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Memory and mood outcomes after anterior thalamic stimulation for refractory partial epilepsy

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ABSTRACT

Purpose: Bilateral deep brain stimulation (DBS) of the anterior nucleus of the thalamus (ANT) reduces seizures and is relatively safe but may be accompanied by complaints of memory problems and depression. This study examined incidence of memory and depression adverse events (AE) in the SANTE study blinded phase and their relationship to objective neurobehavioral measures, baseline characteristics, quality of life and long-term neurobehavioral outcome.
Method: The neurobehavioral AE and neuropsychological data from a previously reported prospective randomized trial (SANTE) were analyzed. Reliable change indices (RCI) were calculated for memory and mood measures. Analyses examined relationships among AEs, RCIs, demographic and seizure variables, and long-term neurobehavioral outcome.
Results: No significant cognitive declines or worsening of depression scores were observed through the blinded phase or in open-label at 7-years. Higher scores were observed at 7 years on measures of executive functions and attention. Depression and memory-related AEs were not associated with reliable change on objective measures or 7-year neurobehavioral outcome. The AEs were without significant impact on life quality. Memory and depression AEs were not related to demographic or seizure characteristics, change in seizure frequency, frequency of AE or depression report.
Conclusion: Bilateral ANT DBS was associated with subjective depression and memory AEs during the blinded phase in a minority of patients that were not accompanied by objective, long-term neurobehavioral worsening. Monitoring and neuropsychological assessment of depression and memory are recommended from a theoretical standpoint and because more memory and depression AEs occurred in the active stimulation than control group.

1. Introduction

Approximately a third of persons with epilepsy continues to experience seizures despite treatment with anti-seizure drugs (ASDs) [1,2]. Of those with refractory epilepsy undergoing resection surgery, it is estimated that 32% of those with brain lesions and 57% of those without lesions are still not seizure free after surgery [3]. In addition, many patients with refractory partial epilepsy cannot undergo resective surgery due to poorly localized or multifocal onsets. This large prevalence of refractory epilepsy has profound implications for neurobehavioral morbidity because chronic epilepsy is associated with a host of cognitive and neurobehavioral deficits [4] and perhaps even cognitive disadvantage during aging [5]. Chronic partial seizures, specifically, are associated with declines in memory and executive functions [6].

Abbreviations: AE, adverse event; ANT, anterior nucleus of the thalamus; ASD, anti-seizure drug; BVMT-R, Brief Visual Memory Test-Revised; CVLT, California Verbal Learning Test; DBS, deep brain stimulation; D-KEFS, Delis–Kaplan Executive Function System; EEG, electroencephalogram; FrSBe, Front Systems Behavior Scale; Hz, hertz; IQ, intelligence quotient; MRI, magnetic resonance imaging; POMS, Profile of Mood State; RC, reliable change; RCI, reliable change indices; QOL, quality of life; QOLIE-31, quality of life in epilepsy inventory, 31-item; SANTE, stimulation of the anterior nucleus of the thalamus in epilepsy; V, volts; WASI, Wechsler Abbreviated Scale of Intelligence; WTAR, Wechsler Test of Adult Reading; μs, microseconds.

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Consequently, new, efficacious and safe therapies might, among many other benefits, ameliorate or prevent neurobehavioral morbidity associated with epilepsy in proportion to the extent that seizures cause cognitive problems.

One therapy involves electrical stimulation of the anterior nuclei of the thalamus (ANT). Following the success of initial unblinded studies [7–12], the initial blinded phase [13] and 5-year follow-up [14] results of a controlled, randomized trial (SANTE) of bilateral ANT deep brain stimulation (DBS) in 109 randomized (110 implanted) subjects were reported. At 5 years, the median percentage seizure reduction was 69% relative to baseline and during the 5 years 16% of subjects were seizure-free for 6 months or more. Given the role of the anterior thalamus in the Papez circuit (notably its inputs from hippocampus via the mammillothalamic tract and outputs to cingulate gyrus and downstream limbic structures via cingulum), and the observation of reversible memory impairment after high frequency stimulation of amygdala–hippocampus [15], it is important to evaluate the neurobehavioral safety of ANT stimulation. This evaluation is especially pertinent regarding episodic memory, complex attention, executive function, and emotion (depression/dysphoria).

One small study of 9 patients who underwent bilateral ANT stimulation and pre-surgical baseline and repeat neuropsychological testing at least 1 year after surgery reported improvements in the group as a whole in verbal memory and verbal fluency [16]. In the SANTE trial, there were no significant differences in objective neuropsychological test scores for mood and cognition between active and control groups at the end of the blinded phase; however, self-reported depression and memory adverse events (AEs) were more frequent in the active as compared to the control group [13]. Further, compared to baseline, there were no significant declines across the five years in objective test scores in any domain of cognition assessed, including verbal and visual memory, attention, executive function and expressive language [14]. Indeed, significant gains were seen in composite scores of attention and executive functions and subjective cognitive (executive) function. Although no significant verbal or visual memory score changes were observed at the group level, subjective complaints of at least transient memory dysfunction were common among individuals (25.5% in 5 years). Similarly, despite observed gains on self-report scales of symptoms of depression, anxiety, and overall mood disturbance, depression events were reported in 32.7% of subjects in 5 years. It is emphasized that AE reports of depression do not necessarily imply a syndromal depression. Specifically, persons may report that they experience "depression" when they perceive themselves having individual or several symptoms (e.g., dysphoria, anhedonia, pessimism, hopelessness, sleep disturbance, etc.), but such symptoms need not meet criteria for the diagnosis of a depressive syndrome (disorder) per Diagnostic and Statistical Manual (DSM) [17] criteria. An important aspect of depression is its association with suicidality. Over 5 years, 8.2% of individuals in the SANTE trial reported suicidal ideation and there was one completed suicide, unrelated to the device or stimulation.

Given the apparent contradiction between objective neuropsychological evaluation findings at the group level and AE reports at the individual level, this study focuses on individual patient outcomes, especially during the blinded phase, in order to put into perspective the clinical impact of subjectively reported memory or mood problems. Individual neuropsychological change is quantified via the reliable change (RC) index and the relationship between RC changes and AE reports concerning mood and memory are evaluated. The potential clinical relevance of neurobehavioral changes are assessed by comparing quality of life (QOL) using the Quality of Life in Epilepsy Inventory (QOLIE-31) in those with and without neurobehavioral adverse events.

Potential correlates of memory and depression AEs are explored, including pre-operative neurobehavioral morbidity and demographic variables. The time and course of depression and memory complaints during the study are examined. If events were similarly frequent in the active stimulation vs. implanted but not stimulated control groups during the 3-month-blinded phase, it might be that surgical implantation impacted cognition or the subjective perception of impaired cognition (i.e., produced a nocebo effect). Following the blinded phase, clustering of events early in the study might suggest a stimulation-related effect; whereas, a more random scattering of events over the study duration, or a late occurrence raises the possibility that events at different time points might have different causes and associations with various potentially mediating or moderating variables, such as seizure occurrence or frequency, medication changes, or psychosocial factors. An examination of the temporal contiguity between depression and memory events is of importance given the oft-reported much stronger relationship by which depression is associated with memory impairment [18–21]. Finally, the study presents neuropsychological test scores from baseline compared to long term follow-up at 7 years to further address stability of neuropsychological findings.

2. Material and methods

Full details of the SANTE trial design, including inclusion and exclusion criteria, have been reported [13]. Briefly, subjects were 18–65 years old and had at least 6 partial seizures per month that had proved refractory to pharmacotherapy (with at least 3 ASDs). Neurobehavioral exclusion criteria included intelligence quotient (IQ) <70, inability to take the neuropsychological tests, non-epileptic seizures, and any of the following in the 5 years preceding baseline evaluation: history of substance abuse, psychiatric illness hospitalization, suicide attempt, or symptoms of psychosis (hallucinations, delusions) not related to medication or an ictal or post-ictal state.

After 3 months during which ASDs remained stable, subjects had the device implanted with lead location verified by MRI. One month after implantation, subjects were randomized to stimulation (n = 54) or no stimulation (n = 55) at fixed device settings (5 V or 0 V, 90 μs, 145 Hz), on an intermittent stimulation schedule (1 min "on" then 5 min "off"). After 3 months of blinded treatment, all subjects received stimulation (limited range of parameters) from Month 4 to Month 13 in an unblinded fashion. Neuropsychological evaluation during that time was conducted per the schedule in Fig. 1 and annually thereafter. The neuropsychological assessment time points were chosen a priori with several considerations in mind and to allow a variety of inferences to be made about the neurobehavioral impact of surgery and DBS. Initial IQ assessment at Week-12 was designed only to determine whether the IQ inclusion criterion was met. The baseline neuropsychological assessment (Week-4) was timed to balance several competing issues: maximization of test–retest (baseline to post-implantation) interval to minimize practice effects, while minimizing the test–retest interval to minimize the likelihood that factors extraneous to surgical implantation affect test score changes, and to minimize pre-surgical anxiety (which likely peaks close to surgery) effects on testing. The second (Week 4, operative phase, post-implantation assessment without stimulation) was included to distinguish potential neurobehavioral effects of surgery vs. stimulation via comparison to baseline and to provide a measure close in time before stimulation onset to most accurately compare neurobehavioral impact of DBS by comparing change in the active and control groups from operative phase to end of blinded phase. The third assessment at the end of the 3-month blinded stimulation phase (Month 4) permits comparison of change from baseline and