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Laboratory Investigation

LABORATORY INVESTIGATION

Altered stimulus representation in rat auditory cortex is not causal for loss of consciousness under general anaesthesia

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Abstract

Background: Current concepts suggest that impaired representation of information in cortical networks contributes to loss of consciousness under anaesthesia. We tested this idea in rat auditory cortex using information theory analysis of multiunit responses recorded under three anaesthetic agents with different molecular targets: isoflurane, propofol, and dexmedetomidine. We reasoned that if changes in the representation of sensory stimuli are causal for loss of consciousness, they should occur regardless of the specific anaesthetic agent.

Methods: Spiking responses were recorded with chronically implanted microwire arrays in response to acoustic stimuli incorporating varied temporal and spectral dynamics. Experiments consisted of four drug conditions: awake (pre-drug), sedation (i.e. intact righting reflex), loss of consciousness (a dose just sufficient to cause loss of righting reflex), and recovery. Measures of firing rate, spike timing, and mutual information were analysed as a function of drug condition.

Results: All three drugs decreased spontaneous and evoked spiking activity and modulated spike timing. However, changes in mutual information were inconsistent with altered stimulus representation being causal for loss of consciousness. First, direction of change in mutual information was agent-specific, increasing under dexmedetomidine and decreasing under isoflurane and propofol. Second, mutual information did not decrease at the transition between sedation and LOC for any agent. Changes in mutual information under anaesthesia correlated strongly with changes in precision and reliability of spike timing, consistent with the importance of temporal stimulus features in driving auditory cortical activity.

Conclusions: The primary sensory cortex is not the locus for changes in representation of information causal for loss of consciousness under anaesthesia.

Keywords: consciousness; dexmedetomidine; isoflurane; neocortex; propofol

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Editor's key points

- Loss of consciousness is thought to involve altered information processing in cortical neuronal networks.
- This hypothesis was tested in a rat model of auditory sensory representation in the cortex by recording multiunit responses at sedative and anaesthetic doses of three mechanistically distinct anaesthetics.
- All three drugs reduced spontaneous and evoked spiking activity and timing, however changes were inconsistent with altered stimulus representation being causal for loss of consciousness.
- Changes in neuronal activity producing loss of consciousness do not occur in the primary sensory cortex, but more likely involve changes in connectivity between higher order cortical areas.

Understanding what changes in the brain upon loss of consciousness (LOC) under anaesthesia has broad implications both for improving clinical practice and for understanding the neural basis of consciousness. Theoretical considerations suggest that anaesthetics impact cortical representations of information and its communication across cortical and thalamic brain regions.[1,2] Non-invasive studies have provided indirect evidence for these models in patients and volunteers.[3,4] However, changes in the representation of sensory information in primary sensory areas have not been explored in detail. During anaesthesia LOC, sensory input activates the primary sensory cortex,[5–8] suggesting that single cell stimulus representation there is relatively unaffected, but higher order cortical responses are largely suppressed.[9]

However, there is a large body of evidence suggesting that sensory responses in A1 are affected dramatically by anaesthetic agents. For example, imaging and EEG studies in both experimental animals and humans show that sensory responses in the cortex are suppressed under anaesthesia, even at sedating doses,[10–12] and thalamo-cortical synaptic responses are suppressed in brain slices, albeit less than cortico-cortical synaptic responses.[7] Anaesthetics suppress activity in the thalamus both *in vivo*[13] and in brain slice preparations,[14] supporting a model in which anaesthetics cause LOC by disconnecting the cortex from the periphery.[13] Suppression of thalamo-cortical connectivity by dexmedetomidine[15] is consistent with this hypothesis. Thus, we still lack a basic understanding how anaesthetics affect encoding and processing of sensory responses, a critical step in the mechanisms of loss and recovery of consciousness under anaesthesia.[16]

We investigated the effects of propofol, dexmedetomidine, and isoflurane on unit activity in the auditory cortex of rats. These agents have diverse pre- and postsynaptic molecular targets, but all produce LOC and all have direct actions on cortical neurones.[7,17–23] We assayed information content in spike trains using information-theory analysis.[24] If anaesthetic suppression of information in cortical networks is tightly linked to LOC, this should show differences between stimulus representation under sedation *vs* LOC. We did not observe this expected relationship, suggesting that changes in stimulus representation in the sensory neocortex are not causal for anaesthesia LOC.

Methods

All experimental protocols conformed to American Physiological Society/National Institutes of Health guidelines and were approved by the University of Wisconsin Animal Care and Use Committee. The data reported here were recorded from six female August Copenhagen Irish (ACI) rats (Harlan; 139–204 g) housed on a reverse 12:12 light/dark cycle so that recordings performed during the day were during the animals' 'active' period.

Surgeries

Animals were implanted with multichannel microwire arrays to record unit activity and intrajugular catheters for administration of i.v. anaesthetics as described (also see Supplementary material).[7,25] Briefly, microwire arrays (2×8, rows×columns, column spacing 250 μm, row separation 500 μm) were targeted to primary auditory cortex (Supplementary Fig. S1a), and intrajugular catheters were chronically implanted under isoflurane anaesthesia and aseptic conditions. Animals were allowed to recover 5–7 days before the first recording session.

Electrophysiological recordings

Experiments on each animal were performed over a period of 3 weeks, with at least one rest day between experiments. On the day of each experiment, animals were placed inside a gas-tight acrylic enclosure (20×19×11 cm) inside an anechoic sound-attenuation chamber (Industrial Acoustics Company, Inc., Bronx, NY, USA) and allowed to accommodate to the enclosure for 1 h. The enclosure had gas inflow/outflow and sampling ports used to provide room air in all experiments and to deliver isoflurane during that subset of experiments. Animals were kept warm using a heating pad placed in the bottom of the enclosure. Microwire signals were accessed by connecting a 16-channel headstage (ZC16, Tucker Davis Technologies, Alachua, FL, USA) with a flexible tether to a connector on the animal's head. The headstage and tether did not impair the animal's ability to move about the enclosure, though the small size of the enclosure ensured that the animals stayed in approximately the same position relative to the overhead speaker. Responses were bandpass-filtered at 1–7500 Hz, digitised at 24 kHz, and amplified at 5000–20,000× (RZ5, Tucker Davis Technologies).

Free-field acoustic stimuli were presented via a small speaker (TDT- ES1, Tucker Davis Technologies) mounted in the top of the enclosure. During the first recording session, frequency response areas (FRAs) were obtained using pure tone stimuli (50 ms duration, 5 ms increase/decrease, 4–60 kHz in 11 log-spaced steps, 20–65 dB SPL). For each subsequent experiment, a stimulus set and anaesthetic agent (see below) were selected randomly. Stimuli consisted of click trains (0.1 ms clicks, 20 dB attenuation, 1 s train, interclick intervals 10–333 ms), upward and downward frequency modulated (FM) sweeps with variable frequency range and start and stop frequencies (250 ms duration, range 4–32 kHz, f_{Low}=4–32 kHz, f_{High}=8–64 kHz), and a set of animal vocalisations (250 ms duration) recorded from birds, insects, and rodents (Avisoft Bioacoustics; www.avisoft.com) that have distinct spectro-temporal properties (Supplementary Fig. S2). Specific FM sweep frequencies were chosen for each animal to span the