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Effects of 40 Hz Auditory Stimulation on Postoperative Delirium: A Prospective Single-Arm Study

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Postoperative delirium (POD) is one of the most common and serious complications following major surgery in elderly patients. It is characterized by fluctuating attention, awareness, and cognition.[1] The reported incidence of POD ranges from 15% to 50%, and is associated with prolonged hospitalization, increased healthcare costs, higher mortality, and a greater long-term risk of cognitive decline, including dementia.[2] Despite its clinical significance, standardized, effective, and safe treatments remain unavailable. Dysregulation of neural network connectivity, particularly in the gamma-frequency band, has been implicated in the pathogenesis of POD.[3]

Emerging preclinical and clinical evidence suggests that 40-Hz gamma-band entrainment can enhance neural synchrony and improve cognitive function.[4] Based on this concept, we conducted a prospective, single-arm pilot study to evaluate the safety and efficacy of 40-Hz pure-tone auditory stimulation for established POD in elderly non-cardiac surgical patients. The study at Shanghai Jiao Tong University was approved by the Institutional Ethics Committee (approval number: ChiCTR2500098286, date: 30.04.2024) and was conducted between February 2022 and April 2025. Written informed consent was obtained from the relatives of all patients.

A total of 124 patients aged 65-80 years who underwent elective noncardiac surgery were screened. After applying inclusion and exclusion criteria and accounting for dropouts, 97 patients completed follow-up. Sixteen patients (16.5%) developed POD and received the aforementioned intervention. Baseline characteristics included a mean age of 69 ± 4.25 years, a median body mass index of 26.2 kg/m² (24.5-28.1) kg/m², 7 males (43.8%), and 13 American Society of Anesthesiologists II (81.3%). The surgical types were abdominal (43.8%), orthopedic (31.3%), and spinal (25.0%). Common comorbidities included hypertension (68.8%) and diabetes (31.3%). The median duration of anesthesia was 135.6 min (Table 1).

The intervention consisted of two daily 1-h sessions of 40-Hz pure-tone stimulation (50-60 dB) administered in a quiet ward, with patients listening to the sound while keeping their eyes closed. The intervention time window was 24-72 h postoperatively. Each session lasted 30 minutes and was conducted twice daily, from 9:00-9:30 a.m. and from 3:00-3:30 p.m. Delirium was assessed daily using the Confusion Assessment Method, which evaluates acute onset, inattention, disorganized thinking, and altered consciousness. Severity of delirium was further quantified with the Delirium Rating Scale-Revised-98 (DRS-R-98; score range 0-46, higher scores indicating greater severity) and the memorial delirium assessment scale (MDAS; score range 0-30, with scores ≥ 13 considered diagnostic). After one session, 7 patients (43.8%) recovered; 4 (25.0%) and 3 (18.8%) recovered after 2 and 3 sessions, respectively-yielding an overall 87.5% resolution rate within 3 days. Only two patients with refractory delirium required escue treatment with dexmedetomidine.

Both DRS-R-98 and MDAS scores showed a significant decline over 3 days ($p < 0.001$; Figure 1). No adverse events (e.g., dizziness, headache) were observed.

In summary, this pilot study suggests that 40-Hz auditory stimulation may represent a safe, non-invasive, and potentially effective approach for POD in elderly patients. By entraining gamma-band oscillations, it may enhance neural synchrony, modulate glial activity, and facilitate the clearance of pathological proteins. Nevertheless, given the limitations of a single-arm design and small sample size, these preliminary findings should be interpreted with caution and require confirmation in larger, multicenter randomized controlled trials to establish efficacy and evaluate its potential as a standardized therapeutic option for POD.

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TABLE 1. Baseline Characteristics of Patients Treated with 40 Hz Auditory Stimulation (n = 16).

Variable	Value
Age, years	69 ± 4.25
Weight, kg	62 ± 5.67
Body mass index, kg/m²	26.2 (24.5-28.1)
Education, year	9.0 (9.0-12.0)
ASA classification, n (%)	
II	13 (81.3)
III	3 (18.7)
Surgery type, n (%)	
Abdominal	7 (43.7)
Orthopedic	5 (31.2)
Spinal	4 (25)
Preoperative comorbidities, n (%)	
Hypertension	11 (68.7)
Diabetes mellitus	5 (31.2)
Coronary heart disease	4 (25)
Lacunar infarction	1 (6.3)
Hepatic dysfunction	2 (12.5)
Renal dysfunction	1 (6.3)
History of malignancy	2 (12.5)

Data are presented as mean ± SD, median (25^{th}-75^{th} percentiles), or n (%), as appropriate.
ASA, American Society of Anesthesiologists; SD, standard deviation.

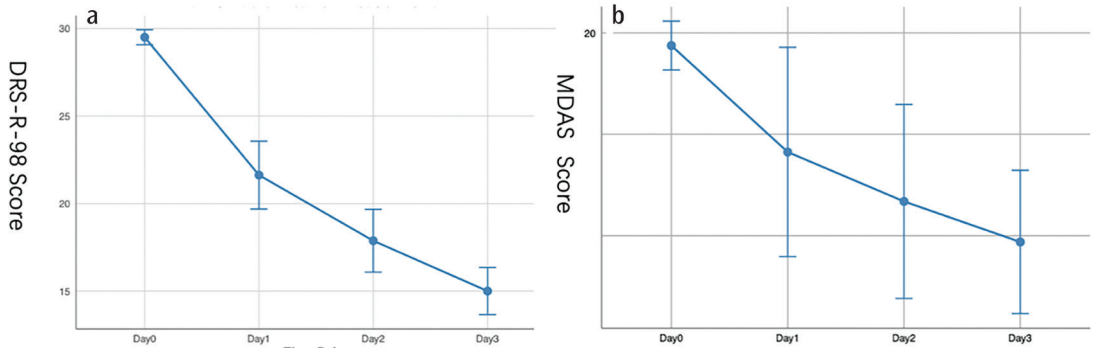

FIG. 1. DRS-R-98 and MDAS scores over four treatment days of 40 Hz auditory stimulation. (a) DRS-R-98 scores. (b) MDAS scores. Data are presented as mean ± SD. Statistical significance was determined by repeated-measures ANOVA ($p < 0.001$).
DRS-R-98, Delirium Rating Scale-Revised-98; MDAS, memorial delirium assessment scale; SD, standard deviation.

Ethics Committee Approval: The study at Shanghai Jiao Tong University was approved by the Institutional Ethics Committee (approval number: ChiCTR2500098286, date: 30.04.2024) and was conducted between February 2022 and April 2025.

Informed Consent: Written informed consent was obtained from the relatives of all patients.

Conflict of Interest: The authors declare that they have no conflict of interest.

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