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CLINICAL INVESTIGATION

Spoken words are processed during dexmedetomidine-induced unresponsiveness

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Abstract

Background: Studying the effects of anaesthetic drugs on the processing of semantic stimuli could yield insights into how brain functions change in the transition from wakefulness to unresponsiveness. Here, we explored the N400 event-related potential during dexmedetomidine- and propofol-induced unresponsiveness.

Methods: Forty-seven healthy subjects were randomised to receive either dexmedetomidine (n=23) or propofol (n=24) in this open-label parallel-group study. Loss of responsiveness was achieved by stepwise increments of pseudo-steady-state plasma concentrations, and presumed loss of consciousness was induced using 1.5 times the concentration required for loss of responsiveness. Pre-recorded spoken sentences ending either with an expected (congruous) or an unexpected (incongruous) word were presented during unresponsiveness. The resulting electroencephalogram data were analysed for the presence of the N400 component, and for the N400 effect defined as the difference between the N400 components elicited by congruous and incongruous stimuli, in the time window 300–600 ms post-stimulus. Recognition of the presented stimuli was tested after recovery of responsiveness.

Results: The N400 effect was not observed during dexmedetomidine- or propofol-induced unresponsiveness. The N400 component, however, persisted during dexmedetomidine administration. The N400 component elicited by congruous stimuli during unresponsiveness in the dexmedetomidine group resembled the large component evoked by incongruous stimuli at the awake baseline. After recovery, no recognition of the stimuli heard during unresponsiveness occurred.

Conclusions: Dexmedetomidine and propofol disrupt the discrimination of congruous and incongruous spoken sentences, and recognition memory at loss of responsiveness. However, the processing of words is partially preserved during dexmedetomidine-induced unresponsiveness.

Clinical trial registration: NCT01889004.

Keywords: dexmedetomidine; event-related potentials; N400 evoked potential; propofol; semantics

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Editor's key points

- Electroencephalographic N400 event-related potentials were used to assess semantic processing during dexmedetomidine- and propofol-induced unresponsiveness in healthy volunteers.
- Both dexmedetomidine and propofol disrupted discrimination of congruous and incongruous sentences at doses sufficient to induce unresponsiveness.
- The persistence of the N400 component indicates residual stimulus-dependent activity during dexmedetomidine-induced unresponsiveness.
- Thus, processing of words was partially preserved during dexmedetomidine-induced unresponsiveness.

Studying whether complex cognitive processing in response to semantic stimuli is preserved during anaesthetic-induced unresponsiveness could elucidate how brain functions change in the transition from wakefulness to unresponsiveness, and eventually to unconsciousness. Previous studies based on functional magnetic resonance imaging (fMRI) have shown brain activation related to auditory stimuli during propofol and dexmedetomidine sedation,[1–3] yet anaesthesia can disrupt higher-order processing of spoken words.[4] Based on fMRI, the discrimination between words and other sounds is preserved during propofol sedation,[1,5] although the processing of ambiguity of words is lost at low doses.[1] It is, however, poorly known how anaesthetics affect the processing of words in a context, which is the fundamental form of natural speech.

The electroencephalogram-based N400 event-related potential (ERP) could provide a method to study semantic processing during sedation.[6–9] The N400 ERP component is a negative deflection typically observed in the centroparietal electrodes 300–600 ms after a meaningful stimulus.[10,11] The N400 component is related to processing of meaning, and it is not confined to linguistic stimuli or a specific sensory modality.[7,12] The N400 component has been suggested to reflect the activation of semantic–conceptual representations, which comprises retrieving the representation of the stimulus and integrating it into the context.[7] Processing unexpected stimuli requires a more extensive search of representation in the semantic–conceptual network and produces a larger N400 component, whilst repetition of the same stimulus decreases the N400 amplitude.[13] The amplitude of the N400 component is inversely proportional to the expectancy of the stimulus,[10,14] and reflects the ease with which the stimulus is processed. The difference between the N400 components elicited by expected and unexpected stimuli is called the N400 effect. The N400 effect can be studied by comparing the N400 components evoked by related and unrelated pairs of stimuli, or sentences with expected and unexpected last words.

We studied semantic processing during dexmedetomidine- and propofol-induced unresponsiveness using the N400 component, which has not previously been reported in conjunction with anaesthetic drugs. The effects of the anaesthetics on N400 were examined in healthy subjects at doses individually determined based on loss of responsiveness (LOR). Our aim was to test the hypothesis that semantic processing can be preserved despite anaesthetic-induced unresponsiveness.

Methods

The study (ClinicalTrials.gov NCT01889004) was approved by the Ethics Committee of the Hospital District of Southwest Finland and the Finnish Medicines Agency Fimea. All subjects gave their written informed consent according to the Declaration of Helsinki. Spectral analysis of electroencephalogram[15] and subjective experiences[16] from the same study are reported elsewhere.

Subjects

The subjects were healthy (ASA physical status 1), fluent in Finnish language, and had normal hearing. Exclusion criteria included smoking, substance abuse, susceptibility for nausea, and history of psychiatric disorder. A total of 79 right-handed 20- to 30-yr-old male subjects were screened awake, and the 47 subjects with the most prominent visually identified N400 effect were enrolled to ensure that all subjects exhibited N400 in the absence of anaesthetics. The mean age of the subjects was 23.7 yr (range: 20–30 yr); they were on average 180 cm (range: 165–198 cm) tall and weighed 79.5 kg (range: 53–122 kg). The subjects were randomised to receive either dexmedetomidine (n=23) or propofol (n=24) in this open-label parallel-group study.

Stimuli and electroencephalogram recording

The stimuli were 620 Finnish auditory high-cloze-probability sentences. Twenty psychology students were asked to fill in the missing last word of the sentences using a word that first comes to their mind and fits the context. At least half of the participants had to complete each sentence with the same word (i.e. cloze probability $\geq$50% was required). Half of the sentences were randomly selected, and the expected (congruous) last word was replaced with an unexpected (incongruous) word, matched on inflection, word class, number of syllables, and word lemma frequency.[17] The resulting congruous and incongruous sentences did not differ in terms of last-word lemma frequency, the number of syllables in the last word, or sentence word count (Mann-Whitney U; P>0.05 for all). The stimuli were digitally recorded by a female native Finnish speaker (A.S.), and their amplitudes were normalised. There was a 1 s silence before and after the last word of each sentence. The sentence was followed by a response cue, which was a 100 ms sine sound, and 2.3 s for responding before the next sentence. The stimuli were organised into blocks with