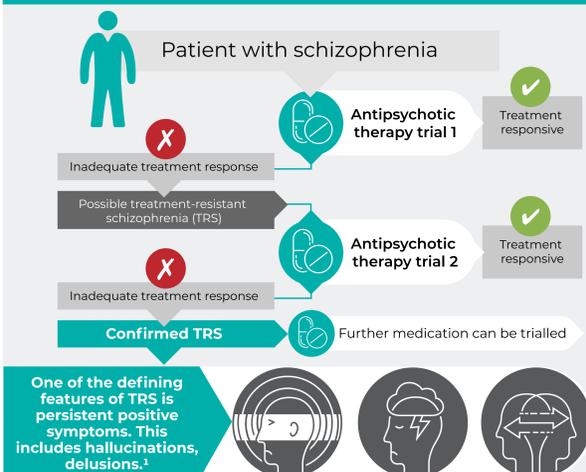


DEEP BRAIN STIMULATION (DBS) FOR TREATMENT-RESISTANT SCHIZOPHRENIA

Why is There a Need for DBS?



One of the defining features of TRS is persistent positive symptoms. This includes hallucinations, delusions.¹



Up to 30% of patients are resistant to treatment with antipsychotics.³

Treatment Resistant Schizophrenia (TRS)

TRS is a sub-group of schizophrenia where symptoms persists despite:

- ≥ 2 trials of antipsychotics
- Adequate duration
- Adequate dose
- Documented adherence

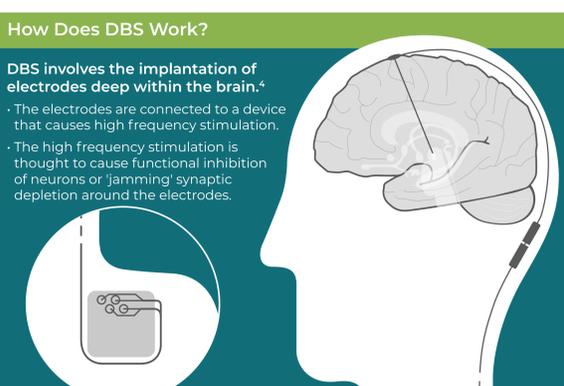
DBS if Antipsychotics Fail?

DBS is being investigated as an alternative to antipsychotics in TRS as its use is established in other diseases such as movement disorders (>100,000 DBS cases).⁴

Parkinson's Disease. ^{5,6}	OCD ⁷	MDD ^{7,9}	Schizophrenia ¹⁰
1986	1999	2005	2008

MDD, major depressive disorder; OCD, obsessive compulsive disorder

How Does DBS Work?



DBS is reversible
Electrodes can be switched off and, if necessary, explanted.³

Which Brain Areas Should Be Targeted?

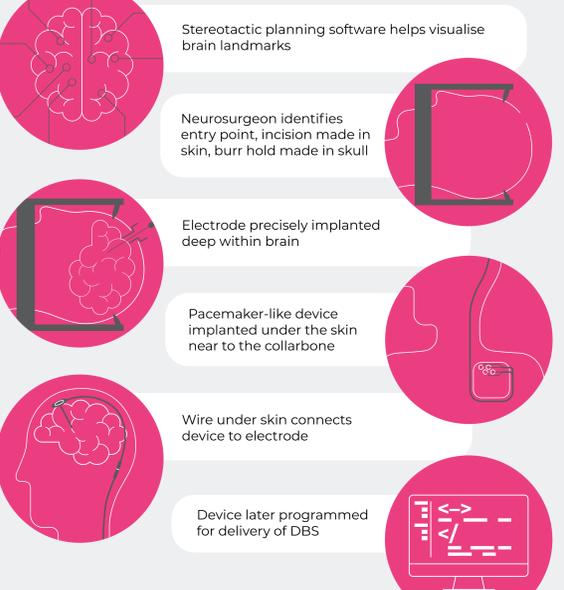
Several areas of the brain have been proposed for DBS in schizophrenia, but there is no agreed target.^{2,11-14}



- Subgenual anterior cingulate cortex (ACC)¹¹**
 - Increase in dopamine leads to decrease in glutamate signalling¹⁵
 - Already targeted in obsessive compulsive disorder (OCD)/major depressive disorder (MDD)
- Habenular nucleus¹²**
 - Modulates dopaminergic midbrain function and serotonergic raphe nucleus activity
- Substantia nigra¹³**
 - Inhibition linked to positive and cognitive symptoms
- Nucleus accumbens^{13,14}**
 - Hypoactive in patients with negative symptoms
 - Already targeted in in OCD/MDD
- Ventral tegmental area¹⁴**
 - Hypoactive in patients with negative symptoms

MDD, major depressive disorder; OCD, obsessive compulsive disorder

How is DBS Surgery Performed?



Consent and DBS

DBS is an Invasive Procedure – Patient Informed Consent
Three main tenets¹⁵

- 1. Respect of persons**
Subject must be capable of self-determination. Ensure capacity for informed consent.
- 2. Justice**
Equitable distribution of risks, burdens and benefits.
- 3. Beneficence**
When is it justifiable to seek benefits despite risks involved? Assess risks and benefits.

Tools to Help Assess Capacity to Consent

California Scale of Appreciation ¹⁶	MacArthur Competence Assessment Tool for Clinical Research (MacCAT-CR) ¹⁷
Measures the "appreciation" component of capacity: • 18 items rated according to concept of "patently false belief" (a belief that is grossly improbable) • Each item scored as "capable," "incapable," or "uncertain capacity"	Four components: • Understanding • Appreciation • Reasoning • Ability to express choice

Researcher's call if patient cannot provide adequate consent?

- DBS is only used in research settings at present
- No legally agreed criteria for confirming consent for DBS
- Additional investigator with no conflicts of interest should also assess capacity to consent
- Consent is dynamic – patient can withdraw

Clinical Evaluation of DBS in Schizophrenia



China
Target: Habenular nucleus¹²
Participants: **2** Status: **Completed**
Outcome:
• Improvement in both patients for first 6 months
• Only one had favourable outcome at 12 months follow-up

USA
NCT02361554¹³
Deep Brain Stimulation in Treatment Resistant Schizophrenia
Target: Substantia nigra pars reticulata (SNr)
Participants: **3** Status: **Ongoing**

Canada
NCT01725334¹³
DBS for the Management Refractory Negative Symptoms in Schizophrenia
Target: Ventral tegmental area and nucleus accumbens
Participants: **0** Status: **Abandoned** (lack of recruitment)

Spain
NCT02377505⁵
Deep Brain Stimulation in Treatment Resistant Schizophrenia (DBS-SCHIZO)
Target: Subgenual anterior cingulate cortex (ACC) or nucleus accumbens (NAcc)
Participants: **8** Status: **Completed**
Outcome:
• PANSS total score 25% improvement (primary endpoint)
• 2/3 patients who received DBS at NAcc
• 2/4 patients who received DBS at subgenual ACC
PANSS, Positive and Negative Syndrome Scale

Expert Opinions of DBS for Schizophrenia

"We don't really know the outcome of the DBS surgery even though there have been a few reports of positive cases."
Judith Gault, ECNP presentation 2020

DBS is not a cure but recruits the healthy self to resist symptoms.
Damiaan Denys, ECNP presentation 2020

Patients need to be highly motivated – lifelong support is required.
Damiaan Denys, ECNP presentation 2020

"Preliminary findings suggest that deep brain stimulation may be a potential option for treatment-resistant patients."
Iluminada Corripio, ECNP presentation 2020

Read the ECNP 2020 Highlights Article on DBS for Schizophrenia

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