Deep Brain Stimulation of the Substantia Nigra Pars Reticulata for Ultra-Treatment Resistant Schizophrenia

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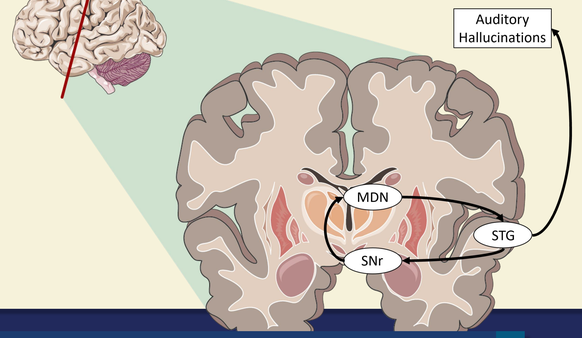
- Introduction -

- Schizophrenia affects approximately 24 million people worldwide, of these, 12-20% may be considered "ultra-treatment resistant" in that symptoms persist despite adequate trials of clozapine as well as two or more other antipsychotics (Siskind *et al.* 2017)
  - There is an urgent need for expanded treatment options in this population
  - Deep brain stimulation (DBS) may leverage current advances in knowledge of underlying neurocircuitry to provide a potential treatment option in these extreme cases
- The substantia nigra pars reticulata (SNr) is a main (largely inhibitory) output of the basal ganglia (Antal *et al.* 2014), with GABAergic hypofunction in schizophrenia (Purves-Tyson *et al.* 2021)
  - The SNr exerts inhibitory control over the thalamus, modulating key thalamocortical and striatothalamocortical circuits (Zhou 2016)
  - One key circuit of interest is: SNr --| Medial dorsal nucleus of the thalamus → Superior temporal gyrus (STG) → SNr, in which hyperactivity in the STG has been implicated in the production of auditory hallucinations (Sasaki *et al.* 2025)
- THEREFORE we hypothesized that *normalization of SNr function by DBS would improve auditory hallucinations in ultra-treatment resistant schizophrenia*



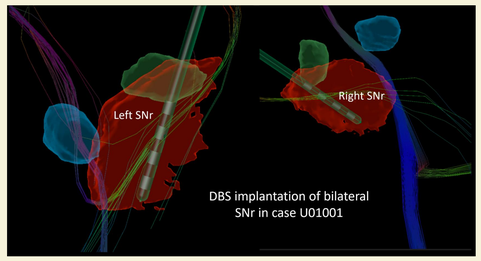
- Methods -

- 4 participants with ultra-resistant SCZ underwent bilateral SNr DBS implantation
  - 3 as part of a pilot study (35F 1/2020, 44F 1/2022, 39M 10/2022)
  - 1 currently as part of an ongoing NIH U01 funded trial (36M 4/2024)
- All participants underwent serial evaluations with scales including the Brief Psychiatric Rating Scale (BPRS), and Scale for Assessment of Negative Symptoms (SANS)
  - The U01 case underwent an expanded battery of scales including the Scale for Assessment of Positive Symptoms (SAPS), Auditory Vocal Hallucination Rating Scale (AVHRS), Clinical Assessment Interview for Negative Symptoms (CAINS)
- U01 case underwent evaluations during double blinded on and off phases (after initial optimization period)
  - Initial unblinded "ON" optimization phase (12 weeks)
  - 3x double-blinded "ON" and "OFF" phase (2 weeks each, 6 weeks total)
  - Unblinded "ON" phase

- Results -

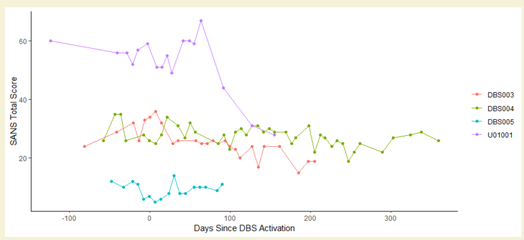
DBS Implantation

- All four participants underwent bilateral SNr implantation, U01 case shown below
- Third case (DBS005) underwent lead revision



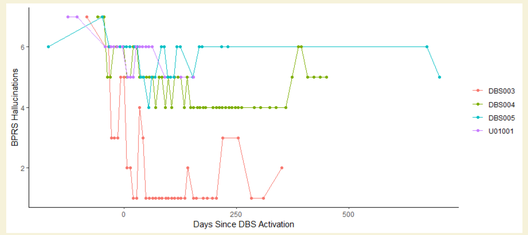
Negative Symptoms

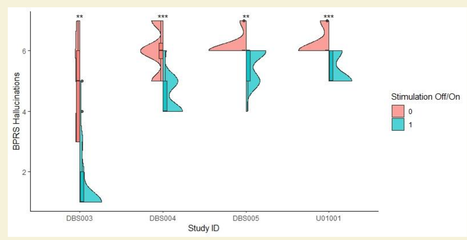
- Improvement on the SANS noted in some cases (DBS003 and U01001)
- Dramatic improvement noted in U01 case with stimulation
- Proportionately similar improvement (~50%) noted in DBS003

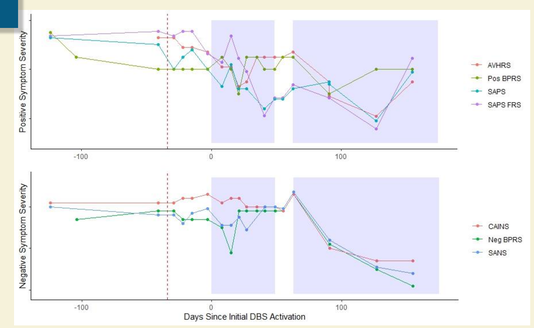


Positive Symptoms

- Some participants with dramatic improvement of hallucinations, one with near-complete resolution of hallucinations
- Recurrence of hallucinations in DBS003 found to be related to battery failure after device interrogation, improved again after replacement
- All participants exhibited at least some improvement in hallucinations on BPRS
- Improvement in hallucinations post-revision in DBS005 (data not shown)







U01 Positive & Negative Symptoms

- High burden of negative symptoms alleviated with stimulation on SANS, BPRS, and CAINS
- Improvement of positive symptoms with stimulation seen on AVHRS, BPRS, SAPS
- Some possible worsening of both positive and negative symptoms during blinded "OFF" phase
- Improvement of hallucinations on SAPS appears driven by Schneiderian first rank symptoms (SAPS FRS):
  - Thought insertion (3.50 vs. 0.63, $p < 0.001$)
  - Thought broadcasting (3.83 vs. 0.88, $p < 0.001$)
  - Delusions of mind reading (2.67 vs. 0.13, $p < 0.01$)
- AVHRS:
  - Number of voices (8.00 vs. 4.75, $p < 0.001$)
  - Duration of voices (2.00 vs. 1.00, $p < 0.001$)
  - Negativity of content (3.17 vs. 2.13, $p < 0.001$)
  - Separate/simultaneous (3.00 vs. 2.38, $p < 0.001$)

- Discussion -

- SNr DBS may represent a promising intervention in the high-need population of ultra-treatment resistant schizophrenia
- SNr modulation may have the capacity to improve positive symptoms, but also negative symptoms
  - Are improvements in negative symptoms driven by improvement in positive symptoms? Connectivity of the SNr to other circuits i.e. reward pathways? This will require further investigation
- Is there relevance to the particular phenomenology which improved with stimulation in our U01 case (E.g. Schneiderian first rank symptoms)?
- Changes in symptoms and specific phenomenology with stimulation may aid in identification of additional networks key to disease phenotypes and may provide new insights into network dysfunction in schizophrenia

References:

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