Subcallosal cingulate DBS produces current-dependent changes in autonomic arousal

Patricio Riva Posse, MD1; Cory S. Inman, MA2; Stephan Hamann, PhD2; Steven Garlow, MD, PhD1 and Helen Mayberg, MD1

1Department of Psychiatry and Behavioral Sciences and 2Department of Psychology
Emory University

Abstract

Subcallosal cingulate (SCC) deep brain stimulation (DBS) has shown preliminary long-term efficacy and safety for treatment resistant depression (TRD). Immediate changes in mood and behavior with sub-threshold DBS have also been observed. These immediate behavioral effects have successfully guided selection of the optimal electrode contact, and these effects are often predicted of long-term outcomes. Spontaneous self-reported intra-operative effects include “feeling lighter, calmer”, “more connected, “feeling warm, flushed”, “more interested”, “tingling”, “feeling aroused”, “more awake, more aware, more reactive” and “like a wave while inattentive”. These subjective effects are accompanied by changes in autonomic markers such as skin conductance responses (SCRs) during sub-threshold irritation. These SCR changes are observed within seconds of initiating acute stimulation and prior to verbalization of subjective feelings, and appear to correlate with the optimal anatomical target for long term stimulation. To test the potential utility of SCC to further define optimal stimulation parameters, SCC was measured during an acute stimulation protocol performed after 3 months of chronic DBS.

Methods

Three participants in an ongoing research study of SCC DBS for TRD were tested. At the time of the experiment, the patients were receiving bilateral stimulation at a single, monopolar contact in each hemisphere with stimulation parameters held constant over a 3 month period. Frequency=130 Hz, pulse width = 91 μs, current=8 mA. Time-locked changes in SCC were recorded simultaneously varying the current amplitude on the chronically stimulated DBS contacts. SCC was recorded from the medial phalanges of the index and middle fingers on the nondominant hand. Participants were instructed to remain quiet and refrain from verbal or non-verbal communication. Baseline stimulation was performed at the beginning and end of the protocol.

Four measures were derived for each of the two minute stimulation periods: (1) the average maximum SCC amplitude, (2) the proportion total number of SCRs, and (3) the proportion cumulative SCR magnitude showed a similar dose-dependent increase in sympathetic arousal with SCC DBS. Thus, this measure is indicative of SCC reactivity and SCR size during stimulation.

Four measures were derived for each of the two minute stimulation periods: (1) the average maximum SCC amplitude, (2) the proportion total number of SCRs, and (3) the proportion cumulative SCR magnitude showed a similar dose-dependent increase in sympathetic arousal with SCC DBS. Thus, this measure is indicative of SCC reactivity and SCR size during stimulation. To test the potential utility of SCC to further define optimal stimulation parameters, SCC was measured during an acute stimulation protocol performed after 3 months of chronic DBS.

Results

For all subjects, the average maximum SCR amplitude increased as a function of increases in stimulation current across the stimulation period (Figure 3A).

8 mA, the current used in these participants for chronic stimulation, generated the most robust acute SCR effects.

The proportion total number of SCRs also increased with increasing current (Figure 3B).

The proportion cumulative SCR magnitude showed a similar dose-dependent effect to the other SC measures with a larger cumulative SCR magnitude for 8 mA of stimulation than for any other current dose (Figure 3C).

Background

Skin conductance activity is a sensitive index of autonomic arousal, resulting from sympathetic innervation of the skin, and measured by alterations in the conductance of an applied current.

Intraoperative Subcallosal Cingulate Deep Brain Stimulation (SCC DBS) produces spontaneous reports of symptoms that suggest autonomic activation

Skin conductance responses (SCR) were conducted three months after chronic SCC DBS to define additional stimulation parameters

Methods

- Three subjects (2 females, 1 male; mean age 50.6 years old) enrolled in an ongoing research study of SCC DBS for treatment resistant depression were tested. All patients had Major Depressive Disorder. Mean 17.6-item HAMD at inclusion was 22.3 points. Mean HAMD score at time of testing was 14.3 points.

- Subjects had received chronic bilateral DBS with constant stimulation parameters for three months (single, monopolar contact in each hemisphere, frequency 130 Hz, pulse width = 91 μs, current=8 mA) (Figures 1A & B).

- Time-locked changes in SCR were recorded while simultaneously varying the current amplitude on the chronically stimulated DBS contacts. SCR was recorded from the medial phalanges of the left and middle fingers on the non-dominant hand.

- Baseline SCR was recorded (stimulation OFF, chronic parameters). Current amplitudes were then varied using a stepwise design, alternating 2 minutes OFF and 2 minutes ON, with steps at 2, 4, 6, 8 mA and then desensitizing in reverse order. Sham stimulation was performed at the beginning and end of the protocol.

- Three measures were derived for each of the two-minute stimulation periods: (1) the average maximum SCR amplitude, (2) the proportion total number of SCRs, and (3) the proportion cumulative SCR magnitude.

- For all subjects, the average maximum SCR amplitude increased as a function of increases in stimulation current across the stimulation period (Figure 3A).

- 8 mA, the current used in these participants for chronic stimulation, generated the most robust acute SCR effects.

- The proportion total number of SCRs also increased with increasing current (Figure 3B).

- The proportion cumulative SCR magnitude showed a similar dose-dependent effect to the other SC measures with a larger cumulative SCR magnitude for 8 mA of stimulation than for any other current dose (Figure 3C).

Conclusion

- SCC DBS elicits a current-dependent increase in sympathetic arousal in patients with TRD.

- This effect is seen upon initial stimulation in the operating room, maintained with chronic DBS delivered over 3 months and reproduced following short-term discontinuation and repeat acute testing, with maximal effects seen at clinically relevant parameters.

- At present, DBS contact selection is based purely on SCC anatomy and trial and error testing of individual contacts.

- These findings suggest that SCC DBS modulates brain regions involved in autonomic regulation consistent with known anatomical connectivity of SCC to brainstem in humans and animals.

- As such, these physiological findings may both help to optimize contact selection as well as identify thresholds for stimulation parameters for chronic stimulation.

- Current-dependent changes in sympathetic arousal with SCC DBS provide a novel strategy for examining the interactions of affective experience and the autonomic nervous system in TRD.

Grant Support: Hope for Depression Research Foundation, Dana Foundation
Devices donated by St Jude Medical Inc.
FDA IDE G060028 (sponsor HSM)
Clinicaltrials.gov ID#: NCT00367003
FDA IDE G060028 (sponsor HSM)
Disclosure: HSM has IP licensing and consulting agreements with SMP, Inc.
For more information please email Patricio Riva Posse, MD
privapo@emory.edu