Benzodiazepine alters deep brain stimulation evoked potentials

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CONCLUSIONS

- Benzodiazepines have significant effects on the brain's response to DBS, both increasing and decreasing the effects of DBS, depending on the connection.
- Understanding these effects will be especially important for situations when DBS therapy is considered for use concurrently with benzodiazepine medication.

INTRODUCTION

- **Dystonia** is a movement disorder in which intermittent or sustained muscle contractions cause **repetitive movements and abnormal postures** [3].
- **Benzodiazepines** are commonly used to treat these symptoms [1], [2], by causing increasing inhibition at $GABA_A$ receptors.
- When medications alone do not reach the desired clinical effect, **deep brain stimulation (DBS)** is another treatment alternative [1] that functions by delivering electrical pulses into regions in the motor pathways that are not functioning properly.
- While many studies have investigated the **effects of benzodiazepines** on cortical activity, such as increased beta band power [4]–[6], no data is currently available on its effects **on deep brain regions**, nor on these regions' responses to DBS.
- Hence, we asked: ***Does benzodiazepine have a significant impact on deep brain stimulation evoked potentials (DBS EPs)?***

METHODS

- Three male **pediatric patients with dystonia** (12, 10, and 14 years old)
- **Benzodiazepine vs. control** (not taking medication)
- **25-250 Hz polarity-reversed DBS** through pairs of externalized stereoelectroencephalography (sEEG) electrodes
- Neural data from sEEG leads in:

Basal ganglia (BG)
- ✓ Globus pallidus interna (GPi)
- ✓ Subthalamic nucleus (STN)

& **Pedunculopontine nucleus (PPN)**

Thalamus
- ✓ Ventral anterior (VA)
- ✓ Ventral oralis (VO)
- ✓ Ventral intermediate (VIM)

Freq [Hz]	GPi	STN	VO	VA	VIM	PPN
25	*1*, *2*	*1*, *2*	*1*, *2*	*1*, *2*	*1*, 2	*2*
55	*1*, *2*, *3*	*1*, *2*, *3*	*1*, *2*, *3*	*1*, *2*, *3*	*1*, *2*	*2*, *3*
85	*1*	*1*	*1*	*1*	*1*	
185	*1*	*1*	*1*	*1*	*1*	
250	*1*	*1*	*1*	*1*	*1*	

Table 1. *Stimulation & recording nuclei for the three different subjects (1, 2, 3). Bold/italic = stimulation/recording was performed in this nucleus (in left and/or right hemisphere).*

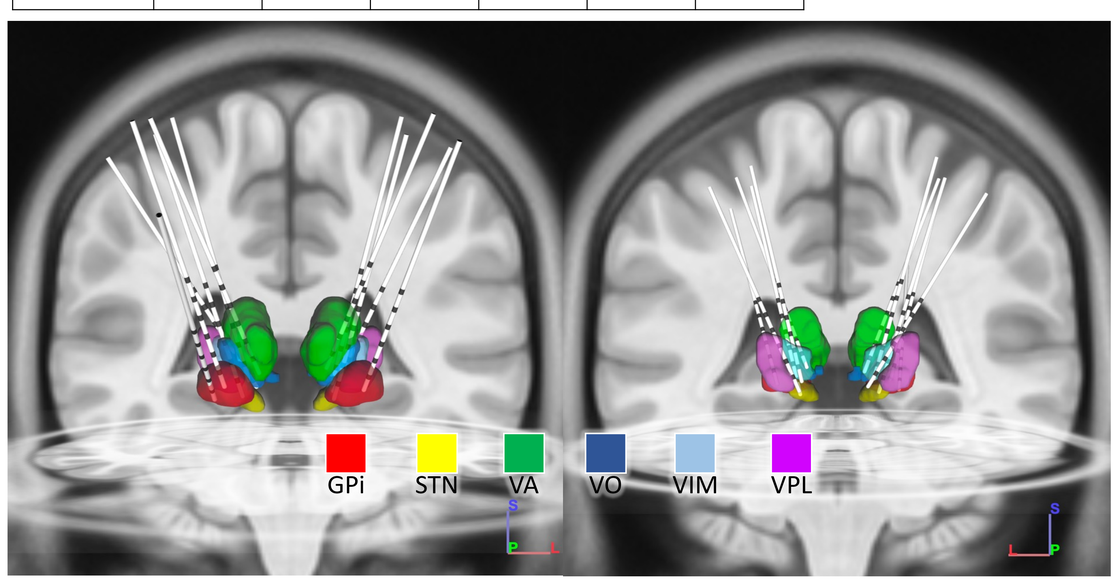

Figure 1. *Coronal views of sEEG leads in thalamic and basal ganglia subnuclei. Post-operative CT scans were normalized onto an MNI template and deep brain boundaries defined with the DISTAL atlas.*

- Evoked potentials were **automatically detected** based on correlations between recordings from the polarity-reversed stimulations
- For each connection between target regions (e.g., GPi stimulation → VO recordings), the **amplitudes** of any DBS EPs were compared for Benzodiazepine vs. control cases, using:
  - paired t-test (normally distributed paired differences)
  - Wilcoxon signed rank test (otherwise)

RESULTS

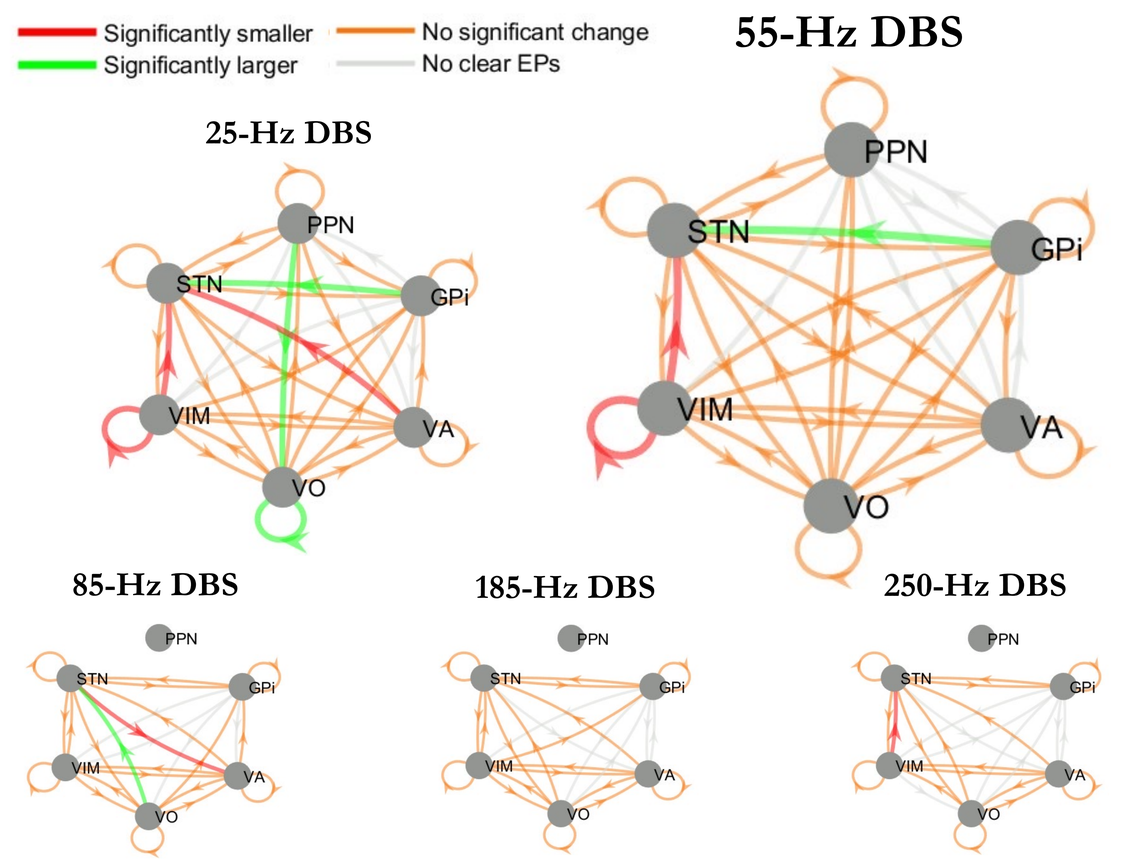

Figure 2. *Directed graphs showing the effects of benzodiazepines on EP amplitude. Results are from the group analysis of all three subjects at the five different stimulus frequencies. The 25 & 55 Hz results are enlarged because they contain data from two and three subjects, respectively, compared to just one for the higher frequencies (see Table 1 for details). The arrows point from each nucleus where DBS was delivered, to each nucleus where recordings were available (and an EP may have been elicited). Red/green arrows denote connections where the amplitudes of the EPs significantly decreased/increased when benzodiazepines were administered. Orange/grey arrows symbolize connections where EP amplitudes were not significantly affected/no clear EPs were seen.*

DISCUSSION

- EP amplitude is a measure of the impact of DBS on a region (i.e., increased or decreased excitation or inhibition). Hence, increased amplitudes would signify an increased effect of DBS, and vice versa.
- While we saw some variability in the results between stimulation frequencies, subjects, and hemispheres, the two frequencies with data from multiple subjects (25 & 55 Hz) had many common trends, which is a good sign of the reliability of the results.
- These common themes included **larger STN EPs during GPi DBS** and **smaller VIM EPs & STN EPs during VIM DBS**.
- Although GPi → STN is an antidromic connection, it may still be affected by the increased inhibitory output of GPi caused by benzodiazepine, which would explain why the medication amplified the effects of GPi DBS on STN.
- The reduction in EPs stemming from VIM DBS may be similarly affected by increased GPi inhibition of thalamus: increased inhibition would make depolarization in VIM from DBS more difficult, leading to a smaller response in VIM.
- Moreover, while there is no direct neurological pathway between VIM and STN, any EPs elicited in STN during VIM DBS would be expected to follow a trend similar to that of the VIM "self-EPs".

FUTURE WORK

- A larger pool of subjects will be necessary to generate significant results in more connections. Moreover, additional EP measurements such as delay and/or frequency components may also help generate a a clearer understanding of the impact of benzodiazepines on DBS EPs.
- Similar studies in other patient demographics would be insightful to understand which, if any, of these trends are unique to dystonic patients, and which others may be a good representation of healthy brain activity.

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