NeuroImage 141 (2016) 326–340

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/ynimg

Cerebral responses to local and global auditory novelty under general anesthesia

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ARTICLE INFO

Article history:
Received 1 January 2016
Accepted 3 August 2016
Available online 5 August 2016

Keywords:
Anesthesia
Sequence violation
Cortex
Thalamus
fMRI
Primate

ABSTRACT

Primate brains can detect a variety of unexpected deviations in auditory sequences. The local-global paradigm dissociates two hierarchical levels of auditory predictive coding by examining the brain responses to first-order (local) and second-order (global) sequence violations. Using the macaque model, we previously demonstrated that, in the awake state, local violations cause focal auditory responses while global violations activate a brain circuit comprising prefrontal, parietal and cingulate cortices. Here we used the same local-global auditory paradigm to clarify the encoding of the hierarchical auditory regularities in anesthetized monkeys and compared their brain responses to those obtained in the awake state as measured with fMRI. Both, propofol, a GABAA-agonist, and ketamine, an NMDA-antagonist, left intact or even enhanced the cortical response to auditory inputs. The local effect vanished during propofol anesthesia and shifted spatially during ketamine anesthesia compared with wakefulness. Under increasing levels of propofol, we observed a progressive disorganization of the global effect in prefrontal, parietal and cingulate cortices and its complete suppression under ketamine anesthesia. Anesthesia also suppressed thalamic activations to the global effect. These results suggest that anesthesia preserves initial auditory processing, but disturbs both short-term and long-term auditory predictive coding mechanisms. The disorganization of auditory novelty processing under anesthesia relates to a loss of thalamic responses to novelty and to a disruption of higher-order functional cortical networks in parietal, prefrontal and cingular cortices.

Introduction

Anesthetic agents are capable of suppressing conscious experience, verbal reportability and behavioral responsivity, partially or totally, in a reversible manner. Several molecular and cellular pharmacological mechanisms of anesthetics have been identified (Alkire et al., 2008; Franks, 2008; Uhrig et al., 2014a). Neural circuit mechanisms of anesthetics are covered in two recent reviews (Brown et al., 2010; Purdon et al., 2015). In the recent years, the cerebral consequences of anesthetic administration at the systems level have been increasingly characterized using different modalities of functional neuroimaging (reviewed in MacDonald et al., 2015). Anesthetics induce a functional disruption of large-scale cortico-cortical networks (Lee et al., 2009a; Ku et al., 2011; Lee et al., 2013), and generate slow delta and alpha oscillations in thalamo-cortical circuits (Ching et al., 2010; Cimenser et al., 2011). The functional organization of brainscale networks can also be studied by measuring spontaneous coherent fluctuations of functional magnetic resonance imaging (fMRI) signals in the brain. In awake monkeys, these fluctuations engage widely distributed default-mode networks that underlie the "intrinsic functional architecture" of the brain (Buckner et al., 2008; Mantini et al., 2011). Surprisingly, this intrinsic architecture is partially preserved even in deeply anesthetized macaques (Vincent et al., 2007). However, we recently showed by using dynamical functional connectivity measures that anesthesia decreases the repertoire of resting-state functional configurations to a limited number of states, mainly correlated to brain anatomy (Barttfeld et al., 2015).

Here, we specifically ask how anesthesia affects auditory information processing. While early sensory processing of external stimuli is preserved during anesthesia (Plourde et al., 2006; Hudetz et al., 2009; Boveroux et al., 2010), few experiments have studied how anesthesia affects the higher-order brain responses to more complex auditory stimuli (Kerssens et al., 2005; Adapa et al., 2014). Here, we use a

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http://dx.doi.org/10.1016/j.neuroimage.2016.08.004
1053-8119/

hierarchical paradigm to evaluate the auditory processing of rule violation during anesthesia, and to test the hypothesis that anesthesia relates to a functional disruption of higher-order cortical interactions that support information integration and broadcasting (Dehaene and Changeux, 2011; Oizumi et al., 2014).

The local-global paradigm probes auditory sequence processing at first-order (local) and second-order (global) sequence violations (Bekinschtein et al., 2009). The global novelty effect activates a widely organized network that is considered as a signature of conscious processing, as validated in patients with disorders of consciousness (Faugeras et al., 2011). Using the local-global paradigm, we previously demonstrated that the macaque brain is capable of hierarchical predictive coding through a ≪macaque Global Neuronal Workspace (GNW)≫ that is homologous to the human GNW (Uhrig et al., 2014b). The GNW framework is a theoretical model which stipulates that the global availability of sensory information to widely distributed prefronto-parietal and cingulate cortical areas subtends conscious access (Dehaene et al., 1998; Dehaene and Naccache, 2001; Baars, 2005; Shanahan and Baars, 2005; Dehaene and Changeux, 2011).

Examining whether auditory responses to sounds are preserved, and which cortical stage of auditory processing is disrupted, should help dissect the functional reorganization underlying the information processing under anesthesia. Anesthetics may act through the disruption of the GNW, but they may also alter early auditory thalamo-cortical information processing. To evaluate these possibilities, we employed EEG-controlled anesthesia and fMRI in macaques presented with the local-global auditory paradigm (Bekinschtein et al., 2009). The results demonstrate, surprisingly, that anesthesia does not fully suppress the cerebral responses to second-order (global) sequence violations. Instead, an absence of cerebral activations to the global effect in parietal cortex and thalamus appears as the common denominator for anesthesia with propofol and ketamine.

Material and methods

Animals

Four rhesus macaques (Macaca mulatta), 1 male (monkey J) and 3 females (monkeys K, Ki and R) (5–8 kg, 8–12 years of age), were tested, 3 for each arousal state (awake: monkeys J, K and R (Uhrig et al., 2014b), moderate propofol sedation: monkeys J, K and R; deep propofol anesthesia: J, K and R; deep ketamine anesthesia: monkeys K, Ki and R). All procedures were conducted in accordance with the European convention for animal care (86-406) and the National Institutes of Health's Guide for the Care and Use of Laboratory Animals. Animal studies were approved by the institutional Ethical Committee (CETEA protocol #10-003).

"Local-global" auditory paradigm (Fig. 1)

We used an event-related auditory paradigm based on local (within trials) and global (across trials) violations of temporal regularities, as previously described (Bekinschtein et al., 2009; Wacongne et al., 2011; Uhrig et al., 2014b; Strauss et al., 2015). The paradigm was strictly identical to our previously published work with awake monkeys (Uhrig et al., 2014b). At the local level (first hierarchical level), a deviant sound is introduced after 4 identical sounds (denoted xxxxY, where x is the repeated sound and Y the deviant sound), and such trials are contrasted with sequences of 5 identical sounds (xxxxx). At the global level (second hierarchical level), a sequence of trials, called the 'global standard', is repeatedly presented (e.g. xxxxY), and then this regularity is violated by rare trials called 'global deviants' (e.g. xxxxx). Each trial comprised five consecutive sounds (50 ms duration, 150 ms stimulus onset asynchrony (SOA) between sounds, total duration of 650 ms), separated by 850 ms of silence, for a total trial duration of 1500 ms. Each series of 24 trials comprised an initial 4 habituation trials, followed by 20 post-habituation trials with 4 deviant trials (followed by at least 2 consecutive standard trials) and 16 standard trials. The sounds were presented within runs comprising a period of rest (14.4 s), followed by 5 series of 24 trials (36 s,) and at the end of each trial another period of rest (14.4 s), for a total duration of 266.4 s. Two runs used as global standard the xxxxx sequence of 5 identical sounds (either high pitched 1600 Hz or low pitched 800 Hz) and two other runs used the xxxxY sequence (same pitch, with the final sound swapped). All four run types were presented in random order and comprised both a local regularity (the fifth sound could be different or identical to previous sounds) and a global regularity (one of the series of sounds was less frequent than the other). Auditory stimuli were presented using the E-prime software (E-Studio 1.0, Psychology Software Tools; http://www.pstnet.com) and delivered using MR-compatible headphones (MR CONFON, Germany).

Anesthesia protocols

Monkeys received anesthesia with either propofol or ketamine.

For propofol anesthesia (Barttfeld et al., 2015), three monkeys (monkey K, R and J) were scanned in different scanning sessions under two different levels of anesthesia, either moderate propofol sedation or deep propofol anesthesia corresponding to a level of general anesthesia. The levels of anesthesia were targeted using both a behavioral monkey sedation scale (Table 1) and electroencephalography (EEG).

First the awake monkeys were trained for i.v. propofol injection in the saphenous vein for induction of anesthesia (propofol bolus, 5–7.5 mg/kg i.v.; Fresenius Kabi, France). Induction of anesthesia was followed by a target-controlled infusion (TCI) (Alaris PK Syringe pump, CareFusion, CA, USA) of propofol based on the 'Paedfusor' pharmacokinetic model (Absalom and Kenny, 2005). The level of TCI for the propofol infusion was adapted to the behavior score and the EEG of each individual monkey on each fMRI session. Based on the behavior and the EEG, the TCI for the moderate propofol sedation state was 3.7–4.6 μg/ml (monkey J 3.7 μg/ml; monkey K: 4–4.6 μg/ml; monkey R: 3.7–3.9 μg/ml) and for the deep propofol anesthesia state 5.8–7.2 μg/ml (monkey J 5.8–5.9 μg/ml; monkey K: 6.5–7.2 μg/ml; monkey R 5.8 μg/ml).

For ketamine anesthesia, three animals (monkeys K, Ki and R) were scanned at a deep level of ketamine anesthesia, defined using the monkey sedation scale and EEG. For ketamine anesthesia induction, monkeys received an intramuscular (i.m.) injection of ketamine (20 mg/kg i.m., Virbac, France). To maintain a deep ketamine anesthesia state, induction of anesthesia was followed by a continuous intravenous infusion of ketamine (15–16 mg/kg/h i.v.; monkey K 16 mg/kg/h; monkey Ki 16 mg/kg/h; monkey R 15 mg/kg/h) based on the behavior scale and the EEG. Atropine (0.02 mg/kg i.m., Aguettant, France) was injected 10 min before ketamine induction, to reduce salivary and bronchial secretions. To avoid artifacts related to potential movements during MRI acquisition, during the moderate propofol sedation and deep ketamine anesthesia, a muscle blocking agent was co-administered when the monkey was inside the scanner (cisatracrium, 0.15 mg/kg bolus i.v. followed by continuous i.v. infusion at a rate of 0.18 mg/kg/h, GlaxoSmithKline, France) (Barttfeld et al., 2015). In all anesthesia conditions, monkeys were intubated and ventilated as previously described (Barttfeld et al., 2015). Heart rate, non-invasive blood pressure (systolic/diastolic/mean), oxygen saturation (SpO2), respiratory rate, end-tidal CO2 (EtCO2), cutaneous temperature was monitored (Maglife, Schiller, France) and recorded online (Schiller, France). I.v. hydration was ensured by a mixture of normal saline (0.9%) and 5% glucose (250 ml of normal saline with 100 ml of 5% glucose; rate of 10 ml/kg/h).

Clinical arousal scale for monkeys (Table 1)

The levels of arousal were defined on a behavioral scale, based on spontaneous movements and the response to juice presentation, shaking/prodding, toe pinch and corneal reflex (Table 1). Such behavioral