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BEHAVIOR (H KIRSHNER, SECTION EDITOR)

Psychiatric and Cognitive Effects of Deep Brain Stimulation for Parkinson's Disease

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Abstract Deep brain stimulation (DBS) is effective for Parkinson's disease (PD), dystonia, and essential tremor (ET). While motor benefits are well documented, cognitive and psychiatric side effects from the subthalamic nucleus (STN) and globus pallidus interna (GPi) DBS for PD are increasingly recognized. Underlying disease, medications, microlesions, and post-surgical stimulation likely all contribute to non-motor symptoms (NMS).

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Introduction

Deep brain stimulation (DBS) successfully treats Parkinson's disease (PD), essential tremor (ET), and certain dystonias [1]. Common therapeutic targets include the subthalamic nucleus (STN), globus pallidus interna (GPi), and VIM thalamus [1]. DBS significantly improves motor symptoms of PD, ET, and dystonia [1–3]. The long-term data of DBS in PD demonstrates reductions in tremor, rigidity, troublesome dyskinesias, and overall improvements in quality of life [1–3]. However, there are cognitive and psychiatric symptoms, some reproducible on stimulation, that practitioners would be remiss to ignore. These NMS can fluctuate after DBS due to changes in dopaminergic medications and stimulation parameters. Much of our knowledge of the NMS of DBS was obtained from patients with STN DBS [1, 4•, 5]. The goal of this review is to summarize these important non-motor post-operative symptoms, discuss strategies to reduce them, and to adequately optimize neuromodulatory therapy for Parkinson's disease.

Subthalamic Nucleus DBS

Anatomy of the Subthalamic Nucleus

The STN is an important relay center of basal ganglia motor pathways. It receives direct excitatory (glutaminergic) inputs from the cerebral cortex and the centromedian parafascicular nucleus of the thalamus and sends excitatory outputs to the GPi, globus pallidus externa GPe, substantia nigra pars reticulata (SNr) and compacta (SNc), and the

pedunculopontine nucleus (PPN). It receives inhibitory (GABAergic) inputs from GPe and modulatory inputs from the PPN (glutaminergic and cholinergic) and SNc. It is subdivided into a motor dorsomedial (interacts with primary motor cortex, GPi, GPe), an associative ventromedial (interacts with frontal eye fields and oculomotor and cognitive centers via the SNr) and medial limbic (interacts with cingulate cortex and ventral pallidum) territories. These territories with their input-output circuitry provide parallel, independent control of motor, oculomotor, cognitive, and limbic pathways [5].

Affective or Psychiatric Effects in STN DBS

Depression

Depression is the most common psychiatric quality of life (QOL) determinant in STN DBS for PD [4•]. Depression in PD may be mediated by CNS monoaminergic cell dysfunction [6]. Dysfunction and loss of norepinephrinergic and serotonergic cells may precede SNc damage in PD [7]. Nearly one out of two Parkinson's patients suffers from clinically significant depression [8].

Functional imaging studies suggest a hypodopaminergic state in depression [7]. In a cohort of 63 subjects, phenotypic variance in mesolimbic D2/D3 receptor density was shown by [^{11}C]-raclopride positron emission tomography (PET) after cessation of dopamine agonist therapy [9]. In this study, depression was reversible by restarting dopaminergic therapy [9]. Patients with comorbid apathy and depression were hypothesized to have a lower density of presynaptic dopaminergic terminals predominantly in the mesocorticolimbic system, likely explaining the link among depression, anxiety, and apathy stemming from a hypodopaminergic syndrome [9].

The data describing depression with STN DBS for PD is mixed. Improvements [10–15] and exacerbations [4•, 9, 11, 16–19] of depression after STN DBS were reported. Pre-operative depression is predictive of post-operative depression and overall decrease in QOL [4•, 17, 20]. A meta-analysis of several studies revealed that of the 1398 who underwent STN DBS, 8 % had post-operative depression [18]. Thus, each patient should undergo individual risk/benefit evaluation prior to DBS implantation [17, 21].

In a prospective study of 33 STN DBS patients, initial and long-term stimulation evoked a significant reduction of depression as assessed by the Beck Depression Inventory (BDI), a self-reported questionnaire, and the Bech-Rafaelsen Melancholia Scale (BRMES), an observer-rating assessment [15]. While no specific DBS parameters were provided, initial improvements in scores were noted at 3 weeks, with continued improvement at 9 weeks, during which time DBS parameters were concomitantly being adjusted. At 9 weeks, BDI scores stabilized, directly correlating with the final DBS adjustments [15].

Two cases demonstrated reversible depression after STN DBS [17, 22]. In the first, a 65-year-old woman acutely expressed suicidal ideations (SI) after bilateral DBS at initial contact 0 located in the central substantia nigra with the following parameters: 2.4 V/60 μs/130 Hz. PET imaging showed activation of the limbic circuitry. Stimulation of more superior STN contacts sufficiently provided relief of motor symptoms without mood effects [22]. In the second report, a previously non-depressed man became acutely depressed and attempted suicide within a 24-h period after the frequency was decreased from 185 to 60 Hz. His depression rapidly improved after restoration of previous settings [17].

There was no difference in post-operative depression prevalence in STN versus GPi groups [4•, 20]. Both pre-operative and post-operative depression assessments are necessary with adjustments in stimulation parameters. Early case reports of suicide after DBS were concerning [16, 17]. Recent meta-analyses demonstrated the incidence of suicide post-DBS is quite rare and appears to be related to rapid reductions in dopaminergic medications rather than to direct stimulation effects [23•]. In a randomized controlled study assessing SI and behavior in DBS [23•], 108 combined STN and GPi patients were compared with 116 medically treated patients over 6 months using the Unified Parkinson's Disease Rating Scale (UPDRS), Parkinson's Disease Questionnaire-39 (PDQ-39), and the Short Form Health Survey (SF-36). The study was then extended beyond 6 months, comparing STN and GPi for a total of 2 years. No patients expressed SI at baseline. There was no significant difference between the DBS group and the medically treated group. Likewise, there was no significant difference between STN and GPi; 1.5 % of STN compared with 0.7 % of GPi DBS patients conveyed SI at 6 months, with complete resolution in both groups at 2 years [23•]. Nevertheless, close psychiatric follow-up post-DBS and regular monitoring of mood and SI are necessary.

Apathy

The prevalence of apathy in PD is estimated as high as 50 % [24]. Current pathophysiological hypotheses suggest a neurochemical basis [25]. Pre-operative severity of dyskinesia from dopaminergic therapy was an independent predictor of apathy after STN DBS [26]. Long-term treatment with dopaminergic agents leads to alterations in dopamine receptor potentiation along the nigrostriatal pathway, possibly causing apathy. Another study demonstrated using PET imaging 3 months before and 3 months after surgery that among 44 patients with PD, reduced pre-operative metabolism within the right ventral striatum was significantly associated with post-operative apathy [27]. Pre-operative degeneration of the right-sided

mesolimbic dopamine pathway, which plays a dominant role in reward-related behavior, could be clinically unveiled during withdrawal of dopamine replacement therapy (DRT) after DBS and further disrupted during STN limbic stimulation [32]. The disease severity of PD does not necessarily correlate with apathy severity [28]. In a study of 15 STN DBS patients compared with medically managed PD controls using the Apathy Evaluation and Starkstein (AES) scales at 3 months prior, 3 months post, and 6 months after DBS [29], 33.3 % of patients had apathy 3 months prior to intervention [29]. In an expanded study of 33 STN DBS patients, a significant and linear increase in apathy over 6 months was identified in the DBS group [30]. Other studies demonstrated significant post-surgical exacerbations of apathy after STN DBS [9, 26, 31, 32], implicating peri-limbic ventral-internal STN implantation in development or worsening of apathy, emphasizing the role of lead location. Thus, it is possible that lead location, stimulation effects, and withdrawal of DRT are all factors in the development of post-operative apathy.

Dopamine Agonist Withdrawal Syndrome

Recent clinical description of the Dopamine Agonist Withdrawal Syndrome (DAWS) increased awareness of potential mood changes with reduction of dopaminergic medications, particularly agonists [33, 34]. DAWS is more prevalent in patients with impulse control disorders (ICDs) and is more likely in patients who were taking dopamine agonists at high doses for long periods of time [34].

In our practice, there are some patients in the early post-operative period who have a very good motor outcome but have subsyndromal mood changes or decreased motivation or apathy. They do not report an overall positive response as expected by neurologists and neurosurgeons. When there is a "mismatch" between the clinician-assessed outcome of DBS and the patient's subjective satisfaction, psychiatric assessment can potentially demonstrate psychological factors (e.g., overly high expectations or the expectation that other life problems will no longer exist after DBS) and/or biological factors for mood changes. Such mood or motivation changes may be akin to low-grade DAWS-like phenomenon and do not necessarily require an increase in dopamine agonists or dopaminergic medications. We had some success remitting these mood symptoms with various antidepressants.

Anxiety

Anxiety is reported in approximately 75 % of PD patients and is attributed to mesolimbic dopaminergic degeneration [9]. In the short-term, STN DBS has a positive effect on anxiety when evaluated by the State and Trait Anxiety Inventory (STAI), Beck Anxiety Inventory (BAI), Hamilton Anxiety Rating Scale (HAM-A), and the Hospital Anxiety and Depression Scale (HADS) [35]. The most notable exception is a recent randomized study of unilateral STN or GPi implantation, which found worsening in the HAM-A at 2, 4, 6, and 12 months postoperatively as compared to baseline [36•]. Unilateral STN DBS achieved a significant worsening in HAM-A scores at 4 months, yet the overall improvement at 1 year. The GPi DBS patients had worsening anxiety at every interval, possibly due to DRT weaning. The medication reduction strategy included increasing intervals between dosages, discontinuing entacapone or amantadine, and decreasing total dosages (levodopa and/or agonists). Medication reduction strategies were deliberately employed slowly, and all changes monitored by clinicians monthly. There was a significant positive correlation between changes in dopaminergics and anxiety and depression scores at 1 year for both targets. The magnitude of the behavioral change was greatest in the anxiety domain, with a positive correlation between changes in levodopa equivalent doses and HAM-A in both DBS groups. Interestingly, more dopaminergic medication was utilized in the GPi group. This relatively higher dose of dopaminergic medications post-GPi DBS could actually prove to be a long-term advantage over STN. The bilateral STN and GPi arm of the study did not produce significant HAM-A score changes at any point throughout the study, likely from small sample sizes [36•]. In our practice, we are less inclined to wean medications after GPi DBS for both neuropsychiatric and motoric reasons.

Other studies suggest an initial improvement with subsequent worsening of anxiety. When comparing 31 bilateral STN DBS patients with 31 medically optimized patients 1 month pre-operatively and at several monthly intervals post-implantation [37], a significant improvement was noted at 1 week and 1 month after DBS but anxiety worsened at 3 months and thereafter. This initial attenuation was attributed to improvements in motor function, but the subsequent worsening may be due to changes in stimulation settings, specifically increasing voltages and pulse widths, affecting current strength and including limbic circuitry. Other studies found no significant effect on anxiety in patients with bilateral STN [38, 39].

Mania

The pathophysiology of PD mania is unclear but may be due to increased activities of dopamine D2 receptor, inositol monophosphatase, glycogen synthase kinase-3, and protein kinase-C [40–42]. In a review of 1398 patients with STN DBS, 4 % had post-surgical mania or hypomania [18]. Case reports [43–46] demonstrated resolution of mania by

changing stimulation settings. In another report, four out of 20 patients experienced mania under high-frequency stimulation over a 4-year follow-up period, but no final outcomes were noted [47]. Another noted resolution by moving the electrodes to a more rostral location [43] or by switching to a more dorsal contact [44] without changing the entire electrode. In the latter report [44], caudal STN electrode placement may trigger mania in those with underlying major depression, due to involvement of the medial forebrain bundle, an integral structure in the mesolimbic dopamine system. A PET study [48] demonstrated that hypomania and mania were significantly associated with asymmetric right anterior cingulate and medial prefrontal cortex activation during STN DBS placement.

Impulse Control Disorders (ICDs)

ICDs are pervasive phenomena associated with dopaminergic agonist therapy, levodopa, and DBS [33, 34]. A large multicenter study identified ICDs in 13.6 % of 3090 Parkinson's patients in a combined cohort of those either treated with or without DRT, with a markedly higher percentage of ICDs in those taking DRT (17.1 versus 6.9 %, respectively) [34]. ICDs are diverse (pathological gambling, binge eating, hypersexuality, and compulsive shopping) [49]. Insight into pathophysiology was obtained through PET studies in a cohort of pathological gamblers which revealed elevated glucose metabolism in both the orbitofrontal and medial frontal cortices [50, 51]. Local field potentials in 28 STN DBS patients revealed greater activation in the ventral subthalamic area in patients with ICDs [52].

Pre-existing ICDs persisted, worsened, or developed de novo after STN DBS implantation in 20 of 21 patients [49]. Punding, hypersexuality, pathological gambling, binge eating, and compulsive shopping were most commonly reported [49]. In another study, loss-chasing behavior, or continuous gambling to recover losses, was significantly elevated in DBS "On" versus "Off" states [53].

In a 3-year study of 56 patients [54] (13 of whom had pre-existing ICDs), 11 had complete remission at the 3-year mark after STN DBS; the remaining two suffered from compulsive eating. The most common pre-procedural ICD in this cohort was punding followed by hypersexuality and compulsive eating. While some patients experienced new-onset, transient (maximum duration of 15 months) ICDs during the study (compulsive eating being the most common), an overall benefit of STN DBS on ICDs was shown [54].

Compulsive behavior in post-implantation DBS and non-DBS PD patients was not different; however, impulsivity in STN DBS patients was significantly higher [55]. In contrast, four PD patients with prior hypersexuality became symptom free 17–41 months after bilateral STN DBS placement [56]. The only exception being recurrence in one patient after an 18-month period likely from his dopaminergic medication regimen. It was successfully treated by decreasing his dose [56].

Dopamine Dysregulation Syndrome (DDS)

DDS is characterized as a disturbance in impulse regulation and behavioral control resulting from long-term use or abuse of DRT [57, 58]. The nigro-mesolimbic dopaminergic pathway, particularly the dopamine D3 receptor in the nucleus accumbens (NA), is likely involved. Patients consume excessive quantities of dopaminergic medications, far exceeding the appropriate intended regimen for motor symptom control. The prevalence of DDS among Parkinson's patients is estimated to be 3–4 %[58]. Risk factors include dopamine agonist therapy, male sex, young age at onset of motor symptom, and premorbid personality traits (obsessive-compulsive behaviors) [57]. Both attenuation [59, 60] and exacerbation [61] of DDS after STN DBS were reported. In a prospective study spanning approximately 1 year in patients pre- and post-STN DBS, all patients previously diagnosed with DDS demonstrated significant improvement [60]. These results were later substantiated [59]. However, analysis of 28 patients with either STN or GPi DBS [61] demonstrated no significant change in post-operative DDS.

Globus Pallidus Interna DBS

An output nucleus of the basal ganglia, the GPi plays a constituent role in normal motor behavior and projects axons from GABA-containing neurons to the dorsal thalamus and PPN [62, 63]. The somatotopic organization of the GPi progresses leg-arm-face along both the anterior-posterior and dorsal-ventral planes.

The psychiatric effects of GPi DBS for PD were considerably less examined to date than those associated with STN DBS. Many of the general points and treatment principles discussed in the previous section on STN DBS also apply to GPi DBS for PD.

Mania

Miyawaki et al. described a single patient with recurrent episodes of mania 15 days after initiating GPi stimulation [64]. He took levodopa for 11 years and was treated with 2500 mg prior to surgery. Mania was observed after initiation of stimulation, and resumption occurred when DBS (either bilateral or unilateral) was on. Changing settings had no sustainable effect. Lowering the dose to 1250 mg per day resolved his mania at 12-month follow-up with DBS on. The authors concluded that the patient's mania was a result of stimulation and not the surgery alone [64].

Impulse Control Disorders

In a retrospective chart review [61], a significant post-operative development (17 of 28 patients) of ICDs was noted. Only two patients had resolution after bilateral implantation—one with STN and the other with GPi. Eleven patients developed newly diagnosed ICDs after unilateral DBS placement, seven of whom had GPi DBS. Six patients developed de novo ICDs after bilateral DBS placement, two with bilateral GPi leads. The comparison between STN and GPi targets did not reveal a significant difference [61]. Another patient who previously underwent right pallidotomy developed prominent hypersexuality after left GPi implantation [65].

Dopamine Dysregulation Syndrome

There was no therapeutic difference between STN and GPi DDS [61]. Five patients with pre-operative DDS who underwent unilateral GPi DBS continued to have symptoms 6 months after surgery. After receiving bilateral GPi implantation, all five continued to have DDS [61].

Cognitive Effects of STN and GPI DBS

People with Parkinson's disease typically exhibit some degree of cognitive dysfunction, with mild cognitive impairment (MCI) reported in 25 % in one large cohort and dementia being reported anywhere from 20 to 70 % in various series [66, 67]. The interaction of MCI and DBS on progression of cognitive deficits is less understood, as cognitive changes following DBS intervention are heterogeneous and related to disease progression [68, 69], medication side effects, and microlesional effects [70].

Including all therapeutic DBS targets for disorders ranging from PD to ET and the dystonias, a recent meta-analysis focusing on post-operative outcome in patients with mean age of 53.7 years reported that cognition improved in 31 %, deteriorated in 12 %, and remained unchanged in 13 % [71]. Specific cognitive effects included dementia, executive dysfunction, and mild memory impairment.

Executive Functions

In six prospective studies of bilateral STN DBS [72–77], significant impairments were noted as early as 1 month after implantation [72, 76], from 3 to 6 months [74, 75, 77] and extending through 1 year [73, 74]. Deterioration in decision-making in non-demented individuals undergoing bilateral STN DBS also was reported during the acute post-operative phase [78], with impaired executive functions at baseline being a predictor of dementia [79]. However, others have found no significant changes in executive functions [80].

In a prospective study of 20 DBS patients undergoing serial neuropsychological exams over 8 years, deterioration was evident in mental flexibility, strategizing, and planning as measured by the Modified Wisconsin Card Sorting Test [73]. A direct correlation between executive dysfunction and postural impairment also was found, the implications of which connect axial motor disability and cognition [73]. However, it is possible that the average PD duration of 21 years skewed the findings as gait and postural stability are likely to be already impaired in this cohort [73]. On the other hand, impulsivity as measured by the Stroop was found to worsen as early as 1 year postoperatively, consistent with data showing that younger people are more susceptible to impulse control problems [68]. Still, a comparison of bilateral STN patients against non-surgical controls found that 36 % surgical patients demonstrated cognitive decline 1 year after surgery. Predictive factors of cognitive decline included pre-operative executive dysfunction (trails B, Stroop Color Word), advanced age, and poor L-dopa response. However, the DBS group notably was younger, was less educated, and had longer disease duration than the non-surgical group, suggesting that the STN patients were sicker than the controls, thus rendering suboptimal group comparisons [81].

Verbal Fluency

Effects of STN DBS on verbal fluency are mostly deleterious [72, 73, 80, 82–90], attributed to stimulation effects, disease progression, and microlesional effects [80, 86]. Functional MRI studies employing verbal fluency tests through task-switching paradigms demonstrated robust activity in the left ventral occipitotemporal cortex, left frontal and parietal cortices, and left caudate and bilateral thalami [91], suggesting that a defect along various pathways can lead to fluency deficits. Both semantic and phonemic fluency were affected [84, 85, 88, 89]. Others demonstrated that unilateral STN DBS of the speech-dominant hemisphere resulted in significantly less verbal fluency decline compared to the bilaterally stimulated cohort, a finding attributed to a possibly healthier cohort [92]. The time noted for decline in fluency was variable (immediately after implantation due to possible microlesional effects [73, 93], 6 months [87], 1 year [87, 88, 90], 2–3 years [72, 84, 90], and 8 years after surgery [73]). Another study spanning 1 year, comparing those with DBS versus best medical management, found that decrement in phonemic fluency was the only cognitive deficit seen in 15 % of DBS patients [79]. Still, a 2-year study comparing STN with best medical treatment found that 26 % DBS patients declined in letter fluency compared with only 11 % of

controls, and 30 % of both groups declined in category fluency [84].

Memory

STN DBS was shown to disproportionately affect rote list learning [94] which is dependent upon frontal-subcortical circuitry [95], measured by the Rey Kim Memory Battery and Hopkins Verbal Learning Test. Decline in word-list recall was established at 6, 12 [87], and 16 months [95] postoperatively, with deficits persisting up to 10 years [68]. In a comparison of 19 bilateral STN DBS patients with 18 medically managed PD controls, 50 % of DBS patients suffered non-verbal memory impairment at 2 years post-operative follow-up. This was 20 % higher than medically managed PD participants as tested through the Brief Visual Memory Test—Revised [84].

Consistent with this, in a group of STN DBS patients with either normal cognition or MCI prior to surgery, approximately 20 % of non-MCI patients converted to amnestic MCI 9 months postoperatively, with list learning being the strongest predictor for this change [96•]. This decline was unrelated to age, PD duration, or UPDRS scores. Similar findings are reported by others up to 5 years post-surgically [79], suggesting that MCI and reduced list learning elevate risk for postoperative dementia. However, in a group of 19 non-demented patients with early onset PD who underwent STN DBS 22 years after disease onset, 5 % of patients developed dementia 1 year postoperatively, 26 % by the third post-surgical year, and 43 % patients by the 7th year following surgery [97]. This conversion to dementia 30 years after diagnosis was reported to be consistent with the prevalence of dementia in PD and, in such, was attributed to typical disease progression. While the rate of dementia reported by Merola reportedly was higher than that reported by Fasano et al. [73] in a similar STN DBS cohort, this was attributed to shorter disease duration and older age of disease onset in the latter. It also was posited that DBS renders better cognitive prognosis when completed earlier in disease course [97, 98].

With consideration for other DBS targets, a prospective study comparing best medical therapy (BMT) with either bilateral STN or GPi DBS [99•] found that STN patients showed greater bradyphrenia whereas GPi patients demonstrated greater list learning deficits 6 months postoperatively, although the difference was small. On an individual level, 20 % DBS patients deteriorated in one cognitive domain and 11 % declined in multiple domains, compared with 3 % decline in the BMT group. Deterioration was unrelated to surgical target. Two years following surgery, those with multidomain deficits declined significantly more than individuals with single domain dysfunction. It is unclear how these groups fared compared to the BMT group.

In a prospective randomized study comparing unilateral STN and GPi stimulation in moderate-to-advanced PD patients, there were no significant differences in cognition and mood between groups [100]. The COMPARE trial explored differences in both locations among 45 (22 STN, 23 GPi) patients and found a trend towards decreased verbal fluency in the STN group compared to the GPi group, likely due to an insertional or microlesional effect.

Conclusion

DBS is a rapidly evolving field, encompassing potential therapies for a growing number of neurologic disorders. Tandem with innovations in DBS therapies are unanticipated non-motor symptoms, now vastly prevalent in the literature and raising the importance of neuropsychiatric screening prior to intervention. Various psychiatric symptoms may arise or worsen after DBS. Cognitive effects such as development and progression of MCI to dementia additionally are worth discussing with any prospective DBS candidate, as these factors greatly contribute to QOL. However, cognitive dysfunction is not necessarily a contraindication to surgery, the risks and benefits of which are patient specific. In our practice, DBS was performed to improve the quality of life of those with refractory tremor or severe dyskinesias, despite considerable cognitive impairment. As there are no studies on DBS in those with dementia, we recommend that it can be considered to improve QOL in these cases as well. Additionally, while previously suggested that DBS be reserved for advanced PD, recent data suggest that cognitive outcome may be better when surgery is completed earlier in the disease course. Also, with regard to psychiatric complications, unless the patient has a premorbid psychiatric condition, a DBS lead will not cause psychiatric phenomena unless it is placed outside the motor territory of the basal ganglia. A comprehensive team of movement disorders specialists, neurosurgeons, neuropsychologists, psychiatrists, and nurses is necessary for adequate care of patients. As novel DBS targets are being explored for refractory disease, more non-motor effects may surface, and adequate knowledge and understanding of these will surely facilitate a more comprehensive patient-centered approach to therapy.

Compliance with Ethical Standards

Conflict of Interest Adam Nassery, Christina A. Palmese, Harini Sarva, and Mark Groves declare that they have no conflict of interest.

Joan Miravite is a Faculty Trainer for Medtronic.

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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