on neurochemical imaging studies that have documented increased synaptic release of dopamine in the basal ganglia in drug free schizophrenic patients after amphetamine challenge [104-106], and increased presynaptic dopamine synthesis in never-treated patients [103, 107, 108]. However, it should be noted that there have two recent negative findings with respect to this latter finding [109, 110]. Another unresolved issue is that increased presynaptic dopamine synthesis appears to predominate in the associative (ie the dorsal portion of the caudate nucleus) and sensorimotor (ie the putamen) regions of the striatum rather than the ventral striatum [111].

The dopamine hypothesis implies dysfunction in the ascending dopamine projections (the 'mesotelencephalic' dopamine system) that arise from the A8, A9 and A10 cell groups in the substantia nigra and the ventral tegmental area. In the present state of knowledge, this system appears to fulfil two distinct functional roles: on the one hand is its well known involvement in motor performance and motor learning [112] (with reduced function giving rise to Parkinsonism); on the other, it is involved in reward processing, where there is strong evidence that it provides a neural signal coding for reward prediction error [113]. Importantly from the point of view of targeting DBS, the subcortical innervation of the mesotelencephalic dopamine system is circumscribed – it includes the dorsal and ventral striatum, but not (or at least to only a minor degree) the pallidum, and also the hippocampus and amygdala [114]. The dopamine hypothesis has less localizing value, however, at the cortical level, since the entire cerebral cortex receives dopamine innervation, at least in man [114].

If positive symptoms reflect a functional dopamine excess, could negative symptoms be due to a functional deficiency of the same transmitter? While theoretically attractive, it is important to note that direct evidence for the so-called revised or extended dopamine hypothesis [103] currently rests on a single study. Using the above amphetamine stimulated dopamine release neurochemical imaging paradigm, Slifstein et al [115] found significantly reduced dopamine release in the dorsolateral prefrontal cortex in drug-free schizophrenic patients compared to healthy controls; even then it was not significantly correlated with negative or other symptoms. Some additional circumstantial evidence exists, in the form of a) functional imaging studies that have found increased prefrontal cortex activity and improvement of negative symptoms after switching drug treatment from conventional to atypical antipsychotics [116]; and b) findings of an association between negative symptoms and reduced reward related activations in the ventral striatum (for a meta-analysis see Radua et al [117]. However, the former evidence has to be regarded as very indirect and the latter finding is equivocal: in Radua et al's [117] meta-analysis there was evidence for a significant inverse correlation with negative symptoms and activation in the left, but not the right ventral striatum.

The other main neurochemical theory of schizophrenia proposes that hypofunction of postsynaptic NMDA receptors leads to reduced transmission at glutamateregic synapses [118]. Since glutamate is the brain's main excitatory neurotransmitter, this proposal does not by itself implicate particular brain regions in schizophrenia. Nevertheless, the hippocampus has often been singled out in this respect,

seemingly on the basis that many of its intrinsic and extrinsic connections are glutamatergic [119]. Proponents of this approach typically argue that the hippocampus is overactive at rest but shows reduced activation during memory and other tasks [120-123]. However, this evidence is not particularly strong or convergent: functional imaging studies have had positive, negative and equivocal findings concerning increased resting hippocampal activity [124-131]. One of two meta-analyses of activations during performance of memory tasks, found evidence of reduced hippocampal activation in schizophrenia [132] but another did not [133].

## Rationales for electrode placement in schizophrenia

In the present limited state of knowledge, approaches to target selection for DBS in schizophrenia are constrained. They include on the one hand, what might be termed pragmatic considerations based on existing clinical experience with other disorders and with schizophrenia itself; and, on the other, theoretical arguments based on what is known about underlying brain dysfunction – especially localizable dysfunction – in the disorder. Elements of both these approaches are evident in the small body of evidence concerning use of DBS in schizophrenia to date.

Other than possible extrapolations from other psychiatric disorders, the pragmatic database for DBS in schizophrenia is very small. Plewnia et al [42] described a 51-year-old woman who developed obsessions and compulsions in childhood. Later on she also developed delusions, hallucinations and other psychotic symptoms. By the time she became a candidate for DBS she was severely disabled by obsessive-compulsive symptoms and also showed minor odd beliefs, paranoid ideation and disorganized behaviour, which met DSM-IV criteria for residual schizophrenia. Unilateral, right-sided DBS using an electrode placement in the right anterior limb of the internal capsule with the tip in the approximate centre of the nucleus accumbens was followed a substantial improvement in her obsessive-compulsive symptoms that took place over a matter of weeks. There was a concomitant improvement psychosocial functioning. Importantly for the present purposes, there was no worsening of the patients' residual psychotic symptoms.

In contrast, Graat et al [134] reported a 31-year-old man with treatment-resistant major depression who was also treated with a nucleus accumbens electrode placement. Although his depressive symptoms showed a good response, several months later he developed persecutory and other delusions. These disappeared over a few hours when the voltage was lowered. However, this caused his depression to return and it then proved difficult to increase the voltage again without the delusions re-appearing. Eventually, however, a balance between control of symptoms and emergence of delusions was achieved.

Two of the three formal trials of DBS in treatment resistant schizophrenic patients have relied almost entirely on theoretical considerations. Thus, Daskalakis and co-workers in Toronto [18] developed a protocol for patients with a clinical picture dominated by negative symptoms; this involved delivering DBS to either the ventral tegmental area (N=3) or the nucleus accumbens (N=3). The rationale was that

reduced function in these regions underlies negative symptoms – ie the revised or extended dopamine hypothesis – and would be corrected by DBS. This proposal, it should be noted, assumes excitatory, rather than inhibitory effects of DBS. Unfortunately, this trial was abandoned due to lack of recruitment.

A second trial, which is currently recruiting in Baltimore [19], targets the substantia nigra pars reticulata. Based on the anatomical connections of this structure, the investigators argued that local inhibition produced by DBS would result in disinhibition of the mediodorsal nucleus of the thalamus. Given that the mediodorsal thalamic nucleus provides afferents to the frontal lobe cortex, a normalization of schizophrenia-related hypofrontality might be expected to follow, with consequent beneficial effects on symptoms and perhaps also on cognition. The investigators' theoretical model additionally drew on EEG studies and neuropathological findings in the thalamus [135].

The Sant Pau/FIDMAG trial [20, 21] combined theoretical considerations with findings from the use of DBS in other psychiatric disorders. It aimed to recruit 8 patients with treatment resistant schizophrenia, who had additionally failed to respond to (or were intolerant of) clozapine. In line with definitions of treatment resistance, the patients were required to show persistent positive symptoms, but possible effects of DBS on negative symptoms were also of interest. The patients were to be assigned to electrode placements either in the nucleus accumbens (N=4) or the subgenual medial frontal cortex (N=4). The decision to use these two implantation sites was partly pragmatic, ie it explicitly reflected the fact that they had previously been employed in OCD and/or major depression. On theoretical grounds, both sites could also be considered to be in some sense loci of excessive neuronal activity in schizophrenia, and so potentially susceptible to the functional inhibitory effects of DBS. In the case of the nucleus accumbens, the excessive activity was presumed to be the result of increased dopaminergic activity, in line with the dopamine hypothesis. A further factor relevant to the choice of this target was the fact that the ventral striatum receives major afferent input from the hippocampus [136], which, as noted above, has sometimes been considered to be a key structure in the pathophysiology of schizophrenia, even thoughfunctional imaging evidence does not strongly support the increased activity that has been argued to be a prerequisite for a DBS electrode placement here [137].

For the subgenual anterior cingulate cortex electrode placement, the theoretical rationale was the fMRI finding of failure of de-activation in the medial frontal in schizophrenia. This was considered to make this region a more appropriate target for the local inhibitory effects of DBS than the dorsolateral prefrontal cortex, where the predominant finding is reduced activity both at rest and during cognitive task activation. Choice of a subgenual placement was mainly determined on pragmatic grounds, ie that this was the site used by Mayberg and co-workers for major depression. However, another consideration was that this region has important connections with wide areas of the limbic system [138] and the ventral striatum [139].

Seven patients completed the trial (one patient with a nucleus accumbens placement did not proceed to stimulation due to post-operative complications that eventually led to the electrodes being removed). The combined group of patients

showed improvement over a six-month (or longer in some cases) open treatment phase, and was seen particularly in positive symptoms. Four patients who met predetermined improvement criteria all worsened when the current was switched off under double-blind conditions in a 24-week crossover phase. Improvement appeared to be more marked with the nucleus accumbens placement, with two of the three patients undergoing nearly complete remission of positive symptoms, though they both later developed significant side-effects (apathy/negative symptoms and mood instability, respectively).

## Conclusion

After positive experience with OCD and major depression, it was inevitable that attention would turn to the possibility of using DBS in schizophrenia, where treatment resistance is common and the therapeutic options for such patients are few. The main challenge has been where to site the electrodes in a disorder which, notwithstanding a vast research effort, currently provides only slender clues to the nature of its underlying pathology. However, as reviewed in this article, sites of localizable brain dysfunction can be identified with some confidence in the disorder, and these can be and have been exploited to guide electrode placement for DBS.

The best-established site of brain dysfunction in schizophrenia is the DLPFC. Unfortunately, it is not at all clear that this region could ever represent a meaningful target for DBS – the evidence points overwhelmingly to the dysfunction here taking the form of impaired activity, and so intervention is hazardous in view of DBS's local lesion-like effects. An alternative possibility might be to target regions of the prefrontal cortex that have been found to show hyperfrontality. Such a strategy is probably also not viable: not only is it possible that some of the regions where hyperfrontality has been found (eg in the medial frontal cortex) are actually manifesting failure of de-activation, but also the abnormality is believed, according to the leading theoretical interpretation, to reflect the response of diseased and hypofunctional cortical tissue 'working harder to keep up' [93]. Accordingly, the medial frontal cortex, where the abnormality takes the form of increased activity in the sense of failure of de-activation, appears to be the only realistic cortical location for DBS in schizophrenia.

The next most firmly established finding in schizophrenia is neurochemical, that of a functional dopamine excess, caused by increased synthesis and/or release and giving rise to the positive symptoms of the disorder. The dopamine hypothesis is of obvious relevance for DBS target selection because of its targetability – the mesotelencephalic dopamine system arises from a localized midbrain location and ascends to innervate discrete subcortical structures, of which the nucleus accumbens (as part of the ventral striatum) currently seems the strongest candidate. In fact, this site has already been chosen in two trials. Functional dopamine excess also has the desirable feature of implying pathologically increased function. Here, however, there is a caveat: although the role of ventral striatal dopamine in reward processing is well established [113], and the concept of aberrant reward prediction error forms a plausible theoretical basis for positive

schizophrenic symptoms [102], the ventral striatum has been consistently found to show reduced rather than activation in schizophrenia when imaged in studies using reward paradigms [117]. Interestingly, an alternative, less conflicted site for a DBS intervention aimed at correcting an overactive mesotelencephalic dopamine system in schizophrenia exists in the form of the ventral tegmental area, as proposed in the now abandoned Toronto trial [18].

In contrast, the so-called revised or extended dopamine hypothesis, that a functional dopamine deficiency underlies negative symptoms [103], emerges as resting on weak empirical foundations, although it would be wrong to dismiss the proposal altogether. Another complicating factor is the fact that the location of proposed deficiency is not clear – studies to date have implicated two different brain regions, the DLPFC [115] and the ventral striatum [117].

Similar reservations apply to another proposed candidate for DBS in schizophrenia, the hippocampus. The idea that this structure is a key site of pathology in schizophrenia depends on several pieces of circumstantial evidence: that it shows one of the largest volume reductions in the disorder [84]; that some of its intrinsic circuits are glutamatergic [119]; and that it is a subcortical destination of the mesotelencephalic dopamine projection [114]. Some of this evidence, it should be noted, is contradictory. Thus, as a site of mesotelencephalic dopamine innervation it could be argued that the hippocampus would be maintained in an excessively stimulated state in schizophrenia; on the other hand, if there is a glutamate deficiency in the disorder, its function would be impaired. Regardless of the theoretical arguments, functional imaging findings to date have not convincingly documented either increased activity at rest or reduced activation during task performance.

Clearly, until there is definitive knowledge about pathophysiological basis of schizophrenia, pragmatic considerations will continue to play a part in target selection for DBS, as they have in other psychiatric disorders. The single case report by Plewnia et al [42], which found that nucleus accumbens DBS at least did not worsen psychotic symptoms in a patient with residual schizophrenia, is of relevance here. On the other hand a second case report [134] suggests that this may not always be the case. With the completion of the first trial in schizophrenia, the pragmatic database has now expanded significantly. The indications from the Sant Pau/FIDMAG trial are that a nucleus accumbens placement may alleviate and seems not to exacerbate positive psychotic symptoms. The subgenual anterior cingulate cortex is currently less promising but is by no means ruled out as a potential target.

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## 10.5. ESTUDIO 6

# Gray matter microstructural alterations in schizophrenia patients with treatment-resistant auditory verbal hallucinations

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## Abstract

**Objective:** Treatment-resistant auditory verbal hallucinations (TRAVH) are a relatively prevalent and devastating symptom in patients with schizophrenia (SCZ). Even though its pathological mechanisms are poorly understood, they seem to differ from those underlying non-hallucinating SCZ.

**Methods:** In this work we characterize structural brain changes in SCZ patients with TRAVH. With respect to non-hallucinating patients and healthy controls, we studied macrostructural gray matter changes through cortical thickness and subcortical volumetric data. Additionally, we analyzed microstructural differences across groups using intracortical and subcortical mean diffusivity data. This latter imaging metric has been suggested to detect incipient neuronal damage, as water can diffuse more freely in regions with reduced neural density.

**Results:** We found brain macrostructrural and microstructural alterations in SCZ patients with TRAVH (n=29), both with respect to non-hallucinating (n=20) patients and healthy controls (n=27). Importantly, a microstructural –rather than macrostructural– compromise was found in key brain regions such as the ventral anterior cingulate cortex (ACC), the Nucleus Accumbens (NAcc) and the hippocampus. These microstructural alterations correlated, in turn, with clinical severity. Treatment-resistant patients also showed accentuated age-related cortical deterioration and an abnormal longitudinal loss of cortical integrity over a one-year period.

**Conclusions:** These findings highlight the potential role of microstructural imaging biomarkers in SCZ. Notably, they could be used to detect and to monitor subtle gray matter alterations in critical brain regions such as deep brain stimulation targets. Moreover, our results support the existence of a more aggressive and active pathological mechanism in patients with TRAVH, providing new insight into the aetiology of this debilitating illness.

## Introduction

Schizophrenia (SCZ) is a highly prevalent and severe psychiatric disorder with devastating mental and social consequences. It is characterized by a wide range of psychotic positive, negative and cognitive symptoms. Up to 30% of patients with schizophrenia fail to respond adequately to available antipsychotics and the persistence of auditory verbal hallucinations are a core symptom of this condition (treatment resistant schizophrenia, TRS) [1].

The etiology of SCZ is complex, and probably involves multiple mechanisms including neurodevelopmental abnormalities and subtle neurodegenerative processes(2) , which is still a matter of debate. In particular, the etiology of treatment resistant auditory verbal hallucinations (TRAVH) has been scarcely addressed. Differential pathological mechanisms might be involved TRAVH, probably overlapping those described in TRS where extensive frontotemporal gray matter volume reductions have been identified(3,4). Most patients with TRS show persistent verbal hallucinations, which have fostered the research of non-pharmacological treatments such as neurostimulation(5). Hence, an in-depth characterization of cortical alterations in TRAVH is still needed to further comprehend its underlying neural mechanisms, aiding in the design of novel therapeutic strategies.

The study of cortical alterations in schizophrenia and AVH can be conveniently assessed by high-resolution and radiation-free magnetic resonance imaging (MRI) indicators. Previous works have investigated MRI differences between TRAVH and non-hallucinating (nH) patients(6). Some evidence have even reported subtle glutamate increments within frontal and temporal regions in TRAVH, which may induce excitotoxicity leading to progressive neuronal damage or death(7).

However, detecting subtle signs of cortical deterioration with this technique may be challenging. Cortical grey matter (GM) assessment via voxel-based-morphometry (VBM) or cortical thickness (Cth) is highly specific but it may not be sufficiently sensitive to detect subtle cortical alterations. White-matter (WM) integrity estimated from diffusion tensor imaging (DTI) does not directly assess the loss or dysfunction of non-projecting cortical neurons. Furthermore and importantly, the clinical or biological interpretation of functional MRI measures such as resting-state connectivity is challenging due to its complex nature and meaning, and especially to the presence of compensatory mechanisms and partial volume effects.

Therefore, novel neuroimaging biomarkers capable of detecting subtle structural alterations within the cerebral cortex of SCZ patients need to be validated. Recently, an increase in the diffusivity of water molecules within the cerebral cortex has been suggested to reflect the loss of cortical neurons, even in the absence of cortical thinning(8). Conceptually, reduced neural density in the cerebral cortex allows regional water molecules to increase their mobility. Quantitatively, this phenomenon can be measured using a surface-based image analysis from DTI data, and is termed as intracortical mean diffusivity (intracortical MD). Alterations in this imaging measure are referred as cortical microstructural alterations(9). In neurodegenerative diseases, this metric has shown significant advantages in terms of effect size and sensitivity in detecting cortical neurodegeneration(9–12). However, cortical microstructural alterations in SCZ, and especially in patients with persistent AVH, have not been addressed.

In this work we characterize cortical microstructural changes in the spectrum of patients with persistent AVH, patients without AVH and healthy controls. We concomitantly study differences in cortical thickness (i.e cortical macrostructure) in order to better characterize the role of intracortical MD as a potential imaging biomarker in this clinical context.

Importantly, we performed both cross-sectional and longitudinal neuroimaging analyses. A major limitation of cross-sectional neuroimaging studies in SCZ is that they do not allow concluding about the origin of the imaging differences. For instance, reductions in cortical GM have been frequently reported in SCZ patients(13). Whether this structural brain compromise is a strict consequence of an abnormal neurodevelopment, or rather an active neurodegenerative process is also involved, cannot be addressed in a cross-sectional imaging design.

We hypothesize that significant cortical macrostructural and microstructural alterations are present in SCZ patients with respect to healthy controls. In detail, we hypothesize that a more extensive cortical compromise is observed in patients with persistent AVH, who would also show a higher longitudinal loss of cortical integrity suggestive of an active neural loss.

**Aim of the study**

The aim of the study is to characterize cortical microstructural changes in patients with persistent AVH, patients without AVH and healthy controls. In addition, this study also aims to investigate differences in cortical thickness in order to better characterize the role of intracortical MD as a potential imaging biomarker.

## Materials and Methods

Sample and assessments

Forty-nine patients fulfilling DSM-IV-TR criteria for schizophrenia (SCZ) were recruited from the Psychiatry Department at the Hospital de Sant Pau in Barcelona, Spain. The recruitment was based upon revision of clinical records and a clinical interview before entering in the study, to include patients with TRAVH –defined as daily presence of AVH in the past year, in face of at least two adequate trials of antipsychotic drugs (with different D2 binding profile) at equivalent doses to 600 mg/ day of chlorpromazine–. Patients with no history of hallucinations and who showed good response to treatment (i.e. not showing acute psychotic symptoms in the last 12 months) were also included. Exclusion criteria were neurological disorders that could explain the present psychopathology, mental retardation and substance use (except alcohol or tobacco).

Accordingly, two SCZ groups were defined: SCZ-TRAVH (n=29)); and SCZ-nH (n=20), which included non-hallucinating patients. Additionally, a group of 27 healthy controls (HC) from the community were included in this study. A subset of 17 HC, 11 SCZ-nH and 10 SCZ-TRAVH participants could be followed up and a second T1-MRI and DTI imaging scan was obtained approximately one year after the baseline scan (average of 0.97±0.15 years).

Sociodemographic data was registered for all participants, included age, sex and educational level. Education was quantified using a 1 to 5 range (1: no studies, 2: primary education, 3: secondary education until 16 years, 4: secondary education until 18 years, 5: university degree). For SCZ patients, clinical symptoms were evaluated using the positive and negative syndrome scale (PANSS). Within the SCZ-TRAVH group, we quantified the severity of the hallucinations using the Psychotic Symptom Rating Scales (PSYRATS). To simplify, we focused on its total score and the disruption of life item, as the latter specifically reflects the impact of hallucinations in daily life.

This study followed the tenets of the Declaration Helsinki. The local research ethics committee approved this study and all subjects and/or legal representative provided written informed consent prior to participation. All participants or their representatives could read and understand the consent form.

Neuroimaging acquisition and preprocessing

All subjects underwent 3-Tesla MRI in a Philips Achieva station. T1-weighted MRI acquisition was performed using a dedicated axial T13D-MPRAGE MRI using the following parameters: TR/TE=13/7.4ms, flip angle=8º, field of view = 23 cm23 cm, in-plane resolution of 256x256 and 1-mm slice thickness. Diffusion Tensor Imaging (DTI) scans were also acquired, using the following parameters: TR/TE=10250/55ms, flip angle=90º, acquisition matrix of 144x144,b-value=800, 15 directions and a 1.75mm slice thickness.

Cortical macrostructural integrity was assessed in terms of vertex-wise cortical thickness (Cth) information from T1-MRI scans using the FreeSurfer 6.0 software package (https://surfer.nmr.mgh.harvard.edu/). The procedure of surface-based cortical reconstruction of structural MRI images and the derivation of Cth data has been fully described elsewhere[11].

We derived vertex-wise intracortical MD information from DTI scans using a previously-reported pipeline(12). Briefly, MD maps were computed and then co-registered with the associated T1-MRI scans. On continuation, after applying partial volume correction, MD values were sampled halfway between the white and pial cortical surfaces to obtain vertex-wise intracortical MD data. Of note, this procedure ensures that MD values are independent of cortical thickness in each vertex. Therefore, observing MD differences in this setting would imply that they are independent of a possibly underlying cortical thinning.

We studied Cth and MD differences across groups both cross-sectionally (at baseline) and longitudinally (relative changes over a one-year follow-up period). Longitudinal Cth and MD changes were computed using the FreeSurfer longitudinal pipeline and measured in terms of symmetrized percent change ($SPC_{Cth}$ and $SPC_{MD}$), a robust measure that has shown increased statistical power in this context(12). In this context, negative $SPC_{Cth}$ values indicate a longitudinal reduction of cortical thickness, and positive $SPC_{MD}$ values indicate a longitudinal increase of MD. Accordingly, lower $SPC_{Cth}$ and higher $SPC_{MD}$ values represent a longitudinal loss of cortical integrity. Finally, and for the sake of completeness, we also compared

subcortical volumetric and MD data across groups, which were computed using standard FreeSurfer procedures.

Statistical analyses

Clinical, sociodemographic, and subcortical quantitative data were compared across groups using two-sample t-test analysis for continuous variables, $X^2$ for categorical variables, and Mann-Whitney U Test for ordinal variables.

Regarding neuroimaging differences across groups, cortical vertex-wise measures (Cth,$SPC_{Cth}$,MD, $SPC_{MD}$) were first smoothed using a Gaussian kernel of 15mm full-width-at-half-maximum to increase the signal-to-noise ratio(9). Then, a vertex-wise general linear model (GLM) was performed to compare these measures across groups, using age, sex and education as covariates of no interest. Clusters surviving $p<0.05$ and family-wise error (FWE) correction for multiple-comparison using a Monte-Carlo simulation with 10000 repeats were considered significant(12). Subcortical volumetric and average MD data in common subcortical structures was also compared across groups using t-tests, and then further controlling for the same confounding factors and performing a false-discovery rate (FDR) correction.

Lastly, we explored the possible clinical translation of the observed neuroimaging differences between the SCZ-TRAVH and SCZ-nH groups. To do so, we first computed average Cth and MD values at the regions showing significant differences between those groups at baseline. Then, within the SCZ-TRAVH group, we then performed a Pearson's and Spearman's correlation analyses between the imaging differences and PANSS and PSYRATS scores, respectively. Additionally, in these regions, we investigated the presence of an age-by-group interaction effect suggestive of an accentuated age-related structural compromise in one of the groups. A $p<0.05$ was considered significant.

## Results

Table 1 summarizes the sample's sociodemographic and clinical data. Regarding socio-demographic profiles, significant differences were only found in terms of educational level between HC and SCZ-TRAVH patients. With respect to SCZ-nH, SCZ-TRAVH had longer illness duration, increased PANSS scores, and higher medication dosage. PSYRATS data was not available for 5 patients of the SCZ-TRAVH group.

| HC | SCZ-nH | SCZ-TRAVH | Significance (p-val) |
|---|---|---|---|

| | | | TRAVH | HC vs SCZ-nH | HC vs SCZ-TRAVH | SCZ-TRAVH vs SCZ-nH |
|---|---|---|---|---|---|---|
| **n** | 27 | 20 | 29 | | | |
| **Age [years]** | 37.5±9.9 | 37.2±8.3 | 38.6±9.4 | 0.89 | 0.68 | 0.58 |
| **Sex [% female]** | 37% | 35% | 31% | 0.88 | 0.64 | 0.77 |
| **Education** | 4.1±0.6 | 3.6±1.3 | 3.5±0.7 | 0.20 | **0.003*** | 0.86 |
| **Illness duration [years]** | NA | 8.1±6.0 | 13.1±9.3 | NA | NA | **0.039*** |
| **PANSS** | | | | | | |
| **Positive** | NA | 12.2±4.7 | 19.6±5.5 | NA | NA | **<0.001*** |
| **Negative** | NA | 14.7±4.5 | 21.7±5.0 | NA | NA | **<0.001*** |
| **General** | NA | 28.6±6.8 | 34.5±7.2 | NA | NA | **0.01*** |
| **Total** | NA | 55.6±13.9 | 75.8±15.2 | NA | NA | **<0.001*** |
| **PSYRATS** | | | | | | |
| **Disruption of life item** | NA | NA | 2.2±1.1 | NA | NA | NA |
| **Total** | NA | NA | 26.1±4.7 | NA | NA | NA |
| **Medication** | | | | | | |
| **Total CPZ mEq** | NA | 338.9±201 | 1001.8±503 | | | **<0.001*** |
| **Typical antipsychotics (%)** | NA | 5% | 7% | NA | NA | 0.78 |
| **Atypical antipsychotics (%)** | NA | 75% | 93% | NA | NA | 0.08 |
| **Anticholinergic (%)** | NA | 6% | 22% | NA | NA | 0.17 |
| **Benzodiazepines (%)** | NA | 40% | 63% | NA | NA | 0.15 |
| **Antidepressants (%)** | NA | 13% | 33% | NA | NA | 0.16 |

**Table 1. Clinical and demographic information across groups. Values are expressed as mean±standard deviation or percentage.NA: not applicable. *p<0.05**

Figure 1 displays the set of cortical macro (Cth) and microstructural (intracortical MD) differences across groups. Both SZC groups showed reduced Cth and increased intracortical MD with respect to HC. SZC-nH patients showed reduced Cth in the left caudal anterior cingulate cortex (ACC), right inferior and superior frontal gyrus, right medial orbitofrontal cortex (OFC), right superior temporal and right interior-parietal/lateral-occipital regions. At the same time, SZC-nH patients showed

increased MD in the left ventral ACC, left medial and lateral orbitofrontal cortex, left precentral gyrus, right superior and medial temporal gyrus, and right temporal pole.

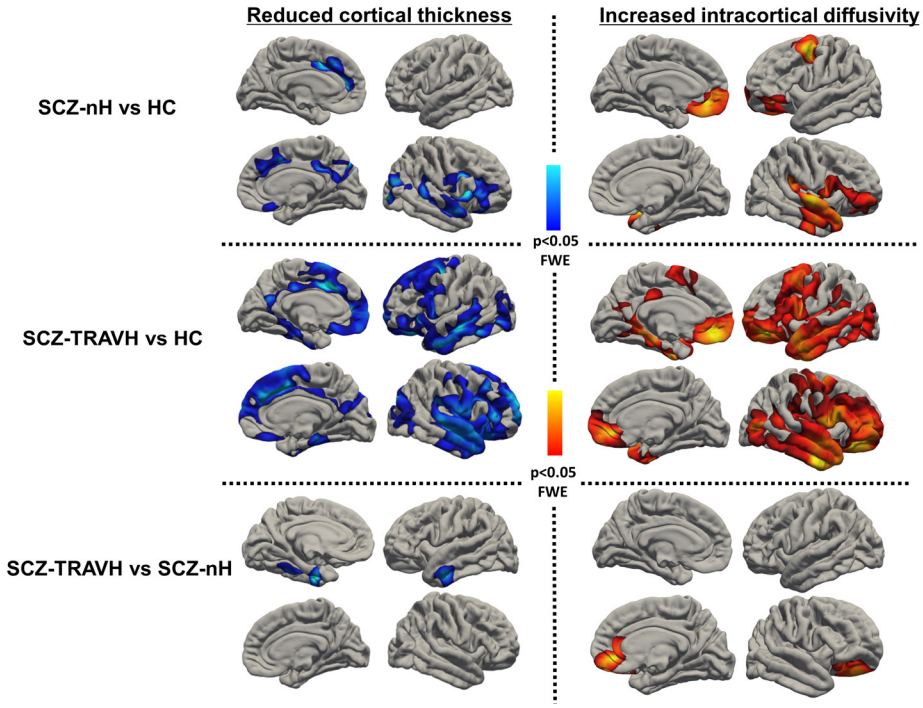


**Figure 1. Cortical thickness and intracortical diffusivity differences across groups at baseline, controlling for age, sex and educational level (p<0.05 corrected).**

SCZ-TRAVH patients showed widespread cortical thinning and increased intracortical MD with respect to HC. Topographically, the pattern included the set of regions showing differences between SZC-nH and HC, but also extended to bilateral parahippocampal gyri, middle and posterior-cingulate regions, supramarginal and parieto-occipital regions. In the ventral ACC and orbitofrontal regions, MD differences were more pronounced that Cth differences. In contrast, superior-frontal Cth differences were more pronounced than MD differences.

When comparing SCZ-TRAVH and SCZ-nH groups, only a Cth cluster located in the right fusiform/middle temporal gyrus (MTG) and a MD cluster located in the ventral-ACC/OFC region survived multiple comparison correction.

Within the SCZ-TRAVH group, a significant association was observed between MD increases in the ventral-ACC/OFC cluster and the disruption of life item of the PSYRATS scales (Spearman's rho=0.49, p=0.016). This item was not associated with cortical thinning in the fusiform/MTG cluster (p=0.44), as shown in Figure 2. No significant correlations were found with PANSS scores in these regions. Accentuated age-related cortical thinning was not observed in the fusiform/MTG cluster in the SCZ-TRAVH group with respect to SZC-nH. However, SCZ-TRAVH patients showed age-

related MD increases in the ventral-ACC/OFC cluster (r=0.41,p=0.026) while SZC-nH did not (r=-0.13,p=0.56, age-by-group interaction p=0.047).

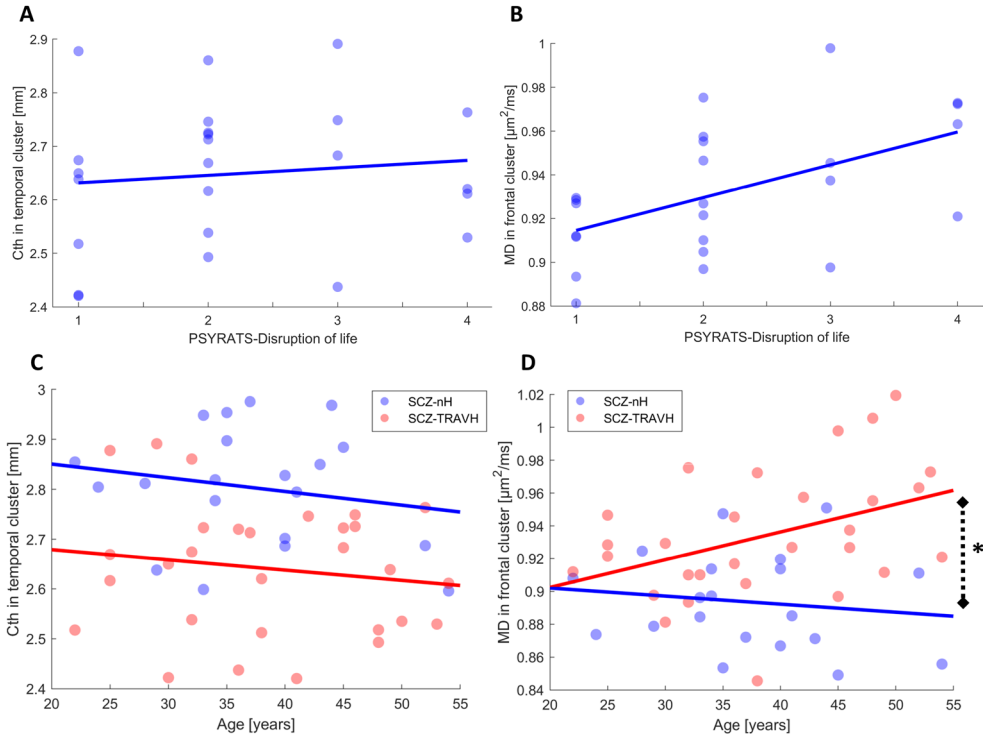


**Figure 2. Within the SCZ-TRAVH group, there was a lack of association between temporal cortical thinning and the PSYRATS-disruption of life item (A), but a significant association was found with this item and intracortical MD in the ventralACC/OFC cluster (B). C and D: Age-by-group interactions on cortical integrity in regions showing Cth and MD differences between the SCZ-TRAVH and SCZ-nH groups. C: lack of significant age-by-group interaction on Cth in the temporal cluster. D: significant age-by-group interaction on MD in the frontal cluster (*p<0.05), indicating that age-related increases in MD were more pronounced in the SCZ-TRAVH group.**

Table 2 shows subcortical volumetric and MD information across groups. With respect to HC, SCZ-nH patients showed lower left hippocampus volume and higher MD, and also showed lower right putamen and nucleus Accumbens (NAcc) MD. SCZ-TRAVH patients showed the following significant differences with respect to HC: increased left Pallidum and right caudate volume, lower hippocampal volume bilaterally, and increased MD in the left thalamus, bilateral hippocampi and right amygdala.

| | | | | | | Significance (p-val) | | |
|---|---|---|---|---|---|---|---|---|
| **Measure** | **Side** | **Region** | **HC** | **SCZ-nH** | **SCZ-TRAVH** | **HC vs SCZ-nH** | **HC vs SCZ-TRAVH** | **SCZ-TRAVH vs SCZ-nH** |
| **Volume (ml)** | **Left** | **Caudate** | 3510.0±397.5 | 3407.0±504.9 | 3701.7±383.8 | 0.44 | 0.07 | **0.02†‡** |
| | | **Putamen** | 5010.8±442.0 | 4933.6±647.3 | 5151.0±530.0 | 0.63 | 0.29 | 0.20 |
| | | **Accumbens** | 510.8±123.7 | 481.6±135.5 | 484.4±130.4 | 0.45 | 0.44 | 0.94 |
| | | **Pallidum** | 2135.2±172.6 | 2094.5±233.3 | 2265.1±237.0 | 0.49 | **0.02†‡** | **0.02†‡** |
| | | **Amygdala** | 1472.1±183.2 | 1434.2±220.7 | 1453.3±184.7 | 0.52 | 0.70 | 0.74 |
| | | **Thalamus** | 8031.7±642.6 | 7692.0±725.6 | 7702.4±714.3 | 0.10 | 0.08 | 0.96 |
| | | **Hippocampus** | 4209.1±411.5 | 3930.4±436.5 | 3931.7±402.8 | **0.03†‡** | **0.01†‡** | 0.99 |
| | **Right** | **Caudate** | 3645.5±406.5 | 3608.3±530.7 | 3870.7±415.3 | 0.79 | **0.04†** | 0.06‡ |
| | | **Putamen** | 4958.0±446.7 | 4984.6±649.6 | 5088.0±504.8 | 0.87 | 0.31 | 0.53 |
| | | **Accumbens** | 568.0±71.6 | 538.0±114.8 | 546.2±109.3 | 0.28 | 0.38 | 0.80 |
| | | **Pallidum** | 2128.6±219.6 | 2068.6±203.8 | 2199.2±244.5 | 0.35 | 0.26 | 0.06 |
| | | **Amygdala** | 1644.4±230.7 | 1579.3±234.0 | 1593.9±160.3 | 0.35 | 0.34 | 0.80 |
| | | **Thalamus** | 7406.0±579.8 | 7219.7±668.5 | 7231.6±749.9 | 0.31 | 0.34 | 0.95 |
| | | **Hippocampus** | 4270.9±361.1 | 4081.6±488.3 | 4030.7±460.1 | 0.13 | **0.04†** | 0.71 |
| **MD (μm²/ms)** | **Left** | **Caudate** | 0.77±0.03 | 0.76±0.03 | 0.78±0.04 | 0.58 | 0.14 | 0.09 |
| | | **Putamen** | 0.75±0.02 | 0.74±0.03 | 0.76±0.03 | 0.08 | 0.24 | **0.01†‡** |
| | | **Accumbens** | 0.84±0.05 | 0.84±0.03 | 0.85±0.05 | 0.62 | 0.47 | 0.21 |
| | | **Pallidum** | 0.75±0.04 | 0.73±0.03 | 0.74±0.04 | 0.12 | 0.18 | 0.75 |
| | | **Amygdala** | 0.86±0.05 | 0.88±0.07 | 0.87±0.03 | 0.35 | 0.40 | 0.62 |
| | | **Thalamus** | 0.81±0.02 | 0.82±0.04 | 0.83±0.03 | 0.24 | **0.03†** | 0.55 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | **Hippocampus** | 1.08±0.05 | 1.13±0.10 | 1.17±0.09 | **0.03†‡** | **<0.001†‡** | 0.10 |
| | **Right** | **Caudate** | 0.85±0.03 | 0.84±0.03 | 0.86±0.04 | 0.12 | 0.77 | 0.12 |
| | | **Putamen** | 0.80±0.02 | 0.78±0.03 | 0.79±0.03 | **0.01†‡** | 0.07 | 0.40 |
| | | **Accumbens** | 0.86±0.05 | 0.83±0.04 | 0.86±0.03 | **0.03†‡** | 0.58 | **0.02†‡** |
| | | **Pallidum** | 0.81±0.05 | 0.78±0.05 | 0.77±0.04 | 0.053 | **0.01†‡** | 0.68 |
| | | **Amygdala** | 0.85±0.04 | 0.86±0.05 | 0.88±0.04 | 0.46 | **0.005†‡** | 0.09 |
| | | **Thalamus** | 0.84±0.02 | 0.85±0.03 | 0.85±0.03 | 0.45 | 0.18 | 0.74 |
| | | **Hippocampus** | 1.08±0.05 | 1.11±0.06 | 1.16±0.07 | 0.07‡ | **<0.001†‡** | **0.03†‡** |

**Table 2. Comparison of subcortical volumes and MD values at baseline across groups. Values are expressed as mean±standard deviation. Bold: t-test p<0.05. †FDR-corrected. ‡ p<0.05 controlling for age, sex and education.**

Concerning subcortical differences between both SCZ groups, SCZ-TRAVH patients showed increased left caudate and Pallidum volumes, and increased MD in the left putamen, right NAcc and right hippocampus. In this case, there was no significant age-by-group effect on subcortical integrity in these regions ($p>0.10$).

Regarding longitudinal neuroimaging differences, no significant cortical regions showed increased annual cortical thinning or higher intracortical MD increases in the SCZ-nH group with respect to HC. In contrast, SCZ-TRAVH patients showed increased cortical thinning in a parahippocampal cluster, and higher MD increase in a paracentral/posterior cingulate cluster, both with respect to the SCZ-nH and HC groups (Fig 3). There were no subcortical regions showing significant differences in volume loss or average MD increase across groups.

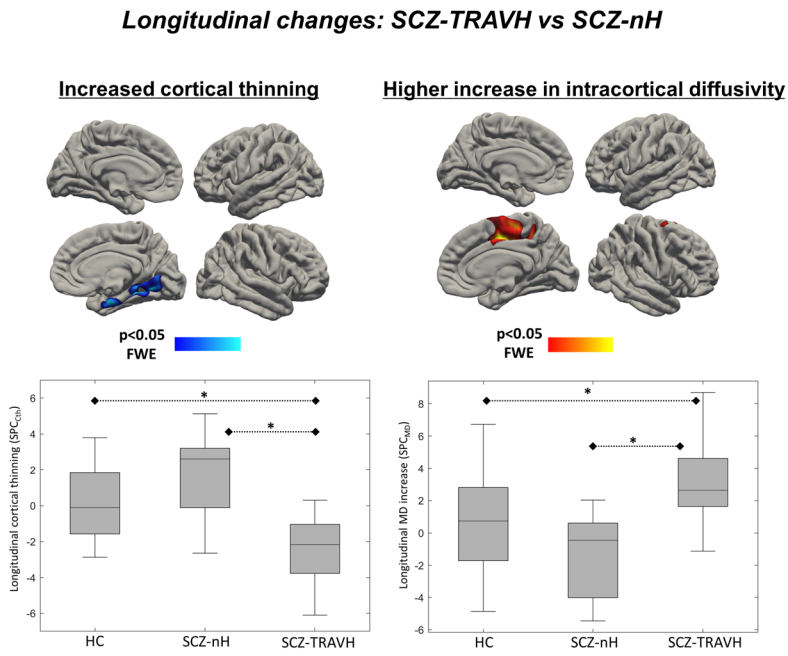


**Figure 3. Top: longitudinal Cth and MD differences between SCZ-TRAVH and SCZ-nH, controlling for age, sex and educational level (p<0.05 corrected). Bottom: boxplots illustrating the effect of the phenomena by showing average Cth and MD changes across groups in each significant cluster. *p<0.05.**

Importantly, most of the presented results remained significant after controlling for differences in medication dosage, except for temporal Cth differences at baseline (which became close to significance: p=0.08), left Caudate and Pallidum volume differences (p=0.43 and p=0.11, respectively), and right hippocampus MD differences (p=0.33). Similarly, when further controlling for illness duration differences, most results remained significant except for baseline temporal Cth (p=0.17) and left Pallidum (p=0.06) volume differences.

## Discussion

We found brain macrostructrural and microstructural alterations in schizophrenia patients with persistent AVH. Importantly, a microstructural –rather than a macrostructural– compromise was found in key brain regions in SCZ such as the ventral ACC, the NAcc and the hippocampus. In addition, treatment-resistant patients, in contrast to patients without AVH, also showed an abnormal longitudinal loss of cortical integrity over a one-year period.

The observed pattern of cortical thinning in SCZ patients with respect to healthy controls is consistent with previous works(15). Cth differences in treatment-resistant patients are less characterized, but a compromise of the temporal lobe, which was

also found in this work, has been suggested to play an important role(16). Temporal lobe alterations have been associated with treatment resistance in SCZ, and specifically with persistent AVH(17,18).

Independently of these macrostructural differences, cortical microstructure as measured by intracortical MD was also altered in SCZ patients. Of note, ventral ACC and OFC alterations were observed primarily at the microstructural level. In fact, in these regions, treatment-resistant patients showed increased MD –but not cortical thinning– with respect to non-hallucinating patients. Furthermore, increased MD in the ventral ACC region correlated in turn with a higher score on the disruption of life item of the PSYRATS scale, reinforcing the clinical role of this microstructural alteration.

This is of particular relevance as recent works have found that treatment resistant patients showed increased ACC glutamate levels compared to responsive SCZ patients(4). Moreover, elevated glutamate ACC levels in drug-naïve First Episode SCZ seems to be associated with poor antipsychotic response, suggesting the existence of this biological alteration before treatment initiation(19). High levels of extracellular glutamate have been related to excitotoxic cell death(20), and altered glial glutamate transporters may also represent a potential underlying mechanism in SCZ and other psychiatric disorders(21). Even though we did not measure glutamate levels, the observed increments of MD in non-projecting neurons could suggest early neuronal loss due to elevated glutamate levels in cortical regions such as the ACC.

Our findings may partially explain the mixing effects of neuromodulation treatments for TRAVH. On the one hand, the variety of results using transcranial magnetic stimulation may be interpreted as though this treatment may not target the inner mechanistic level that induces AVH(22). On the other hand, the ventral ACC has been recently tested, with promising results for AVHs, as a deep brain stimulation (DBS) target both in animal models of SCZ and in treatment resistant patients(23,24). In the light of our results, this invasive neurostimulation procedure could be targeting the microstructural ACC alterations observed in the current study.

In addition, cortical microstructural abnormalities in the ventral ACC region increased with age in treatment-resistant patients, but not in the non-hallucinating group. This phenomenon was not observed in the rest of brain regions showing significant alterations between SCZ groups. This result highlights the potential value of ventral ACC MD as an imaging biomarker in SCZ, and also reinforces the role of this region as stimulation target in TR patients. Additionally, it also suggests the existence of an active process promoting neural damage, as age-related neurodegeneration in anterior frontal regions in the 30-45 years range is not expected(25). Our longitudinal neuroimage analysis confirmed an accentuated loss of cortical integrity in treatment-resistant patients. Longitudinal increases in cerebral damage were more pronounced in TRAVH than in nH patients and, importantly, were also abnormal with respect to healthy controls. Taken together, a possible interpretation of these findings is that whereas non-hallucinating SCZ may have a purely neurodevelopmental origin, in treatment-resistant SCZ a coexisting neurodegenerative component may exist, contributing to the maintenance of psychotic symptoms.

Subcortical alterations were also observed across groups, both in terms of volumetric and MD differences. With respect to healthy controls, more subcortical regions were

affected in the treatment-resistant than in the non-hallucinating group. Notably, when comparing both SCZ groups, a microstructural compromise was observed in the NAcc and hippocampus regions in treatment-resistant patients. This reinforces the idea that alterations in the cortico-striatal pathway are probably involved in the aberrant processes that generates psychotic symptoms(26). Again, these subcortical MD differences were observed in the absence of volumetric differences. Being the NAcc another DBS target for treatment-resistant SCZ(24), and considering the fact that the hippocampus plays a critical role in SCZ(27), this result further highlights the importance of the observed MD differences.

From an imaging perspective, this particular surface-based analysis pipeline of MD data has been mostly applied in neurodegenerative diseases, where it showed a promising potential to identify cortical microstructural degeneration preceding cortical atrophy. Its use –to our knowledge for the first time– in mental disorders suggests that microstructural alterations can be observed even in the absence of a clear underlying neurodegenerative process.

The main strength of this study is the use of a multimodal cross-sectional and longitudinal neuroimaging approach, which allowed a direct comparison of potential imaging biomarkers across modalities. Limitations of this work include a relatively low sample size, especially in the longitudinal imaging analyses. Additionally, the control group had higher educational level than the treatment-resistant SCZ group. Finally, a subset of the presented results was influenced by differences in medication dosage and illness duration, which represent inherent and inextricably linked features of TRAVH known to alter brain structure(28,29).

To conclude, we described cerebral microstructural and macrostructural alterations in SCZ patients with persistent AVH. Microstructural deficits were revealed in these patients in key SCZ-related regions, even in the absence of macrostructural changes. Importantly, these microstructural alterations correlated in turn with their clinical severity. Moreover, they showed accentuated age-related cortical degeneration and an abnormal longitudinal loss of cortical integrity. Overall, these results provided a highly unique insight into the pathological mechanisms involved in this devastating mental illness.

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