

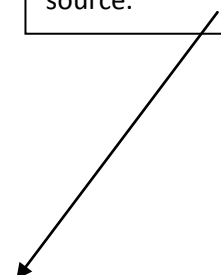
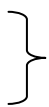
Typical Pattern of Synthesis/Citation

Somatic activity in the stimulated nucleus

The earliest hypotheses on DBS mechanisms attempted to reconcile the similarity in clinical outcome after a lesion and during DBS by proposing that high frequency stimulation inhibits neurons and decreases output from the stimulated site.¹⁷ Consistent with this hypothesis are several studies showing that high frequency stimulation in either the subthalamic nucleus (STN) or globus pallidus internus (GPi) suppresses somatic activity around the stimulated electrode.¹⁸⁻²⁷ For example, Meissner et al.²⁷ recorded STN neuronal activity for several minutes before, during, and after HFS with parameters (100 μ A amplitude, 130 Hz frequency, and 60 μ s pulse width) that improved contralateral rigidity in parkinsonian monkeys. In this study, therapeutic stimulation decreased the mean firing rate in the majority of STN neurons, from 19 Hz to 8 Hz. They proposed that the decrease in mean firing rate resulted from resetting the firing probability of STN neurons by each stimulus pulse. Neurons resumed activity after about 3 milliseconds following a stimulus pulse and returned to baseline after approximately 7 milliseconds. By stimulating at 130 Hz, which corresponded to a 7.7 ms interpulse interval, these cells fired at their baseline rate for only a brief period of time, resulting in an overall reduction in mean firing rate. Bar-Gad et al.²⁵ reported that HFS in the globus pallidus (GP) resulted in a similar time-locked response in 70% of the GP cells recorded adjacent to the stimulation electrode. The average firing pattern of these cells consisted of an initial inhibitory response followed by two excitatory phases at 3 milliseconds and 7 milliseconds. They also found an additional 12% of neurons in the globus pallidus were completely inhibited over the stimulation period.

First sentence of review sets the scene by introducing first major idea

Discussion of idea itself, beginning with several references (18-27), then exemplifying – note that since it is clear that the next few sentences all come from the same source, it isn't necessary to keep repeating the citation. Also note that the citation comes after FIRST mention, not at the end. The pattern repeats with the next source.



Topic-driven Discourse

Regularization of pathological activity

A proposed mechanism of DBS that is consistent with an increase in neural output from the targeted region is that stimulation overrides pathological neuronal discharge by imposing a more regular effect on downstream nuclei.^{74,75} Both experimental^{37,76} and modeling⁷⁷ studies have shown that **high frequency stimulation** replaces intrinsic irregular activity with one that is time-locked to the stimulus. Regularization of GPi firing by STN-HFS appears to reduce the disorder (entropy) of neuronal signals (A. Dorval, personal communication) and restores the responsiveness of thalamocortical cells to synaptic inputs (e.g., sensorimotor information) despite increased inhibitory drive.⁷⁸ **Frequencies above 100 Hz** typically provide symptom relief while frequencies below 20 Hz often worsen symptoms, perhaps by adding spikes to an already irregular pattern of spontaneous firing or by promoting bursting behavior in downstream nuclei. Neurochemical studies support this claim showing that low frequency stimulation does not lead to the neurochemical and molecular changes seen with high frequency stimulation.^{52,79} **However**, not all nuclei or clinical indications require stimulation at frequencies above 100 Hz. DBS in the pedunculopontine nucleus (PPN), for example, is most effective at **stimulation frequencies between 20–60 Hz.**⁸⁰ Interestingly, PPN neurons **exhibit lower baseline firing rates** (~15 Hz on average) than those observed in other nuclei.^{81,82} In dystonic patients, where pathological GPi firing rates are thought to be lower than in PD, therapeutic DBS frequencies may also be lower.^{83,84}

The paragraph is about a proposed mechanism and a hypothesized identifying quality (high Hz). The writer organizes the discussion around evidence that *supports* or *conflicts* with proposed identifying quality. Since there is more than one kind of evidence under discussion, the writer chooses to make the topic (the evidence) the grammatical subject of the sentences. The paragraph is “about” the conflict regarding the identifying quality.

Author-Driven Discourse

The ‘output activation’ hypothesis appears to hold for other target nuclei as well.^{36,45-47} A study examining motor scores in parkinsonian monkeys during GPe-HFS⁴⁸ found that therapeutic stimulation parameters led to a **pronounced reduction in firing rate and bursting in 67% of the recorded STN neurons**, whereas only 31% of STN neurons were significantly inhibited for non-therapeutic stimulation. In untreated monkeys, **Anderson et al.**³⁶ reported that GPI-HFS **inhibited 77% of thalamic neurons**, which is consistent with orthodromic activation of GABAergic projections. **Montgomery**⁴⁵ described a similar **reduction in thalamic neuronal activity** in humans during GPI-HFS with time-locked responses involving an overall suppression in the firing probability except for a brief excitatory phase at 3.5–5 ms. In a dystonic patient, **Pralong et al.**⁴⁶ observed that GPI-HFS induced **thalamic inhibition** only in a subpopulation of ventralis oralis anterior (Voa) thalamic neurons that exhibited intrinsically high firing rates and a low burst index. Voa neurons expressing lower firing rates and a higher burst index were unaffected by GPI-HFS. Since these unaffected neurons were located primarily in the anterior and medial regions of Voa,⁴⁹ the disparity of thalamic responses could have reflected weak pallidal innervation. Alternatively, GPI-HFS could have a less pronounced effect on Voa neurons with low (3–6 Hz) firing rates or with higher modulatory thresholds.

In this paragraph, the same topic, “output activation” as a reduction in firing rate, is the topic of the whole paragraph; this is what the paragraph is “about”. Each supporting point offers corroborating evidence; there are not multiple perspectives on the topic being offered. The writer then lays out each bit of evidence by using the authors’ names to organize the explanation. In this case, it is likely because using the topical points themselves would require repeated passive sentences, e.g., “A similar reduction in thalamic neuronal activity was observed in humans...”, “a 77% of thalamic neurons were inhibited by GPI-HFS..”. It’s simply more direct to name the authors and keep the grammatical objects of the sentences in the clearer, direct grammatical voice.