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Title: Alternate subthalamic nucleus deep brain stimulation parameters to manage motor symptoms of Parkinson's disease: Systematic review and meta-analysis

Running title: Alternate deep brain stimulation parameters

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ABSTRACT

Background: The use of alternate frequencies, amplitudes and pulse widths to manage motor symptoms in Parkinson's disease (PD) patients with subthalamic nucleus deep brain stimulation (STN-DBS) is of clinical interest, but currently lacks systematic evidence.

Objective/Hypothesis: Systematically review whether alternate STN-DBS settings influence the therapy's efficacy for managing PD motor symptoms.

Methods: Systematic searches identified studies that; involved bilateral STN-DBS PD patients; manipulated ≥1 STN-DBS parameter (e.g. amplitude); assessed ≥1 motor symptom (e.g. tremor); and contrasted the experimental and chronic stimulation settings. A Mantel-Haenszel random-effects meta-analysis compared the UPDRS-III sub-scores at low (60-Hz) and high frequencies (≥130 Hz). Inter-study heterogeneity was assessed with the Cohen's χ^2 and I^2 index, while the standard GRADE evidence assessment examined strength of evidence.

Results: The meta-analysis indicated a very low quality for the pooled evidence due to risks of bias, significant heterogeneity and imprecision. Separate analyses involving studies that attempted to maintain the total electrical energy derived by increasing amplitude at 60-Hz frequencies suggested that low-frequency STN-DBS reduced UPDRS-III sub-scores by 5.8 points (95% CI=1.5-10.2; Z=2.6; P=0.009) compared to frequencies ≥130 Hz. This alternate stimulation strategy may be beneficial for those with severe axial symptoms post STN-DBS, however, benefits may only be short-term.

Conclusion(s): The meta-analysis reported a very low quality of evidence for the efficacy of low-frequency STN-DBS for managing PD motor symptoms. Furthermore, it highlighted that lower amplitudes lead to the re-emergence of motor symptoms and further research is needed to understand the potential benefits of alternate STN-DBS parameters for PD patients.

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INTRODUCTION

Deep brain stimulation (DBS) of the subthalamic nucleus (STN-DBS) has become one of the most prominent therapies for the management of motor symptoms associated with Parkinson's disease (PD).[1] Studies have reported patients may experience improvements in tremor, stiffness (rigidity) and slowness (akinesia) of movement for a number of years following STN-DBS, which has significant implications for their independence and overall quality of life.[2 3] However, symptoms of postural instability and gait disability (particularly gait freezing) can benefit less from STN-DBS therapy.[4] Some research has reported; i) no significant improvement in trunk rigidity;[3] ii) a worsening of postural instability;[2] iii) poorer performance on clinical assessments of gait (compared to off stimulation);[5] and iv) increased gait freezing episodes.[5 6]

A significant advantage of STN-DBS over other stereotactic neurosurgical procedures (e.g. thalamotomy) is that clinicians can adjust the stimulation parameters in response to disease progression to ensure optimal patient management. Clinicians may elect to adjust one or more stimulation parameters to find the optimal collection to manage the patient's symptoms while limiting unwanted side-effects. However, given the optimal stimulation parameters for each patient are likely to differ, programming guides have been developed.[7] Such guides outline a number of key considerations and describe the effect of altering key parameters that include the; i) frequency (the rate at which stimulation is delivered to the target structure (e.g. the STN)); ii) amplitude (the electromotive force delivered to the target structure as either constant voltage or constant current); iii) pulse width (the duration of each stimulation pulse); and iv) electrode polarity (cathodic/anodic stimulation). When the STN-DBS parameters have been established for chronic stimulation, the total electrical energy delivered (TEED) for the patient is calculated by multiplying the values for amplitude, frequency, pulse width and biological impedance.[8]

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Given the relatively lower efficacy of STN-DBS for managing the axial versus appendicular motor symptoms of PD, investigations have targeted whether stimulation parameters other than those traditionally used may be better suited to managing axial motor symptoms. This study sought to systematically review the available evidence regarding changes in PD motor symptom severity in response to different stimulation frequencies, amplitudes, pulse widths and/or electrode polarities compared to chronic stimulation parameters in people with PD receiving STN-DBS treatment. Furthermore, a meta-analysis was conducted to determine the evidence for using low-frequency STN-DBS for improving the severity of PD motor symptoms.

MATERIALS AND METHODS

Search Strategy

A search for studies indexed in three scientific databases (PubMed, EMBASE, CINAHL) was completed in February 2017 to identify studies for inclusion in this review. The search aimed to identify studies concerning PD, the alteration of STN-DBS parameters and the assessment of motor symptoms and was prospectively register with PROSPERO (CRD42017056565).

Selection Criteria

To be eligible for inclusion in the review, studies were required to: i) involve an idiopathic PD population who had undergone STN-DBS; ii) include at least one experimental condition that manipulated one or more DBS parameter (e.g. frequency, amplitude, pulse width, polarity); iii) present at least one outcome regarding tremor, rigidity, bradykinesia, postural stability or gait; and iv) include an assessment of these outcomes while the stimulators were active with the

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parameters recommended by their neurologist (i.e. chronic stimulation). Furthermore, all included studies were required to involve people with bilateral STN-DBS therapy, as differences have been noted for the efficacy of bilateral and unilateral STN-DBS for managing motor symptoms.[9] Studies that included patients receiving stimulation of any other neural region (e.g. globus pallidus internus) were deemed ineligible. Studies were also excluded if they were not; i) written in English; ii) a cohort-based study (e.g. case report, commentary or letter to the editor); or iii) a full-length original research publication (e.g. conference abstract). Following the initial search and the removal all duplicates, two authors (ZJC and MHC) independently screened the titles and abstracts to determine their eligibility. Following this process, any discrepancies between the two independent assessments were discussed until a consensus was reached for each study. The full-text of all articles considered to be potentially eligible based on their titles and/or abstracts were retrieved and further screened for possible inclusion by one assessor (ZJC). Reference lists of the retrieved studies were also screened to identify any other potentially relevant articles (Figure 1).

Methodological Reporting Quality

To assess the quality of methodological reporting for each study, a previously-developed checklist designed to accommodate both randomised and non-randomised studies was used.[10] The checklist used to evaluate the quality of methodological reporting comprised 27 criteria (maximum total score = 32) that included; i) 25 items scored on a scale from 0 (not met) to 1 (met); ii) 1 item scored from 0 (not met) to 1 (partially met) to 2 (met); and iii) 1 item assessed on a 5-point Likert scale. The item assessed out of 5 was concerned with the reporting of statistical power, with studies that achieved <70% power for their primary outcomes assigned a score of zero, while those reporting powers of 80%, 85%, 90%, 95% and ≥99% given scores of 1

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to 5, respectively. In situations where an appropriate power calculation was not reported by the authors, statistical power was estimated using data presented for the primary outcomes. If means and standard deviations were not reported, the study was given a score of zero for this criterion. Similarly, for all other items, where it was not possible or unreasonably difficult for the assessors to determine whether a particular criterion had been met in the study, a score of zero was given for that item. After each study was assessed against the 27 criteria, the scores for each individual item were summed and divided by the maximum total points to yield a final score that represented the percentage of the total points available. The percentage score was subsequently used to categorically label the overall reporting quality of each study as either very low (≤20%), low (>20%, but ≤40%), moderate (>40%, but ≤60%), high (>60%, but ≤80%) or very high (>80%).

Meta-analysis

For the purposes of the planned meta-analysis, the sub-score for the motor sub-section of the UPDRS (UPDRS-III) was used to provide insight into any changes in symptom severity with low-frequency STN-DBS treatment. Specifically, weighted mean differences and 95% confidence intervals were calculated for the UPDRS-III to compare different low-frequency stimulation experimental conditions with high-frequency stimulation (≥130 Hz). A Mantel–Haenszel random-effects model was used to conduct the meta-analysis, while Cochran's χ^2 and the I-squared statistic were used to identify any significant heterogeneity among the included studies (indicated by a $p<0.10$ for Cochran's χ^2 and/or an I^2 index >50%).[11] Lastly, the standard GRADE evidence assessment of outcomes was used to determine the overall strength of the evidence resulting from the outcomes of the meta-analysis.[12]

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RESULTS

The initial database search (February, 2017) identified 4157 studies and following the pre-defined inclusion criteria and study selection process is illustrated in Figure 1. 21 articles were considered relevant for inclusion in this systematic review. Demographic data including age, disease duration, time since surgery are presented in Table 1.

Methodological Reporting Quality

Based on the appraisal of methodological reporting quality, 2 (9.52%) studies were identified as having low reporting quality (range: 37.50-37.50%), 12 (57.14%) studies had moderate reporting quality (range: 40.63-59.38%) and 7 (33.33%) studies had high reporting quality (range: 62.50-71.88%) (Table 1). Overall, the reporting of information important for determining the statistical power, selection bias and external validity of the studies was 'low' or 'very low', while the reporting of items related to the internal validity (or bias) of the studies was generally 'very high'.

STN-DBS Parameter Changes

Of the 21 included studies, 17 (80.95%) investigated the effect of changing stimulation frequency on the severity of PD motor symptoms (Supplementary Table 1). Of these 17 studies, seven investigated very low stimulation frequencies (below 60 Hz),[13-19] 12 investigated low-frequencies (60–80 Hz)[5 6 16 17 20-27] and one investigated very high frequency stimulation (i.e. greater than the usual clinical recommendation of ~130 Hz).[22] Given these data, it is evident the majority of research has contrasted high-frequency stimulation with low-frequency stimulation. Nine of the 17 studies examining the effects of alternate stimulation frequencies did so while the other STN-DBS parameters remained unchanged from their chronic stimulation values (i.e. the

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TEED varied between experimental conditions).[6 13-15 18 20 22 24 27 28] In contrast, six of the remaining 8 studies increased the amplitude of stimulation in an attempt to maintain the TEED at the same level as for chronic stimulation,[5 21 23 25 26] one study increased amplitude to optimise symptom management,[27] while the other two increased the amplitude to the maximum amplitude the patients could safely tolerate.[5 17] Despite attempts made by some researchers to maintain TEED at the chronic stimulation level, one study reported they were unable to achieve an equivalent value at the lower frequency of stimulation.[21] Follow-up data for periods ranging up to 15 months were reported in five of the 17 studies examined the effects of altering stimulation frequency.[5 6 21 23 25]

While the majority of studies included in this review investigated the effects of varying frequency on the management of motor symptoms, 5 studies (23.8%) specifically focused on the effect of altering amplitude on the management of clinical symptoms (Supplementary Table 2).[5 22 29-31] Of the included studies, those that sought only to alter the amplitude of stimulation (i.e. while maintaining the pulse width and frequency of stimulation at the chronic stimulation settings) all employed constant-voltage systems. Within the five studies, there were seven experimental conditions investigated; five of which included lowering amplitude and two of which involved increasing amplitude. In studies reporting the effects of lowering amplitude relative to the chronic stimulation value, amplitudes were typically reduced; i) by 50% for one hemisphere,[29] ii) to approximately 80%,[31] 70%[30] or 30%[30] of the chronic stimulation values; or iii) to a level that was 0.3 V lower than chronic stimulation.[22] In contrast, studies examining the effects of increasing amplitudes included experimental conditions that involved increasing amplitudes; i) to the highest level tolerable for each patient[5]; or ii) to a level that was 0.3 V higher than chronic stimulation.[22]

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The remaining two (9.52%) studies included in this review investigated changes in the management of motor symptoms in post-operative STN-DBS PD patients in response to shortening or lengthening the pulse width[22 32] (Supplementary Table 3). Specifically, these studies evaluated the effect of shortening pulse widths to 20, 30, 40 and 50 μs[32] or lengthening pulse widths to 90[22 32] or 120 μs.[32] Of the two studies that investigated changes in pulse width, one employed a constant-current amplitude[32], while the other examined a constant-voltage system[22]. Although our systematic search strategy identified a number of studies investigating the effect of different electrode polarities on the severity of motor symptoms in post-operative STN-DBS PD patients, all were excluded for not meeting one or more of the pre-defined inclusion criteria.

Meta-analysis

To establish the effect of lower frequencies of stimulation on motor symptom severity, the results of six studies that reported the UPDRS-III sub-score for STN-DBS PD patients at high- (≈130 Hz) and low-frequency (60 Hz) stimulation were considered for inclusion in a meta-analysis.[5 6 17 24 25 27] Where the studies' results were presented as medians, 95% confidence intervals and/or ranges, the corresponding authors were emailed to request the means and standard deviations for the required outcome. Following this process, data for 5 of the 6 eligible studies[5 6 17 24 27] were acquired, while the sixth study was excluded due to difficulties with obtaining the necessary mean and standard deviation data for inclusion (i.e. data were reported as medians and interquartile ranges).[25] Of the five studies included in the meta-analysis, two implemented a low-frequency stimulation strategy with an increased amplitude to maintain the

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chronic stimulation TEED,[5 25] one study increased amplitude to optimise symptom management,[27] two studies maintained chronic stimulation amplitude[6 24] and one increased amplitude to the maximum level tolerable for each patient.[17] Analysis of the heterogeneity of the five studies (total n = 73 participants) returned a statistically significant outcome, suggesting significant variation among the studies, with respect to their reported results (Cochran's χ^2 = 34.50, $p<0.00001$; I^2 = 88%). On the basis of this heterogeneity, it seemed inappropriate and of limited clinical use to combine the data from the five studies.[33] However, upon reviewing each of the studies, it was evident that much of this heterogeneity was likely attributable to whether researchers sought to alter the amplitude to maintain the TEED after increasing or decreasing frequency. After sub-dividing the studies based on whether they adjusted amplitude or not, it was found that those studies that made an adjustment to stimulation amplitude returned a non-significant outcome for the test of heterogeneity, while those that did not adjust amplitude exhibited significant heterogeneity (Figure 2). On the basis of the GRADE evidence assessment of outcomes, the pooled evidence from the five studies was of very low quality due to risks of bias, inconsistency (presence of statistical heterogeneity) and imprecision.

***** FIGURE 2 *****

DISCUSSION

The results of this review suggested that research concerning the potential utility of alternate STN-DBS parameters is an emerging field and that, for the most part, there has been a specific emphasis on determining the efficacy of low-frequency STN-DBS for managing PD motor symptoms. Synthesis of the available literature concerning low-frequency STN-DBS therapy for people with PD provides some promising results, especially relating to short-term improvements

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in gait outcomes without the inadvertent worsening of other motor symptoms (e.g. tremor). However, despite the promise of these preliminary findings, the assessment of methodological reporting quality identified a number of key areas that have traditionally been overlooked in the reporting of study designs and outcomes in this field of research.

On the basis of the Downs and Black tool, the overall methodological reporting quality of the included studies was largely of a moderate standard. In general, the reviewed studies scored poorly on items relating to the representativeness of their study populations (external validity), as many consecutively enrolled patients from clinics or hospital settings or investigated a specific sub-type of STN-DBS patients. Furthermore, others provided insufficient information to determine where their population was recruited from, which made it difficult to determine the potential for population bias in these studies. The potential for population bias was most notable in studies investigating the influence of low-frequency stimulation on the severity of motor symptoms in people with PD. Specifically, the populations targeted in these studies included patients with; i) tremor-dominant and non-tremor dominant symptoms;[20] ii) symptoms of dystonia;[26] and iii) post-operative deficits in gait or axial function.[5 21 23 25] Another factor that contributed to the low to moderate methodological reporting quality scores was the relatively small sample sizes included in these studies and the large number of studies (14 studies; 66.67%) that did not include a statement regarding an a-priori statistical power calculation or provide data to allow power to be estimated post-hoc. Due to the heavy emphasis placed on this component of the methodological reporting checklist, the omission of such a statement contributed significantly to the overall assessment of the methodological reporting quality for these studies Nevertheless, it is important to emphasise that, in spite of these shortcomings, the findings of such studies are

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still clinically useful and have provided important insights that have assisted with clinical practices and shaping the direction of future research.

Low-frequency STN-DBS conditions that increased amplitude

The studies that evaluated the influence of varying stimulation frequency exhibited considerable heterogeneity with respect to whether or not they made a compensatory change to the stimulation amplitude following their adjustments to stimulation frequency. Given that the TEED represents the product of stimulation frequency, amplitude, pulse width and biological impedance, any changes that are made to one of these parameters (e.g. lowering frequency) ultimately changes the TEED, unless a compensatory change is made to one of the other parameters (e.g. by increasing amplitude). The body of work that has been completed in this area represents a mixture of studies that have increased amplitude in response to a decrease in frequency and those that have not. For clarity, these two sub-groups are discussed separately.

The results of the systematic review highlighted that the outcomes reported by the included studies were almost exclusively based on well-established clinical scales. While these assessments are routinely used in clinical practice, other objective measures of postural stability and gait may provide further insight into the strengths and weaknesses of alternate patterns of STN-DBS stimulation. For example, in spite of a trend toward improved motor symptom management with low-frequency STN-DBS, the results of the meta-analysis reported no significant improvement in motor symptom severity (as assessed via the UPDRS) with this alternate therapy. However, post-operative STN-DBS patients have been shown to complete a standardized gait assessment in a shorter amount of time with fewer steps while receiving low-frequency STN-DBS with the TEED maintained,[5 23] but not when the TEED was not

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maintained.[6] Importantly, the improvements evident for low-frequency stimulation with TEED maintained were achieved without significantly influencing the severity of rigidity, resting tremor or dyskinesias.[5 23 25 26] Furthermore, low-frequency stimulation had a positive effect on akinesia,[23] which is a symptom potentially exacerbated in some STN-DBS patients at 130 Hz.[34] Collectively, these findings suggest low-frequency stimulation may offer short-term benefits for managing the motor symptoms of PD, but the efficacy of this approach is influenced by whether a compensatory increase in amplitude is made. The meta-analysis illustrates a trend towards improved motor symptom management with low-frequency STN-DBS that is combined with an increase in amplitude; however, the optimal amplitude adjustment is likely to vary across patients. Therefore clinicians are encouraged to use specific clinical outcomes (e.g. complete suppression of contralateral rigidity[32]) to guide the titration of alternate stimulation parameters and tailor the therapy to each individual's needs.

Despite the growing evidence for short-term improvements in axial symptoms with low-frequency STN-DBS, the long-term efficacy of this therapy for these symptoms may be no better than high-frequency STN-DBS treatment.[21 23] Furthermore, in the three studies that reported long-term follow-up data for patients receiving low-frequency STN-DBS therapy with TEED maintained, 73%[21], 50%[26], and 18%[23] of the patients requested to revert back to high-frequency stimulation due to negative changes in their tremor, gait patterns and/or rigidity. Interestingly, those patients who continued to receive low-frequency STN-DBS experienced continued therapeutic benefits with respect to the management of tremor and rigidity after 12-[26] or 15-months[23] of chronic stimulation. Furthermore, patients with dyskinesia showed sustained improvements in the severity and duration of dyskinesia after 12-months of low-frequency STN-DBS therapy.[26] Collectively, these long-term follow-up data suggest that low-frequency STN-

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DBS may not benefit all patients in the same way; highlighting the need for improved strategies for determining the potential benefits of non-routine stimulation parameters for patients with sub-optimal responses to routine parameters.

Experimental STN-DBS conditions that did not maintain TEED

While a small number of studies in this area have sought to maintain TEED during their experimental conditions, a large number of experiments have not maintained this parameter. As a percentage of these studies evaluated the effects of very low-frequencies of STN-DBS (e.g. 5, 20, 50 Hz), it was not always possible for these research teams to account for the marked drop in stimulation frequency with adjustments to other stimulation parameters.[13-19] In such studies, STN-DBS at 10 Hz was reported to result in significantly worse symptom severity (based on the UPDRS-III sub-score),[15 18 19] slower upper limb movements,[13 16 19] and increased wrist rigidity[14] compared with high-frequency STN-DBS. Even after the amplitude was increased to the maximum level tolerable for the patients, a 30 Hz stimulation frequency remained inadequate to manage symptoms of tremor, despite some improvements in the total UPDRS-III sub-score and spatiotemporal gait characteristics.[17] Overall, these findings suggested that the frequency of stimulation plays an important role in managing symptoms of tremor and that very low-frequency stimulation may be unsuitable for the ongoing post-operative management of PD motor symptoms.

Mixed results were reported for those studies assessing the effects of low-frequency STN-DBS while not maintaining the TEED. For example, some reported improvements in axial symptoms (based on the UPDRS)[6] and symptoms of freezing of gait (FOG),[6] while others observed no significant improvement in spatiotemporal gait characteristics[24] or rigidity,

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bradykinesia, and gait scores[20] compared with high-frequency STN-DBS. Furthermore, the specific benefits of low-frequency STN-DBS for managing the axial symptoms and gait difficulties associated with PD may begin to diminish in as little as eight weeks[6] and the reduced efficacy of this therapy for symptoms of tremor[20 22 24] would typically require an increase in oral medications.[6] Interestingly, however, one study found that low-frequency stimulation, when combined with amplitudes ≥5.1 V (i.e. higher than the ≈3 V clinical recommendation), significantly improved standardized gait test performances for a group of patients with gait disorders compared with chronic stimulation STN-DBS parameters.[5] Importantly, these stimulation parameters were only tolerated by 11 of the 13 patients (84.6%) and required an increased daily dose of levodopa to counteract the reemergence of other motor symptoms, including tremor.[5] However, given that a separate study reported no significant improvement in postural sway or gait outcomes when low frequencies of STN-DBS stimulation were combined with higher amplitudes,[17] these outcomes should be carefully considered.

In addition to evaluating the effect of alternate stimulation frequencies on the management of motor symptoms in post-operative STN-DBS PD patients, this review also considered the effect of experimentally altering amplitude on motor symptoms. The findings of the reviewed studies demonstrated that increasing STN-DBS amplitude to a level above chronic stimulation (e.g. >3 V) led to muscle activation patterns that reflected a worse disease state.[22] Interestingly, however, one study reported that patients completed the Stand-Walk-Sit test in less time and with fewer number of steps and freezing episodes when STN-DBS amplitude was increased above the chronic stimulation level, suggesting that higher amplitudes may be beneficial for managing gait-related difficulties.[5] In contrast, a separate study indicated that lowering amplitude by 50% for the hemisphere corresponding to the patients' legs that exhibited the longer step length (i.e.

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compared with the contralateral limb), significantly reduced the frequency and duration of freezing episodes without introducing any measurable changes in velocity, stride length, or cadence.[29] However, these improvements in freezing of gait came at the cost of a re-emergence of other PD motor symptoms;[29] a finding that is commensurate with the outcomes of separate studies examining the potential benefits of lower STN-DBS amplitude.[5 22 29-31] Furthermore, reducing STN-DBS amplitude to approximately 30% of the chronic stimulation value were shown to contribute to poorer performances during posturography assessments in a small group of three participants.[30] Collectively these findings demonstrate the apparent sensitivity of PD-related motor symptoms to changes in stimulation amplitude.

Compared to frequency and amplitude, substantially fewer studies investigated the effects of changing pulse width or electrode polarity on the management of motor symptoms in post-operative STN-DBS PD patients. With respect to the small number of studies that have investigated the effects of varying pulse width, longer pulse widths (e.g. 90 μs) were shown to significantly reduce STN-DBS efficacy,[22 32] while shorter pulse widths (e.g. 30 μs) were shown to improve the therapeutic window up to twofold.[32] Simply, the therapeutic window describes the range of amplitudes that offer relief from motor symptoms and is limited when amplitude changes induce dysarthria or impaired motor skills. Therefore, shorter pulse widths led to an increased range of amplitudes that offered therapeutic benefit, while also decreasing the total charge per pulse required.[32] Collectively, these findings highlight the potential value of investigating the effects of shorter pulse width on the management of motor symptoms in post-operative STN-DBS PD patients.

Limitations

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The findings of this review should be considered in light of a number of potential limitations. First, the meta-analysis found a large degree of heterogeneity across studies, which may be attributed, at least in part, to differences in patient characteristics for the cohorts of the respective studies. Specifically, the five studies included in the meta-analysis reported investigating cohorts that included patients who experienced; i) severe gait disorders[5]; ii) freezing of gait with 130 Hz stimulation and dopaminergic medication[6]; or iii) multiple changes in their gait including balance, freezing, and festination[24]. The remaining two studies reported not specifically targeting STN-DBS patients who experience gait impairments[17, 27]. Second, the collection of terms used in our systematic search did not specifically cover studies that investigated the effect of different stimulation configurations (e.g. interleaving) on the efficacy of STN-DBS treatment. Given there have been a number of studies that have investigated this topic recently,[35] future research may seek to establish a consensus from this literature to guide the potential use of this approach for therapeutic purposes. Third, the results of the meta-analysis were limited to reporting on the acute effects of low-frequency STN-DBS (10 to 60 minutes following the change) on the severity of motor symptoms in people with PD. However, research has shown that the severity of motor symptoms can continue to worsen up to four hours after the cessation of STN-DBS therapy.[36] Given the studies included in this review involved a change in stimulation parameters, rather than the complete cessation of treatment, future research should consider assessing the efficacy of alternate stimulation parameters after a longer wash-in period. Lastly, the clinical implications of this review are limited to evaluating the efficacy of STN-DBS for the management of motor symptoms other than speech in people with PD. It is known that one's capacity for speech is heavily influenced by both motor and cognitive factors.[37] Given the complex interaction that seems to exist between high-frequency STN-DBS, cognitive function and speech, a systematic review aimed at establishing the effects of STN-DBS therapy on

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speech-related outcomes should be considered for future research. To improve the scientific rigor of research in this area, there is a clear need for consensus regarding the importance of maintaining the TEED when assessing the influence of alternate stimulation profiles. Furthermore, scientists are encouraged to further examine the effects of alternate STN-DBS therapies (e.g. shorter pulse widths) on symptom management in people with PD and to ensure that patient samples are representative of the wider STN-DBS PD population.

CONCLUSIONS

The results of this systematic review identified significant heterogeneity amongst the included studies, which emphasized the need for a more uniform approach to examining the potential benefits of alternate patterns of STN-DBS. Nevertheless, the presented findings suggested that low-frequency STN-DBS may provide short-term benefits for patients who experience significant axial motor symptoms (balance and gait difficulties) and/or who respond sub-optimally to routine high-frequency STN-DBS. However, there is a need for appropriate techniques to identify patients who will most likely benefit from this non-routine stimulation strategy, as evidence suggests that low-frequency STN-DBS is unlikely to provide the same therapeutic benefits as high-frequency STN-DBS for patients who present with tremor-dominant symptoms. As such, the results of this systematic review and meta-analysis do not support a change to the currently recommended routine stimulation parameters for STN-DBS patients, but rather suggest that non-routine stimulation strategies may offer a viable alternative to be considered for patients whose symptoms are sub-optimally managed with routine therapies.

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Author Roles

1) Research project: **A**. Conception, **B**. Organization, **C**. Execution;

2) Statistical Analysis: **A**. Design, **B**. Execution, **C**. Review and Critique;

3) Manuscript: **A**. Writing of the first draft, **B**. Review and Critique.

4) Other: **A.** Study supervision

Zachary J. Conway:	1A, 1B, 1C, 2A, 2B, 2C, 3A
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Compliance with Journal Ethical Publication Guidelines Statement

The authors confirm that neither the approval of an institutional review board nor patient consent was required for this work. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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Legends for Figure(s) and Table

Figure 1: Flow diagram illustrating the systematic search strategy and review process that was used to identify the articles included in the review.

Figure 2: Motor sub-score of the Unified Parkinson's Disease Rating Scale (UPDRS-III) for the studies that reduced stimulation frequency to 60 Hz (LFS) compared to the chronic stimulation (CS) 130 Hz deep brain stimulation condition. Subgroups include; 1) studies that increased amplitude to a maximum tolerable level; 2) studies that increased amplitude to maintain the total electrical energy derived (TEED) at the CS level; and 3) studies that maintained amplitude at the CS level.

Table 1: Summary of the major characteristics of the included studies' research design, participants, experimental conditions and methodological reporting quality.

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Table 1: Summary of the major characteristics of the included studies' research design, participants, experimental conditions and methodological reporting quality.

Study	Methods quality	N	Age (years)	Disease duration (Years)	Time since surgery (Years)	DBS-STN Changes	Targeted Outcome(s)
Fasano 2011	High	13	63.5 ± 8.4	15.4 ± 4.5	3.5 ± 3.2	Low voltage	Symptom severity (UPDRS-III) Gait characteristics
Fogelson 2005	Moderate	10	61.4 (47.0-72.0)ǂ	15.6 (8.0-29.0)ǂ	2.8 (0.3- 9.0)ǂ	VLFS	Movement time (Finger tapping task)
Khoo 2014	High	14	60.9 ± 9.6*	16.0 ± 5.2*	2.0 ± 1.5*	LFS	Symptom severity (UPDRS-III) 10-metre timed walk test Berg Balance Scale
Krishnamurthi 2012	Moderate	4	62.3 ± 12.5*	11.3 ± 0.9*	1.6 ± 0.9*	Low voltage	Symptom severity (UPDRS-III) Standing balance measures
Little 2013	Moderate	12	61.5 ± 6.4*	13.1 ± 5.4*	2.9 ± 2.6*	VLFS	Symptom severity (UPDRS-III) Rigidity (wearable sensors)
Merola 2013	Moderate	10	59.4 ± 4.8	48.6 ± 4.5 (Onset age)	2.1 ± 1.3	LFS	Symptom severity (UPDRS-III) Complications of therapy (UPDRS-IV) Rush dyskinesia rating scale
Moreau 2008	High	13	70.0 (66.0-72.0)●	18.0 (13.0-22.0)●	5.0 (4.0-5.0)●	LFS, High voltage	Symptom severity (UPDRS-III) Stand–Walk–Sit Test
Moreau 2011	Moderate	11	69.0 (NR)Ŧ	19.0 (17.0-23.0)Ŧ	5.0 (3.0-8.0)ǂ	LFS	Symptom severity (UPDRS-III)
Phibbs 2014	Moderate	20	62.0 (52.0-72.0)ǂ	12.5 (5.0-22.0)ǂ	3.0 (0.3-10.0)ǂ	LFS	Symptom severity (UPDRS-III) Gait characteristics
Reich 2015	Low	4	NR (49.0-62.0)ǂ	NR	0.2-0.3	Shorter pulse width, longer pulse width	Rigidity score (UPDRS item 22)
Ricchi 2012	Moderate	11	62.9 ± 4.3	46.8 ± 4.1 (Onset age)	4.5 ± 1.4	LFS	Symptom severity (UPDRS-III) Stand–Walk–Sit Test
Rissanen 2015	Low	13	57.9 ± 10.6*	NR	1.2 ± 1.0*	LFS, VHFS, Low voltage, High voltage, Longer pulse width	Symptom severity (UPDRS-III) Characteristics of biceps brachii and tibialis anterior activation Correlation between muscle activations and segmental accelerations
Sidiropoulos 2013	Moderate	45	59.5 ± 7.8	17.8 ± 5.7	NR	LFS	Symptom severity (UPDRS-III)
Stegemöller 2013	High	17	61.5 ± 9.5*	14.2 ± 4.9*	2.5 ± 1.7*	LFS	Symptom severity (UPDRS-III)
Timmermann 2004	Moderate	7	60.3 ± 6.7*	16.9 ± 3.7*	1.7 ± 0.7*	VLFS	Symptom severity (UPDRS-III)
Tsang 2012	Moderate	13	60.0 ± 6.0	15.0 ± 4.0	> 0.3	VLFS, LFS	Symptom severity (UPDRS-III)

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Vallabhajosula 2015	High	19	61.8 ± 9.0	13.6 ± 4.2	NR	VLFS, LFS	Symptom severity (UPDRS-III) Gait characteristics Standing balance measures
Wojtecki 2006	Moderate	12	64.0 ± 6.3*	NR	2.3 ± 1.5*	VLFS	Symptom severity (UPDRS-III)
Wojtecki 2011	High	12	64.0 ± 8.0*	18.6 ± 5.9*	3.8 ± 2.2*	VLFS	Symptom severity (UPDRS-III) Reaction time (finger tapping task)
Xie 2015	High	7	64.0 ± 8.0	12.9 ± 4.9	4.4 ± 4.9	LFS	Symptom severity (UPDRS-III) Freezing of Gait Questionnaire Stand–Walk–Sit Test
Zwartjes 2010	Moderate	6	NR (54.0-68.0)ł	NR	NR	Low voltage	Symptom severity (UPDRS-III) Tremor (wearable sensors) Bradykinesia (wearable sensors)

Abbreviations: ACC, Acceleration; EMG, Electromyography; FOG, freezing of gait; FOG-Q, freezing of gait questionnaire; LFS, low frequency stimulation (60-80 Hertz); NR, not reported in the study; UPDRS, Unified Parkinson's Disease Rating Scale; UPDRS-III, Unified Parkinson's Disease Rating Scale (motor sub-score); UPDRS-IV, Unified Parkinson's Disease Rating Scale (motor complications sub-score); VHFS, very high frequency stimulation (>130 Hertz); VLFS, very low frequency stimulation (<60 Hertz).

Symbols: *, Mean and Standard Deviation (SD) calculated from reported participant values; ł, Mean and range reported; ₸, Median and range; ●, Median and interquartile ranges.

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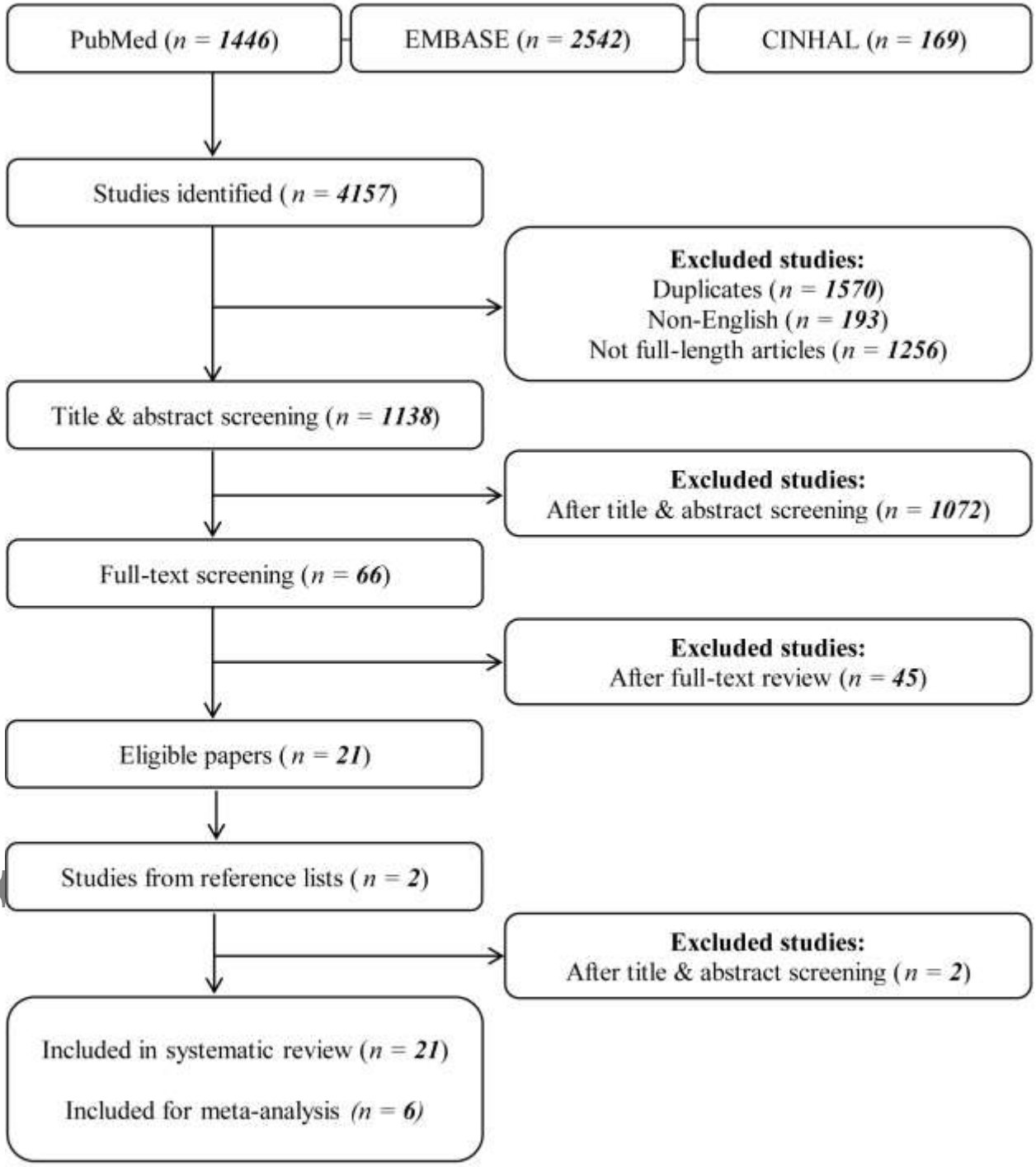

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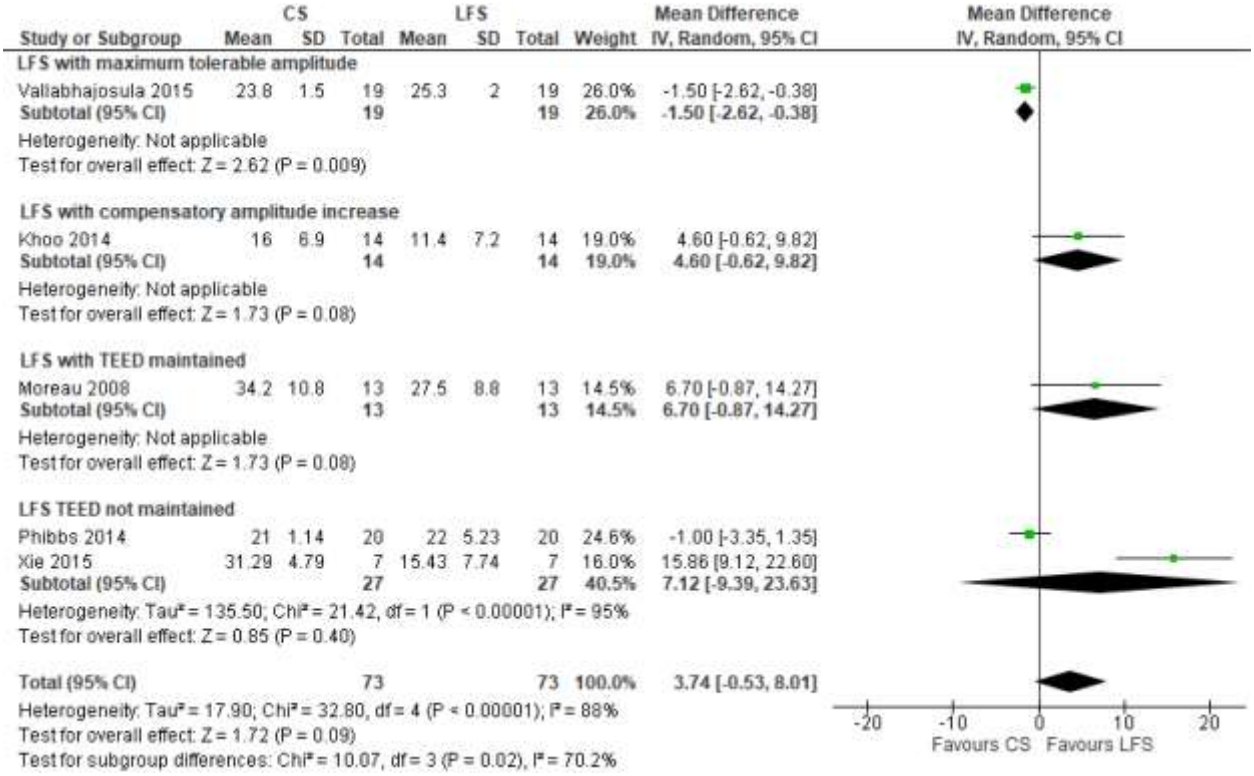

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