Behavioural Improvement in Minimally Conscious State After

Caloric Vestibular Stimulation: Evidence from two single case studies.

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Abstract

Objective: To investigate whether caloric vestibular stimulation, a non-invasive form of neuro-modulation, alters level of awareness in people residing in minimally conscious state.

Design: Single-case (n=2), prospective, controlled (ABAB) efficacy study.

Setting: Tertiary, neuro-rehabilitation in-patient ward within a university hospital

Participants: Two individuals in minimally conscious state

Intervention: Left ear caloric vestibular stimulation was performed in two four/five-week blocks interleaved with two four/five-week blocks of sham stimulation. Session duration and frequency gradually increased within each block from once per day for 10 minutes (week 1) to once per day for 20 minutes (week 2) to 20 minutes twice per day in the remaining weeks.

Measures: Wessex Head Injury Matrix, JFK Coma Recovery Scale – Revised.

Results: Both participants' Wessex Head Injury Matrix scores indicated a transition from involuntary (i.e. mechanical vocalization) to voluntary (i.e. gesture making, selective responses to family members) behaviour that was time-locked to the onset of active stimulation. In one participant, this improvement persisted for at least 4 weeks after active stimulation while in the other it diminished 2 weeks after stimulation. Allied, although less dramatic, changes were seen on the arousal and auditory subscales of the JFK Coma Recovery Scale – Revised.

Conclusion: The data provide the first evidence that vestibular stimulation may help improve outcome in low awareness state although further studies are needed to replicate effect and determine longer-term benefit.

Key words: caloric stimulation, minimally conscious state, disorders of consciousness

Introduction

Individuals in minimally conscious state typically show reflexive or spontaneous behaviours and experience sleep-wake cycles. However, they suffer from a severely degraded consciousness in which minimal and inconsistent but nevertheless reproducible behavioural evidence of self or environmental awareness is demonstrated.[1] Initial study suggests that amantadine may promote recovery,[2] but there are no firm evidence-based guidelines for treatment and emergence from minimally conscious state remains uncertain. The aim of the present study was to make a preliminary assessment of whether caloric vestibular stimulation can promote recovery.

Caloric vestibular stimulation involves the injection of thermal current into the external ear canal which in turn alters the density of endolymph within the nearby semi-circular canals and otolith organs.[3] The subsequent change in afferent firing rate of the vestibular nerve simulates a natural head movement which, via basal forebrain/brainstem projections through central thalamus and hypothalamus,[4] elicits a variety of compensatory responses in distal frontal-parietal and striatal networks associated with arousal and goal-directed behaviour.[5,6] The minimally conscious state is typically characterized by chronic under activation of this brainstem/basal forebrain projection system following diffuse or multi-focal cerebral injury which raises the possibility that caloric vestibular stimulation may have a restorative effect.[7,8] In the sections below we report favourable responses to caloric vestibular stimulation in two individuals diagnosed as minimally conscious.

Method

Participants

Both individuals were residing in a tertiary neuro-rehabilitation unit within a university hospital at the time of enrolment.

Participant 001

- male, aged 70 years
- admitted to hospital following ventricular fibrillation arrest that returned to spontaneous circulation within 20minutes. MRI sequences (FLAIR, T1-weighted, diffusion-weighted) showed changes suggestive of hypoxic damage with prominent lateral ventricles and sulcal spaces. Focal areas of increased signal were also apparent in posterior left parietal lobe.
- enrolled to study 6 months post-onset with a Glasgow Coma Scale of 5.[9] Behaviour compatible with a minimally conscious state[1,10]; did not open eyes on command but had reactive pupils with preserved oculocephalic and corneal reflexes along with episodes of spontaneous teeth grinding, grunting and yawning. Occasional, reproducible evidence of eye contact and visual tracking.

Participant 002

- male, aged 51 years
- sustained a bilateral paramedian thalamic infarction and bifrontal swelling after the removal of an olfactory groove meningioma. The bifrontal swelling required a craniectomy and ventriculoperitoneal shunt (the cranial bone was not reinserted until after study and the shunt remained in place throughout).
- enrolled 5.5 months post-onset with a Glasgow Coma Scale of 6.[9] Behaviour compatible with a minimally conscious state[1,10]; sustained periods of eye opening with preserved oculocephalic and corneal reflexes along with

episodes of spontaneous teeth grinding, grunting, and sighing. Occasional, reproducible evidence of eye contact and emotional reaction to family members.

Design

Both participants were enrolled into a 16 or 18 week (depending on anticipated hospital discharge date) ABAB cross-over design in which four/five weekly periods of caloric vestibular stimulation were alternated with equal periods of sham stimulation. Stimulation was administered daily, excluding weekends, at escalating duration and frequency; in the first week of each block, participants received a single 10minute session of stimulation per day; in the second week they received a single 20minute session per day, and in the third and fourth (and fifth) weeks they received two 20minute sessions per day. Conventional treatment –the Sensory Modality and Rehabilitation Technique - was suspended at study enrolment. Neither were in receipt of neuro-stimulant or suppressive medication in the weeks before or during study.

Intervention

The conventional method of caloric vestibular stimulation involves ice-cold water irrigation of the external ear canal which induces sickness and nausea, is difficult to regulate and produces a relatively swift habituated response. This makes it unsuited for repeated or therapeutic administration.

In the present study, we overcame these problems by means of a novel, hand-held, solid-state device which induces thermal current via a Peltier module encased within an aluminum ear-probe housed within headphones (Scion Neurostim, LLC). We chose caloric over galvanic vestibular stimulation because the former is associated with a broader cortical response,[11] and does not run the risk of skin irritation that can follow from repeated application of trans-mastoidal galvanic current.

Based on the finding that the vestibular nerves reach asymptote at approximately 15^0C,[12] we delivered cool as opposed to cold waveforms that do not elicit unpleasant side-effects and which, by adhering to a sinusoidal rather than box-car profile, reduce physiological habituation. During active sessions, stimulation was applied to the left external ear canal and cycled continuously between 34^0 C and 15^0 C at a rate of approximately 2.5minutes. The device is programmed to shut-down if the temperature falls outside this range and, as an additional safety feature, each stimulation run generates a log-file that is later downloaded (by a non-blinded researcher) to verify that the actual temperature of the ear-piece matches that specified by the software. Cool temperatures were delivered unilaterally to the left rather than right ear because this particular set-up is more common in clinical studies and, partly as a consequence, has the largest evidence base with which to predict a favourable response.

During sham stimulation, the headset was placed on the head and while the hand-held control unit illuminated as usual, the Peltier remained unpowered. Sham and active stimulation sessions were administered by the same individual in blinded fashion.

Outcome assessment

Behavioural outcome measures were collected by a designated member of the participants' occupational therapy team experienced in the administration of assessment scales sensitive to disorders of consciousness. In line with the recommendations of Seel et al.,[13] and in keeping with local practice guidelines, behavioural status was measured using the Wessex Head Injury Matrix and Coma Recovery Scale-Revised.[14,15]

The Wessex Head Injury Matrix is an observational scale designed to capture increasingly complex spontaneous ‘everyday and relevant’ behaviours such as looking at magazines or watching TV, while the Coma Recovery Scale-Revised seeks to elicit specific behaviors within a formal and replicable assessment procedure such as the execution of a movement towards a target object placed nearby. Given these different sensitivities, an increase on one scale may not be apparent on the other yet can still be indicative of recovery. Both indices were administered at the end of each week at the same time and in the same place (both individuals resided throughout study in their own, quiet, overhead-lit room adjacent to the main neuro-rehabilitation ward).

Research ethics

Both individuals were enrolled following approval from the NRES-London Harrow research ethics committee and, following a best interests meeting, the agreement of personal consultees and care teams. Their agreement was motivated by the unchanging state of the individuals concerned and the understanding that mild vestibular stimulation is not typically associated with discomfort or adverse effect.

Results

Both participants showed behavioural improvement that was time-locked to the onset and offset of active stimulation (see Figures 1 and 2). At baseline, Participant 001 showed a limited and inconsistent behavioural repertoire with eyes mostly closed that involved a series of seemingly involuntary actions; spontaneous moaning and groaning in the absence of sensory stimulation, yawning, sighing, teeth grinding, marked arousal and agitation prior to defecation/urination. The first 4 weeks of active stimulation were associated with a steady and dramatic increase in response and culminated with the participant switching gaze from one person to another spontaneously on hearing them speak, and smiling when spoken to by a familiar person. On crossing to the block of sham stimulation, his Wessex Head Injury Matrix score declined and although still indicative of voluntary behaviour (frowning to show dislike to a clinical procedure and silent mouthing), was marked by an absence of smiling and directed attention.

Recommencement of active stimulation was associated with further improvement that again proceeded in a stepwise manner and culminated in the ability to initiate conversation and correctly answer simple questions of orientation (e.g. what day is it, where are you now?). This level of performance persisted throughout the subsequent sham block and was still subjectively evident 2 weeks later at hospital discharge. As can be seen in Figure 1a, increased Wessex Head Injury Matrix scores were mirrored by increased scores on the arousal subscale of the Coma Recovery Scale-Revised which reflected sustained periods of eye-opening. Although increases in the total score of the Coma Recovery Scale-Revised did not coincide quite so tightly with the onset and offset of active stimulation, Figure 1b clearly shows that the total score increased over the course of study, with the majority of improvement occurring during active rather than sham stimulation.

Figures 1a and 1b here

Contrary to participant 001, participant 002 showed no behavioural change during the first block of active stimulation. His drop in Coma Recovery Scale-Revised auditory subscale score during this period coincided with the onset of an acute respiratory infection.

Participant 002 did however show behavioural improvement during the second active stimulation block (see Figure 2). Within three days of starting, his Wessex Head Injury Matrix score increased and remained constant until well into the sham stimulation block. This score was marked by the vocal expression of mood and basic need, a selective response to family members and frowning/grimacing to show dislike when subject to a (sometimes non-pain inducing) clinical procedure. Previously, his frowning/grimacing had seemed spontaneous rather than stimulus-linked. These changes were accompanied by an increase in Coma Recovery Scale-Revised auditory sub-scale score which reflected an ability to localize to sound (see Figure 2a). This increased capacity, coupled with a temporary, inconsistent increase in arousal, also led to a higher total sum score on the Coma Recovery Scale (see Figure 2b).

Figures 2a and 2b here

Discussion

Both participants showed behavioural improvement that was time-locked to the onset/offset caloric vestibular stimulation and subsequent to a 5 to 6 month period in which none of these higher cognitive capacities had been recorded during weekly assessment. We believe it physiologically plausible that the improvement was therefore driven by caloric vestibular stimulation, and a larger study is now needed to both reproduce the observed treatment effects and investigate the degree to which dose, disease chronicity, level of consciousness, brain injury and physical co-morbidity influence response.

The presence of acute respiratory infection during the first period of stimulation may explain why 002 showed a delayed response. His relatively shortlived response to stimulation is perhaps more difficult to determine but we note that, unlike 001, he suffered from bi-thalamic lesions. As suggested by other researchers and evidenced by the neuropathology of Karen Ann Quinlan who was in a vegetative state for many years,[16,17] it may be that this structure is not only critical for arousal but also for the maintenance of cognition and awareness. It is also possible that the thalamic injury sustained by 002 limited the extent to which the ascending vestibular signals triggered by our stimulation procedure could elicit cortical activity.

On a cautionary note, the frequency of observations within each study phase was relatively low which may have masked greater response variability. Also our study involved only two participants and it is possible that they were beginning a spontaneous recovery phase. Recovery from coma following diffuse hypoxic or multifocal cerebral injury may occur slowly and in line with this, both showed a small change in Wessex Head Injury Score in their final baseline session. However, this change was of little functional significance and was consistent with the minor, transient fluctuations occasionally observed in the preceding months. Perhaps more important, if the participants were undergoing natural recovery then this would not be expected to progress in the time-locked fashion observed over the following 16-18 weeks of active and sham stimulation.

From a broader perspective, we note that the re-emergence of voluntary behaviour depends on the reintegration of multiple cognitive functions distributed across large neuronal assemblies.[18] Both animal and human functional imaging studies indicate that caloric vestibular stimulation modulates activity within the thalamic-cortical projection system believed central to this reintegration process,[5,18] but until now the likely relevance of this modulatory activity to overcoming minimally conscious state has not been demonstrated. The sustained improvement observed in participant 001 gives hope that repeated sessions of caloric vestibular stimulation can catalyse lasting neuroplastic change within this activating system.

Our results also give impetus to the idea that the vestibular sense is not only, as traditionally thought, central to autonomic motor control but also to the formation and maintenance of higher cognitive states. Studies indicate that the linear, angular and gravitational accelerations signaled by the vestibular system contribute to egocentric perception and body ownership.[19] The current findings suggest that these signals also help revive global consciousness and purposeful behaviour which points towards an altogether more profound role.

No treatment has yet been adopted within routine clinical practice that reliably improves consciousness in the minimally conscious state. The poor prognosis and the resulting need for prolonged and costly total nursing support, invasive nutrition, hydration and, in some cases ventilation, accounts for the pessimistic view of those in both the medical and legal professions. As highlighted by several, preliminary, pharmacological and neuro-modulatory successes,[20,21] any treatment that could provide even a small, consistent improvement in consciousness would be of major medical, legal and ethical interest, particularly if like caloric vestibular stimulation it were non-invasive and potentially inexpensive.

Clinical Message

- Caloric vestibular stimulation seemed to lead to a time-linked and partially irreversible improvement in the level of awareness and responsiveness in at least one person in the minimally conscious state.

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Conflict of Interest

The authors declare that there is no conflict of interest.

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Figure Legends

Figure 1. Participant 001's scores on the (a) Wessex Head Injury Matrix (max = 62) and the Coma Recovery Score-Revised arousal subscale (max = 3) and (b) CRS-R sum total (max = 23). Abbreviations: WHIM = Wessex Head Injury Matrix, CRS-R = Coma Recovery Score-Revised, AC = active treatment, SH = sham treatment. Baseline sessions were separated by 1 week and performed in the 4 weeks preceding active intervention.

Figure 2. Participant 002's scores on the (a) Wessex Head Injury Matrix and Coma Recovery Score-Revised auditory subscale (max = 4) and (b) CRS-R sum total.

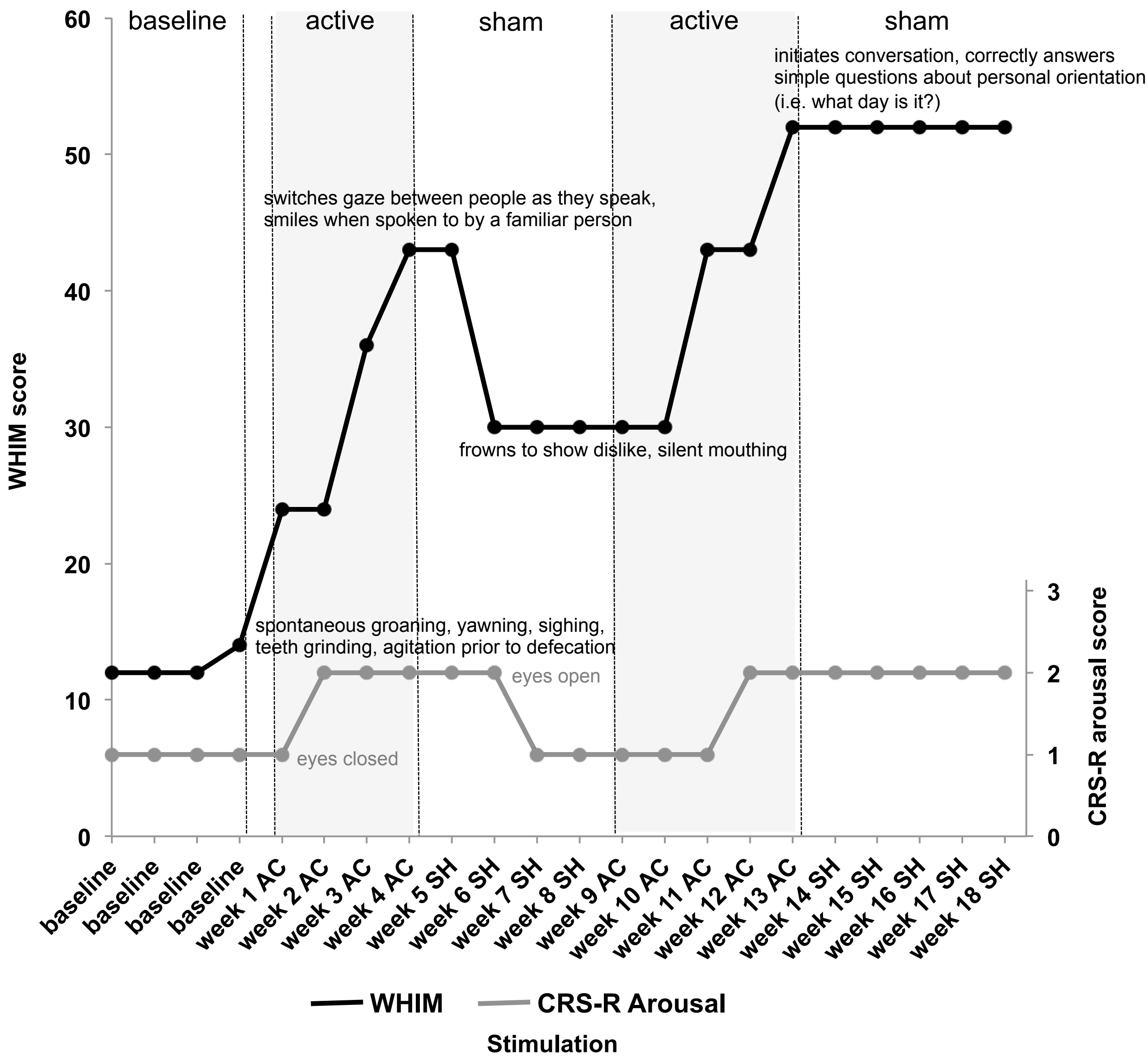

baseline
active
sham
active
sham
initiates conversation, correctly answers
simple questions about personal orientation
(i.e. what day is it?)
switches gaze between people as they speak,
smiles when spoken to by a familiar person
frowns to show dislike, silent mouthing
spontaneous groaning, yawning, sighing,
teeth grinding, agitation prior to defecation
eyes open
eyes closed
WHIM score
CRS-R arousal score
60
50
40
30
20
10
0
3
2
1
0
baseline
baseline
baseline
baseline
week 1 AC
week 2 AC
week 3 AC
week 4 AC
week 5 SH
week 6 SH
week 7 SH
week 8 SH
week 9 AC
week 10 AC
week 11 AC
week 12 AC
week 13 AC
week 14 SH
week 15 SH
week 16 SH
week 17 SH
week 18 SH
WHIM
CRS-R Arousal
Stimulation

Figure 1a

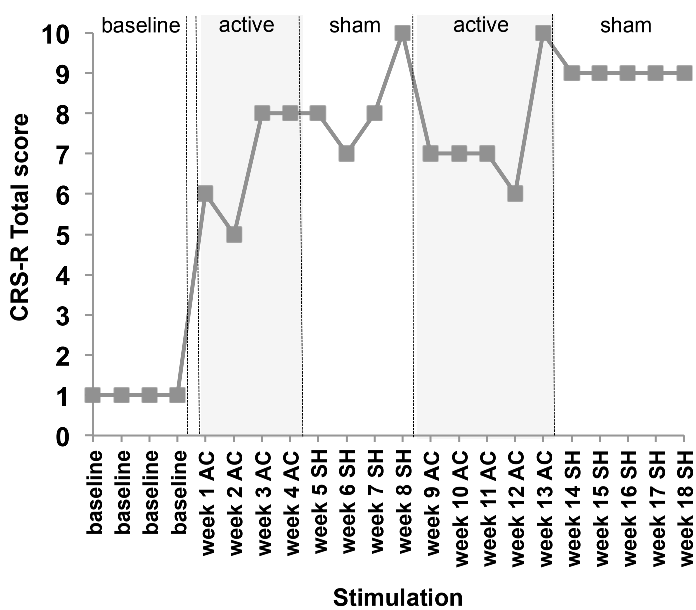
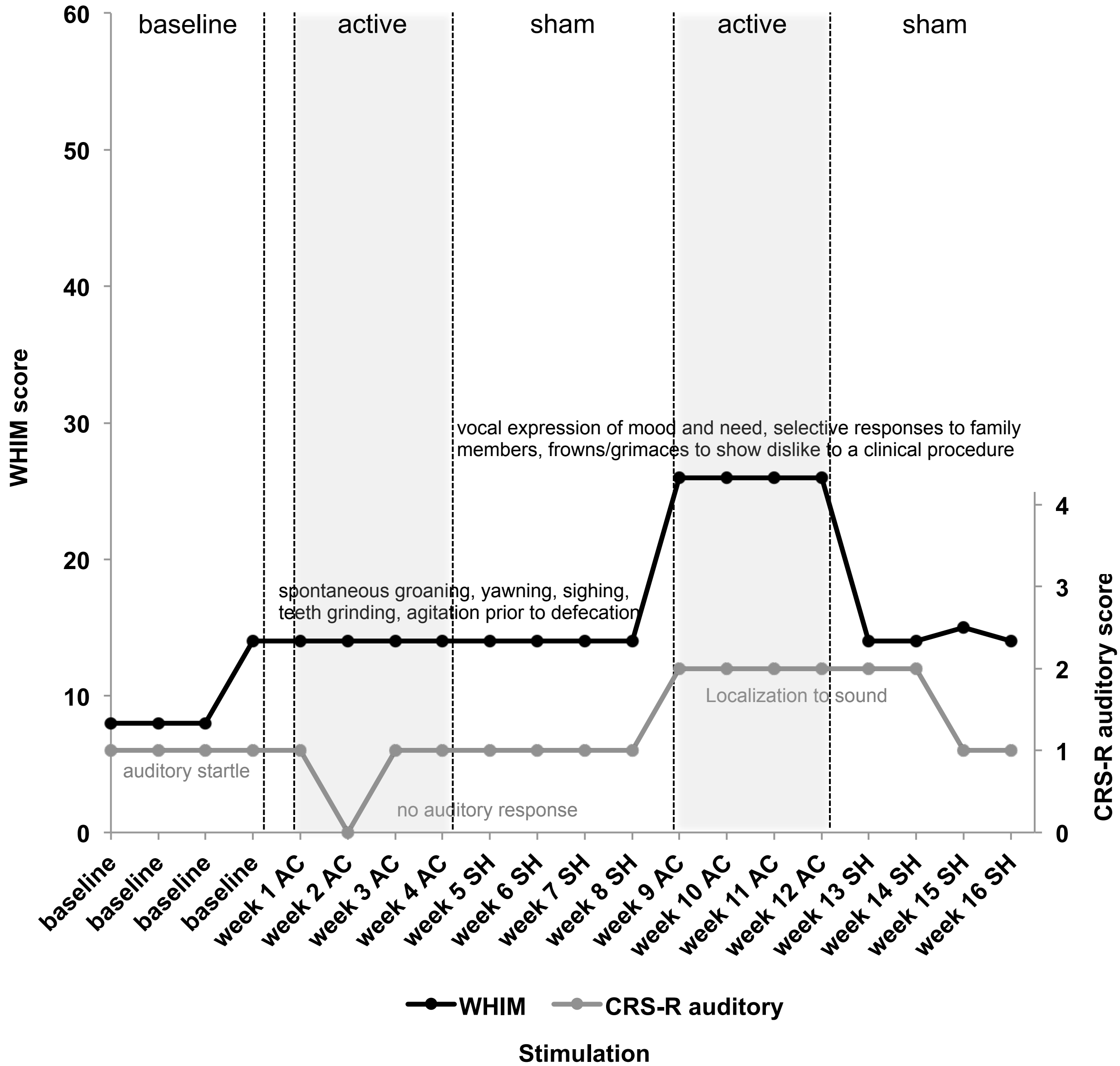

baseline
active
sham
active
sham
CRS-R Total score
0
1
2
3
4
5
6
7
8
9
10
baseline
baseline
baseline
baseline
week 1 AC
week 2 AC
week 3 AC
week 4 AC
week 5 SH
week 6 SH
week 7 SH
week 8 SH
week 9 AC
week 10 AC
week 11 AC
week 12 AC
week 13 AC
week 14 SH
week 15 SH
week 16 SH
week 17 SH
week 18 SH
Stimulation

Figure 1b



baseline
active
sham
active
sham
vocal expression of mood and need, selective responses to family members, frowns/grimaces to show dislike to a clinical procedure
spontaneous groaning, yawning, sighing, teeth grinding, agitation prior to defecation
Localization to sound
auditory startle
no auditory response
WHIM score
CRS-R auditory score
60
50
40
30
20
10
0
4
3
2
1
0
baseline
baseline
baseline
baseline
week 1 AC
week 2 AC
week 3 AC
week 4 AC
week 5 SH
week 6 SH
week 7 SH
week 8 SH
week 9 AC
week 10 AC
week 11 AC
week 12 AC
week 13 SH
week 14 SH
week 15 SH
week 16 SH
WHIM
CRS-R auditory
Stimulation

Figure 2a

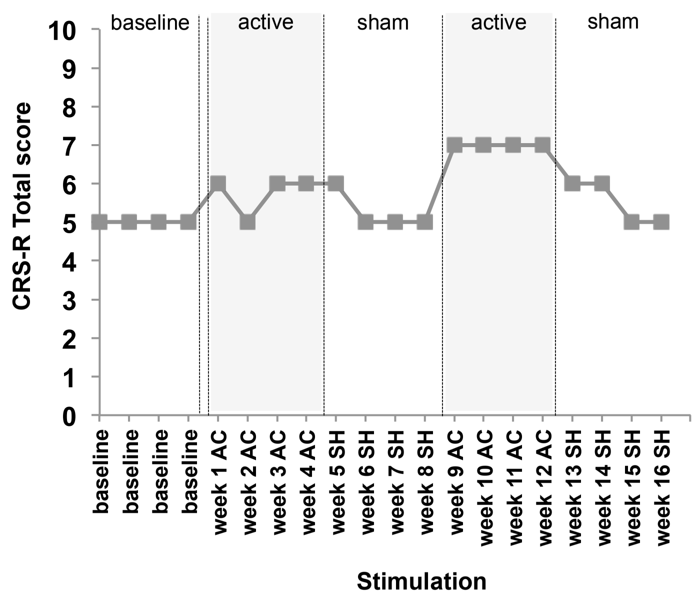

baseline
active
sham
active
sham
CRS-R Total score
0
1
2
3
4
5
6
7
8
9
10
baseline
baseline
baseline
baseline
week 1 AC
week 2 AC
week 3 AC
week 4 AC
week 5 SH
week 6 SH
week 7 SH
week 8 SH
week 9 AC
week 10 AC
week 11 AC
week 12 AC
week 13 SH
week 14 SH
week 15 SH
week 16 SH
Stimulation

Figure 2b