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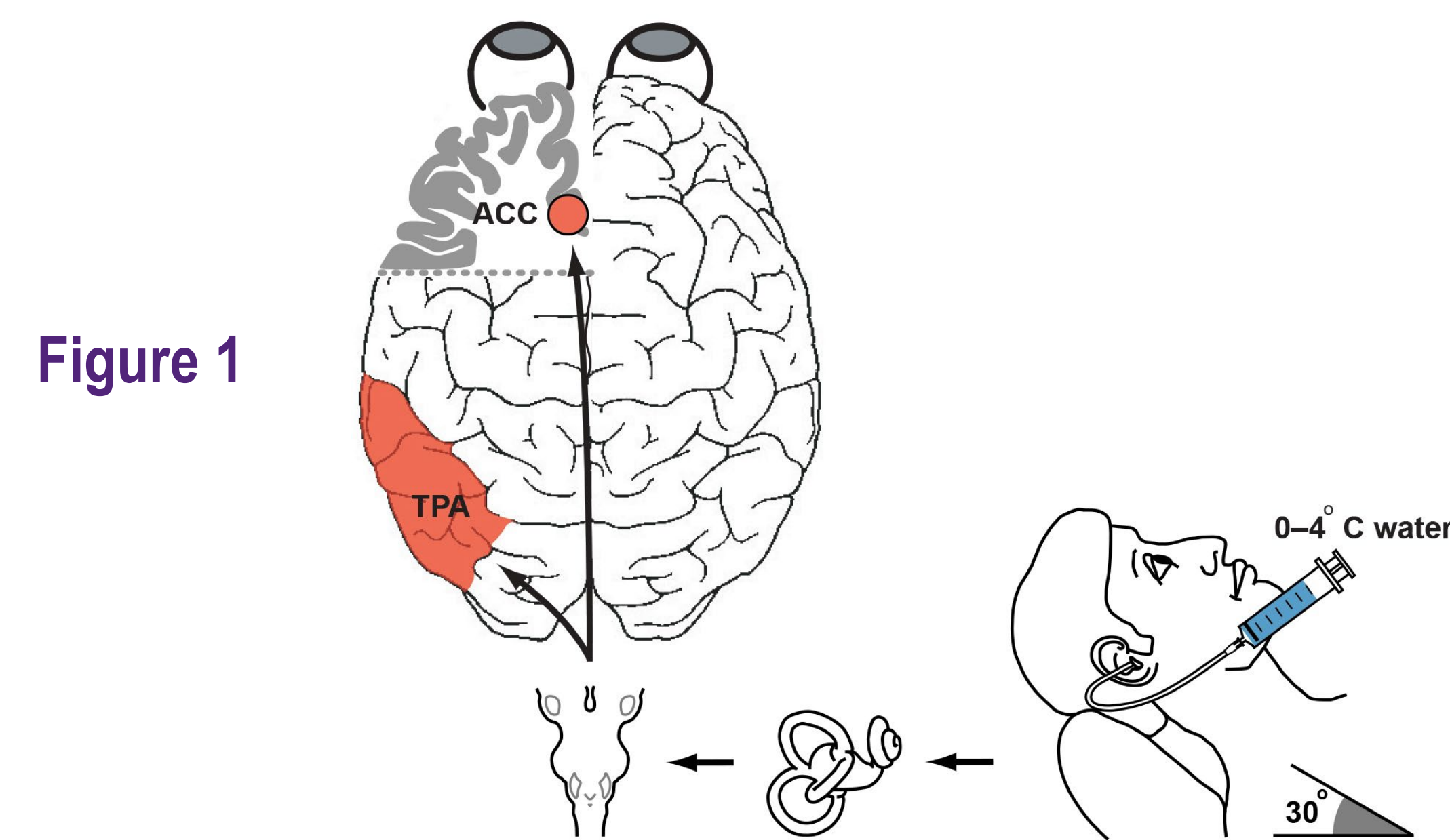
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BACKGROUND

- Fibromyalgia (FM) and myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) are flagship centralized (nociplastic) disorders, characterized by widespread pain & fatigue.
- A recent pilot trial suggests vestibulocortical stimulation (VCS) can rapidly relieve nociplastic pain [1] in refractory FM patients that was sustained for up to 1 week.
- Despite its routine clinical use, concerns remain regarding tolerability. This study aimed to replicate findings of VCS-induced analgesia and assess its effects on quality of life, safety & tolerability.

Vestibulocortical Stimulation (VCS) aka Caloric Test

- Used to assess disorders of balance, dysequilibrium & brainstem reflexes.
- Non-invasive, safe, simple, inexpensive & widely accessible.
- Since the 1940's and esp. 1970's, this neurodiagnostic test — via caloric irrigation — has also been shown as a form of therapeutic neuromodulation [2].



- **VCS consistently activates a multimodal endogenous network [Figure 1]** including vestibular nuclei (brainstem), thalamus & putamen (in basal ganglia), pedunculopontine nucleus, anterior cingulate cortex (ACC), posterior insular & retroinsular cortices, temporoparietal junction (TPA = temporoparietal areas), somatosensory area SII, inferior parietal lobule, parietal operculum & superior temporal gyrus;
- In healthy individuals, notable temporary effects shown on tactile/body perception, positively biased beliefs, mood & affective control;
 - Positive therapeutic effects shown in neurological & psychiatric disorders (e.g., migraine, hemineglect, anosognosia, Parkinson's disease, mania, schizophrenia) and **centralized pain syndromes (CPS)** including central post-stroke pain, migraine, transverse myelitis, phantom limb pain & CRPS/allodynia [3–8].

METHODS

Participants, Study Design, Outcome Measures & VCS Procedure

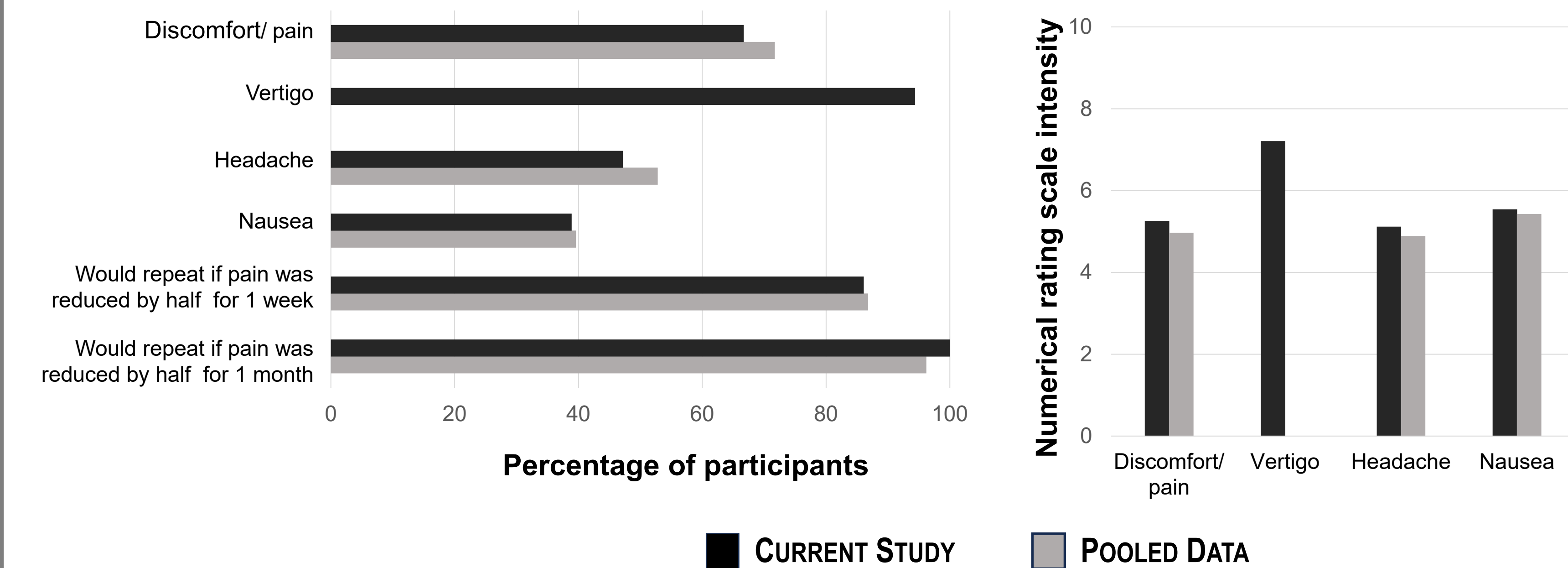
- 39 patients with nociplastic pain & fatigue (mean age = 40.2; 87% female): 23 met criteria for ME/CFS (2015 IOM criteria) and 16 for FM (2011 ACR criteria) +/- ME/CFS;
- Non-randomized open-label effectiveness trial (NCT06559839);
- Each participant completed validated electronic patient-reported outcomes at baseline, prior to receiving a single treatment of unilateral right-ear cold-water (4°C) irrigation at 1–2 cc/second, which was confirmed post-procedure by observing nystagmus & reported vertigo;
- Pain & quality of life measures were reassessed at post-intervention 30 minutes, 1 day, 1 week, 2 weeks & 4 weeks.
- Patients rated their experience of VCS at 24-hours post-procedure,² regarding amplitude of perceived discomfort along with frequency & intensity of any headache, nausea & vertigo.
- Participants were asked if they would have the intervention repeated if their pain was reduced by 50% or more for one week, and for one month.

→ **OBJECTIVE:** Replicate our recent findings of VCS-induced analgesia in FM [1] and assess its broader impact on quality of life in nociplastic disease — including the first examination of VCS therapy in ME/CFS — to inform the design of randomized placebo-controlled trials.

RESULTS

- VCS was found to be safe & generally well tolerated in this cohort of patients with FM and ME/CFS [Figure 1].**
- Subjective feedback was majority positive (47%) and minimally negative (9%), with 44% categorized as neutral.
- Vertigo was nearly universally reported (94%), with an average intensity of 7/10 on a numeric rating scale (NRS 0=very mild, 10=strong). 31% of participants found the procedure non-noxious, and 69% reported it as unpleasant or painful. Other side-effects included headache (47%) & nausea (41%), which were less frequent & less intense (mean = 5/10 on NRS for both).
- Two patients reported symptom flares after the procedure (e.g., worsening cognitive fog, pain relapse after 48h of relief). **The large majority of patients reported they would repeat the procedure if it reduced their pain by half or more for one week (86%) or for one month (100%).** There were no major adverse effects.
- Results were pooled with data from the previous study (total N=56: 39+17) [1] to compare tolerability effects, which overall were relatively stable [Figure 2] — 'Pooled Data'. The previous study did not collect vertigo intensity ratings.

Figure 2 → Tolerability results for the current study (black bars) and pooled data including participant ratings from the current study & previous study (grey bars)



DISCUSSION

- FM and ME/CFS overlap in pathophysiology & phenotype, and patients are often refractory to standard-of-care, highlighting the need for new safe & effective treatments.
- This study provides further preliminary evidence supporting the safety & tolerability of VCS [9], along with its analgesic effectiveness [10].
- These patient-centered results counter the prevailing misconception that the procedure is uncomfortable & intolerable when used for such (novel) therapeutic purposes.
- This work will be further examined in a placebo-controlled randomized trial currently under design.

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