Basal forebrain participation in general anesthesia

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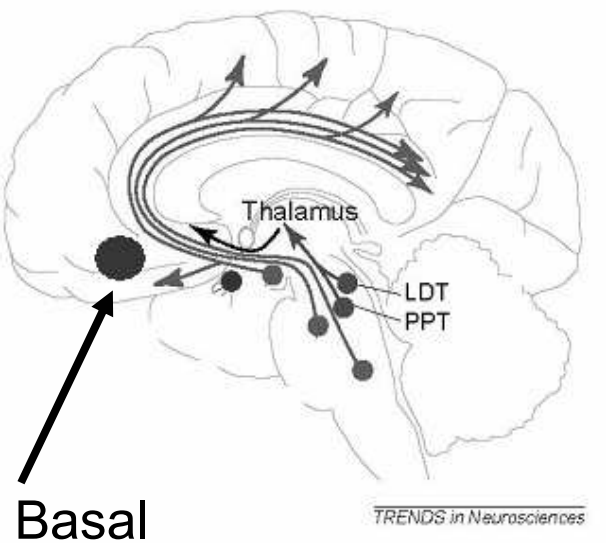
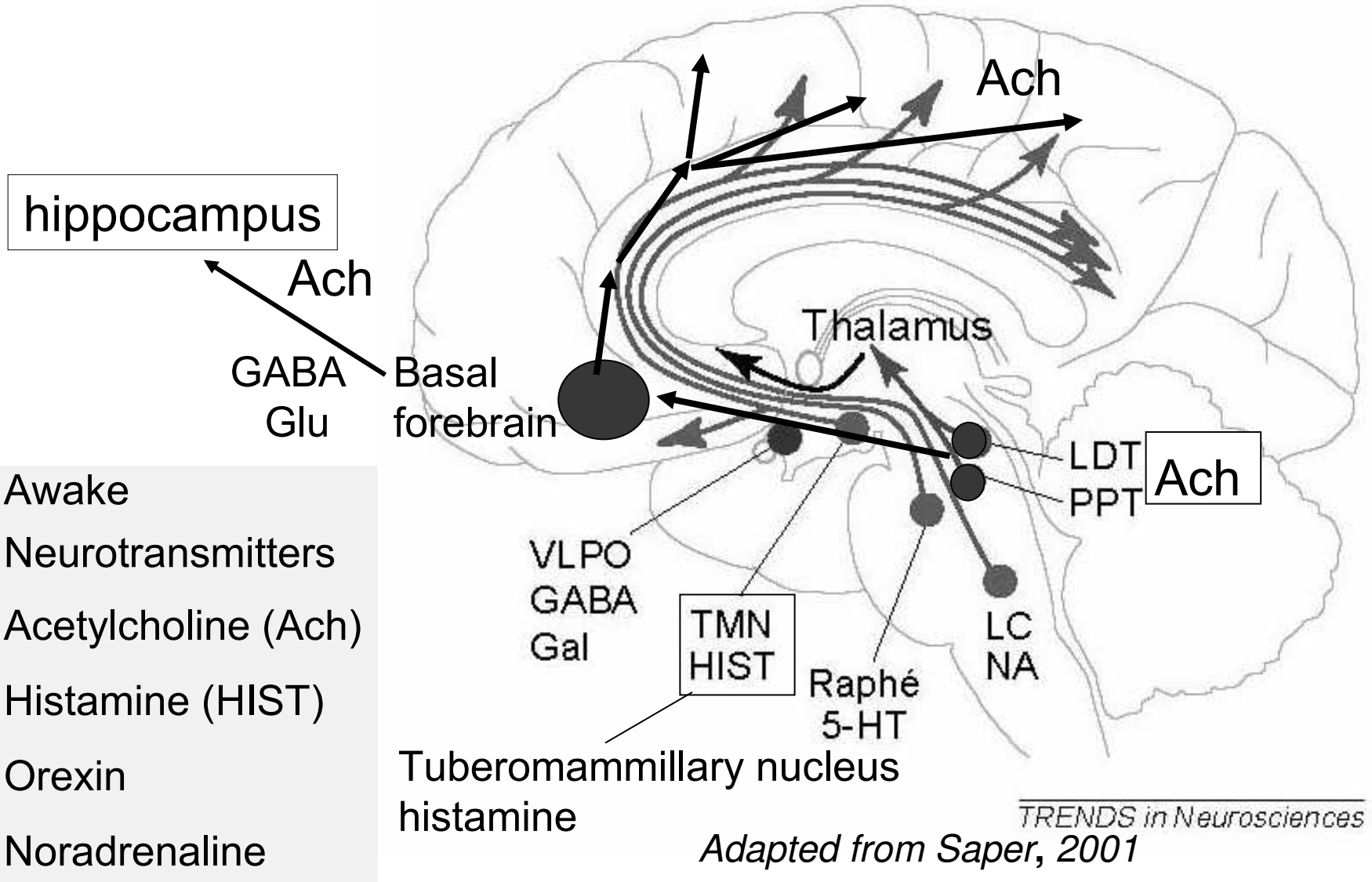
What is the Basal forebrain?



Basal forebrain

- A group of neurons (including cholinergic neurons) at the base of the forebrain
- Receives from the brainstem and controls electrical activity of the cerebral cortex
- Early cholinergic pathology in Alzheimer s disease
- Involved in cortical activation (physiological and functional), cognitive and other behavioral functions

Basal forebrain & wake-sleep circuit



Awake Neurotransmitters

Acetylcholine (Ach)

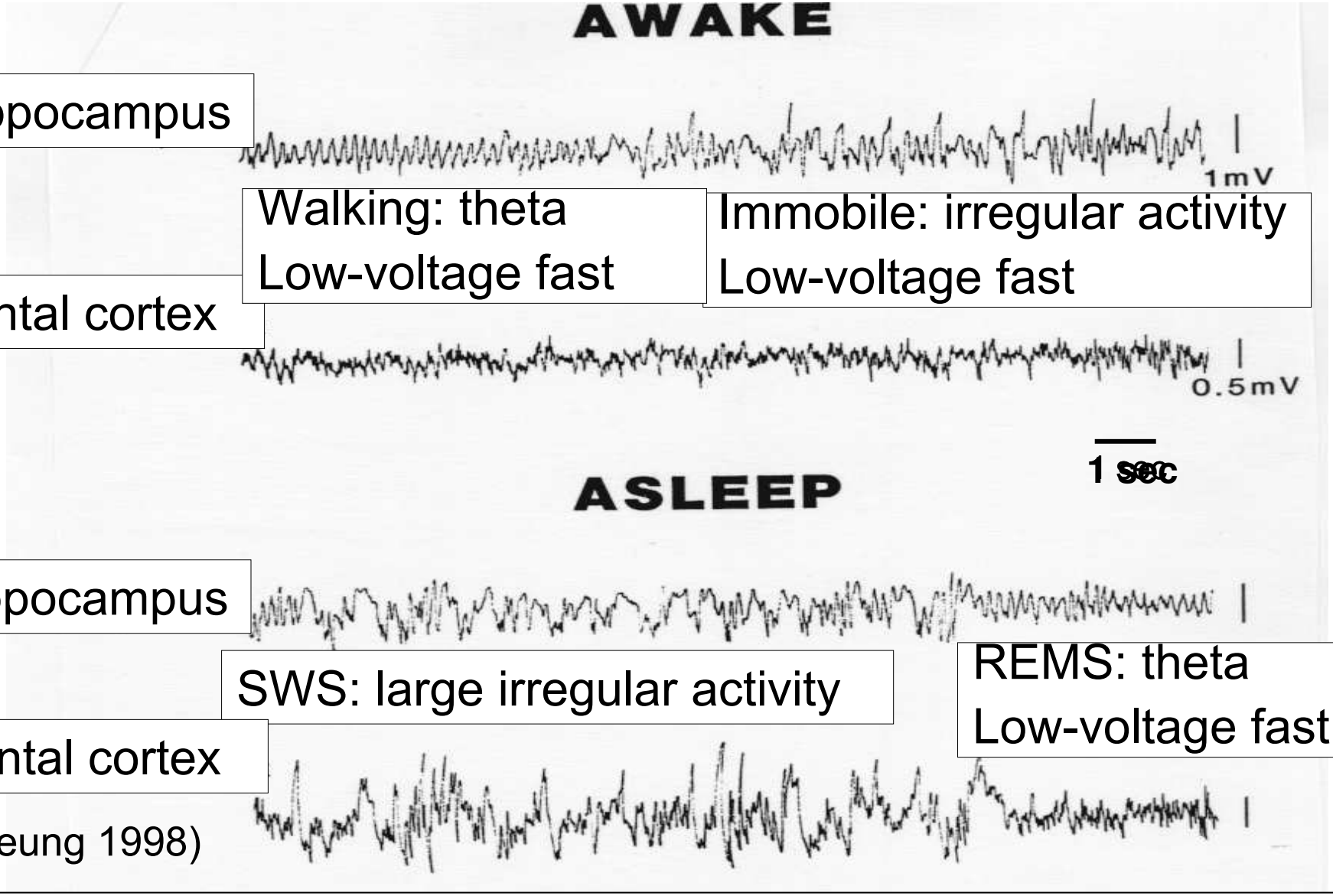
Histamine (HIST)

Orexin

Noradrenaline

Adapted from Saper, 2001

Hippocampal & Neocortical EEG



(Leung 1998)

Leung 1998

General Anesthesia

- state of overall loss of awareness and pain, allowing surgical operations

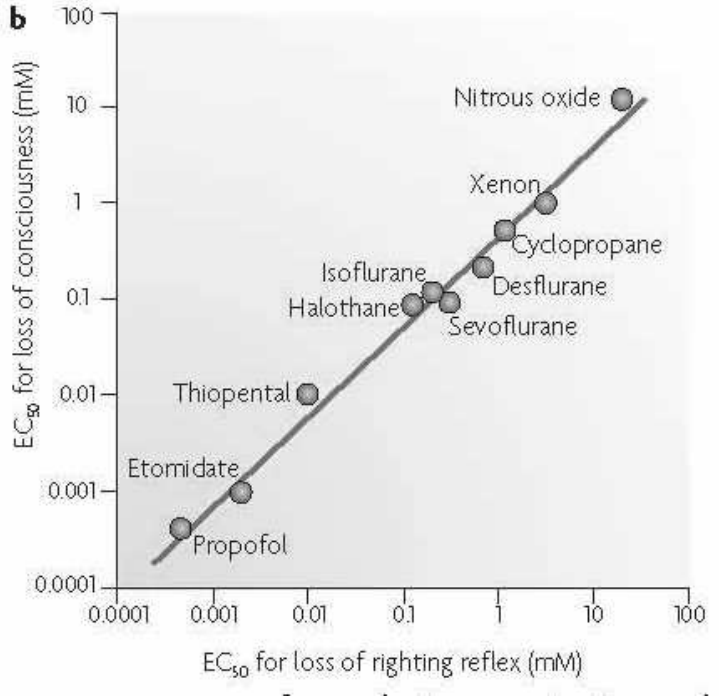
- Components
    1. Loss of awareness
    2. Loss of pain
    3. Loss of voluntary movements
    4. Loss of memory of the surgery

Surgical anesthesia in animals

Loss of Righting Reflex in animals
correlated with loss of consciousness in humans

Response to pain tested by tail-pinch (surgical anesthesia)

Record EEG frontal cortex & hippocampus



Franks, Nat Rev Neurosci 2008

Volatile anesthesia stages *(Guedel 1951)*

I. Analgesia

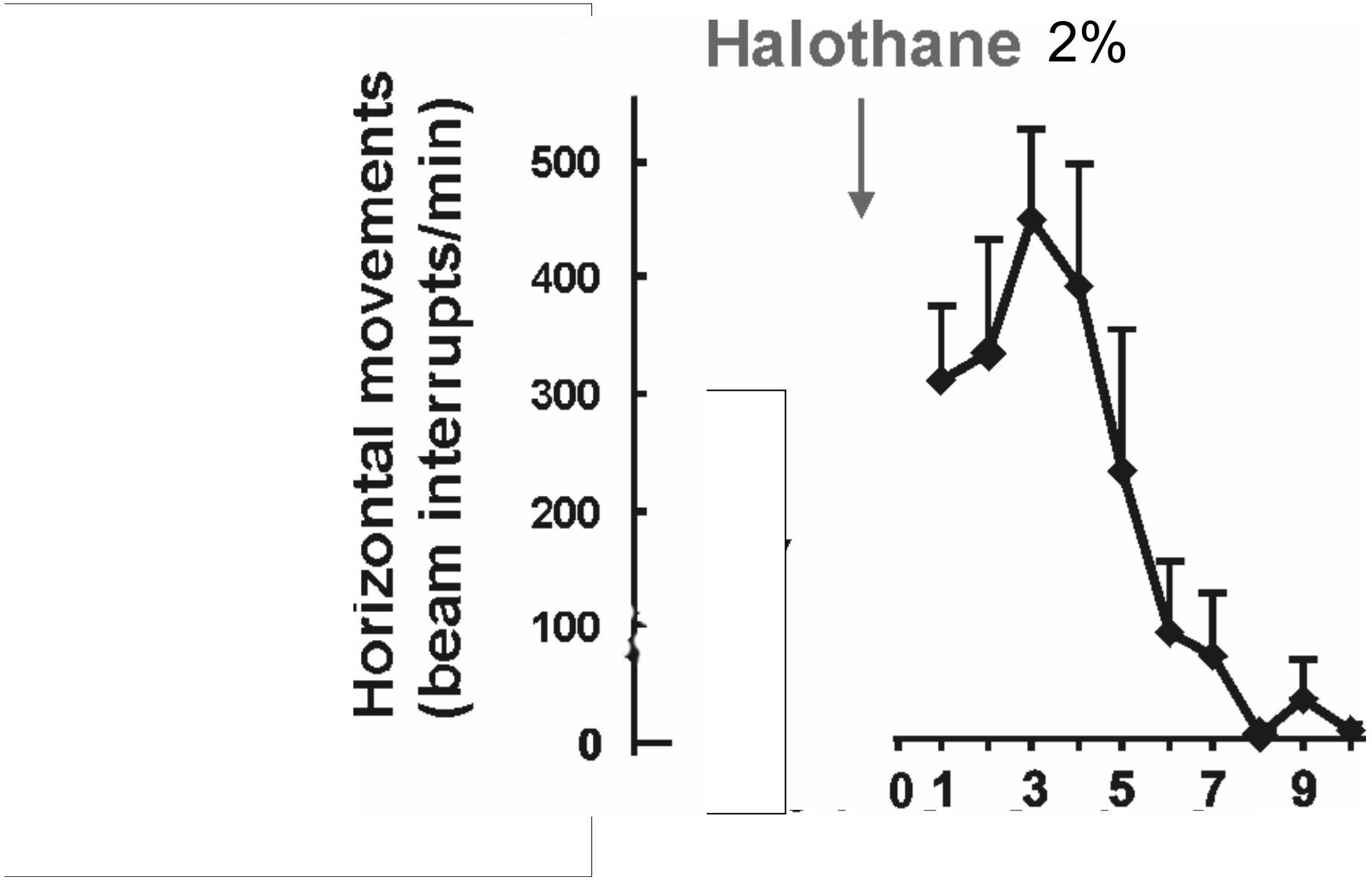
II. Delirium (behavioral excitation)

> Priestley J (1776) on N_2O: "The sense of muscular power became greater, and at last an irresistible propensity to action was indulged in ... before impressions ceased to be perceived .. and voluntary power was altogether destroyed"

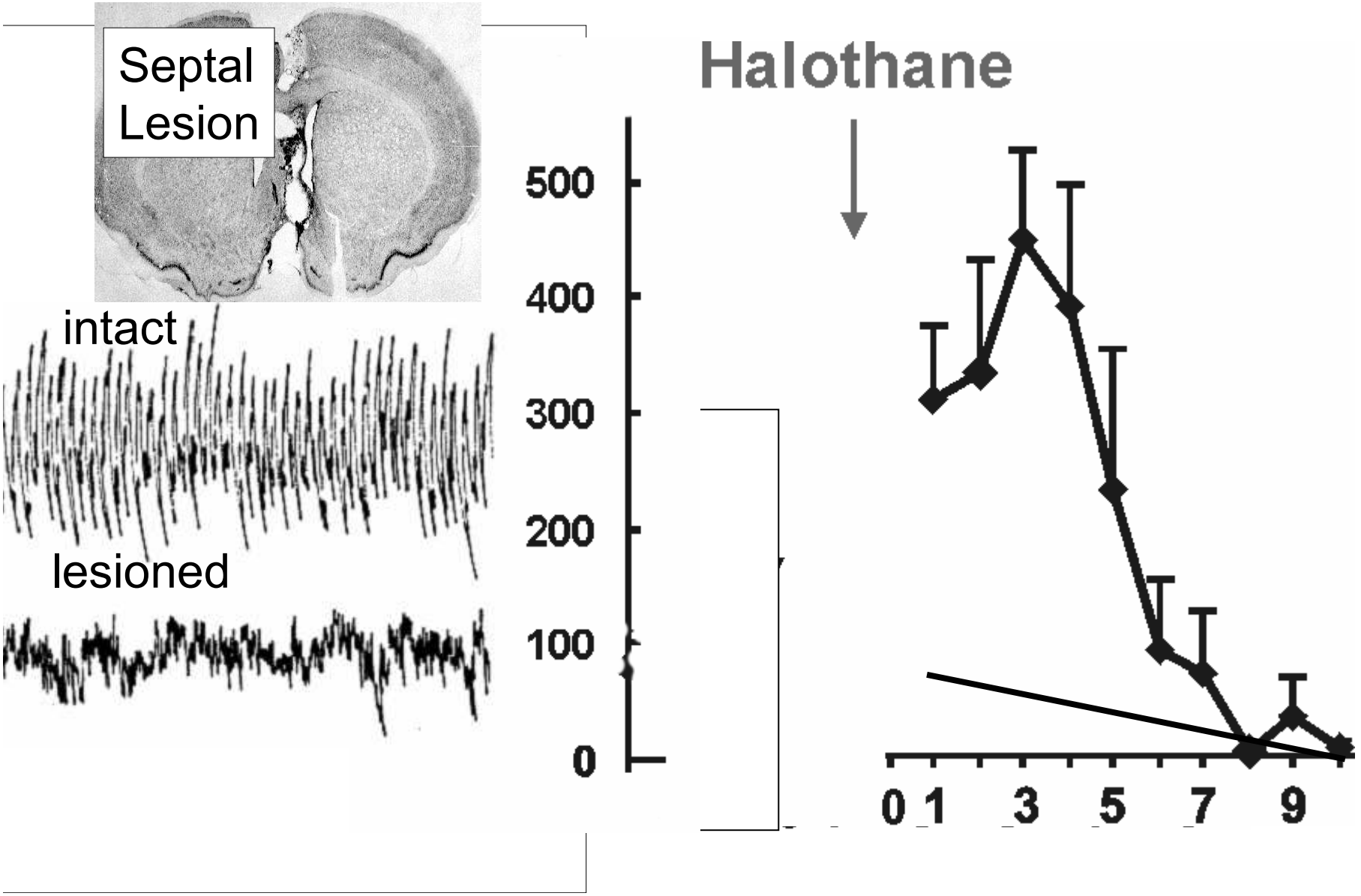
III. Surgical anesthesia

IV. Respiratory Paralysis

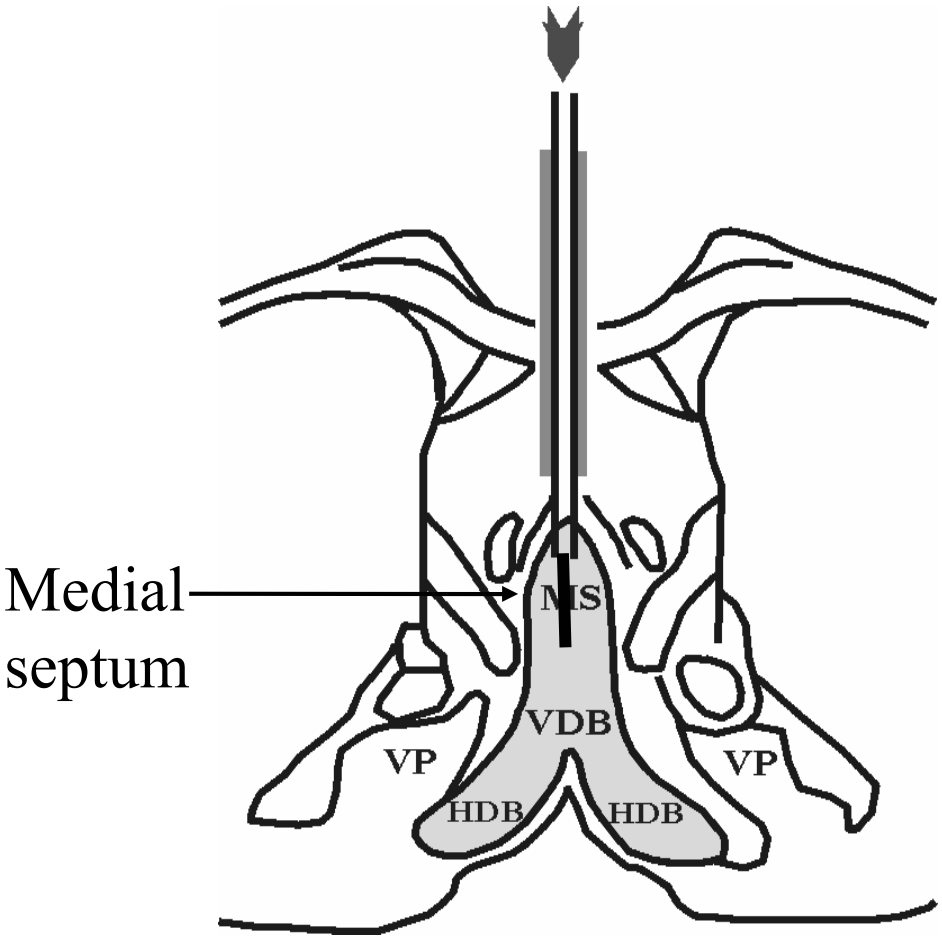
Delirium after halothane in control rats



Septal lesion abolishes anesthetic-induced delirium



Reversible inactivation of brain by GABA-A receptor agonist muscimol



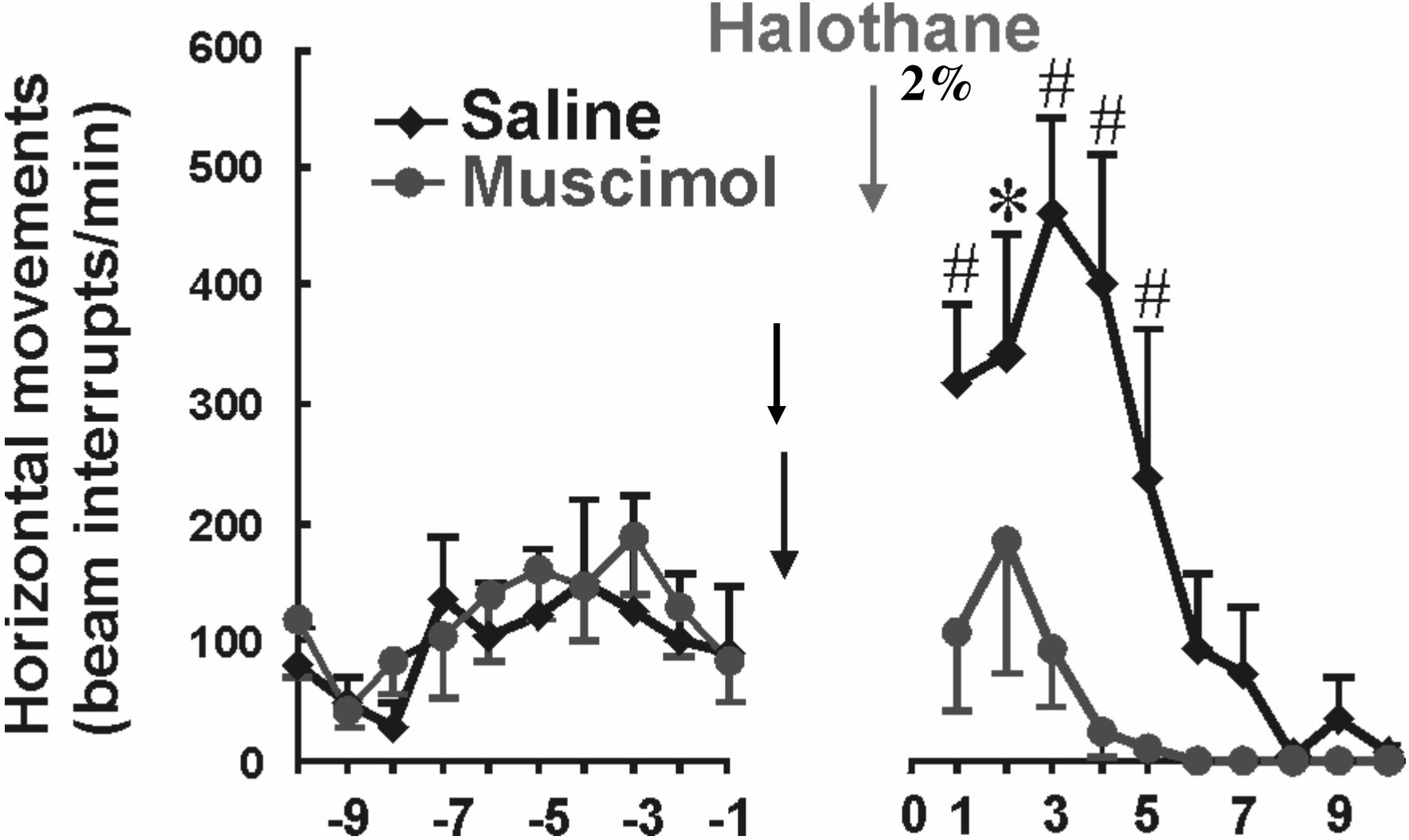
Muscimol (0.4-1 ug) injection 0.3-0.6 ul in ~1 min

hyperpolarizes and stops neuronal firing

Within ~ 1 mm radius

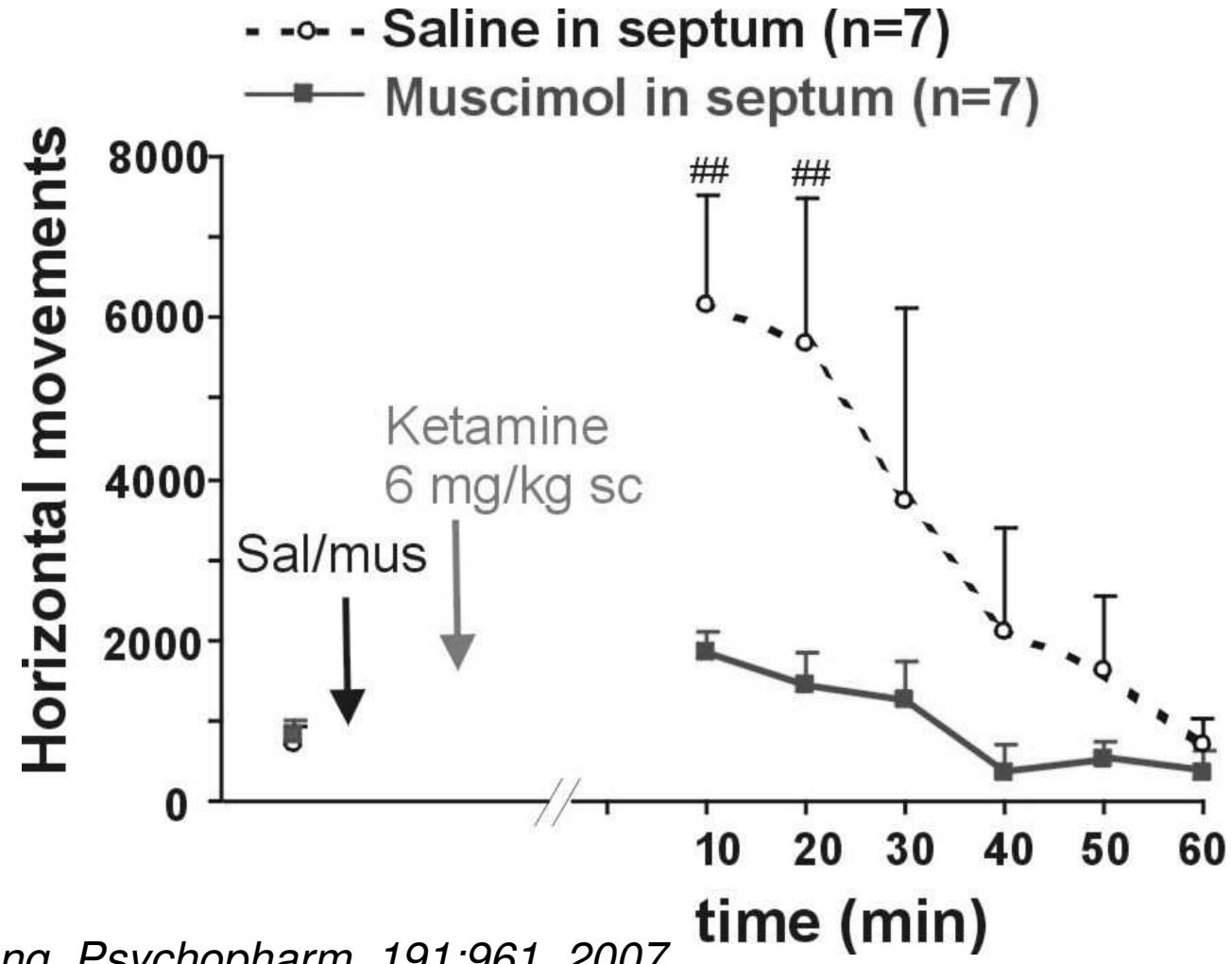
Saline infusion as control

Halothane-induced delirium reduced by inactivation of medial septum



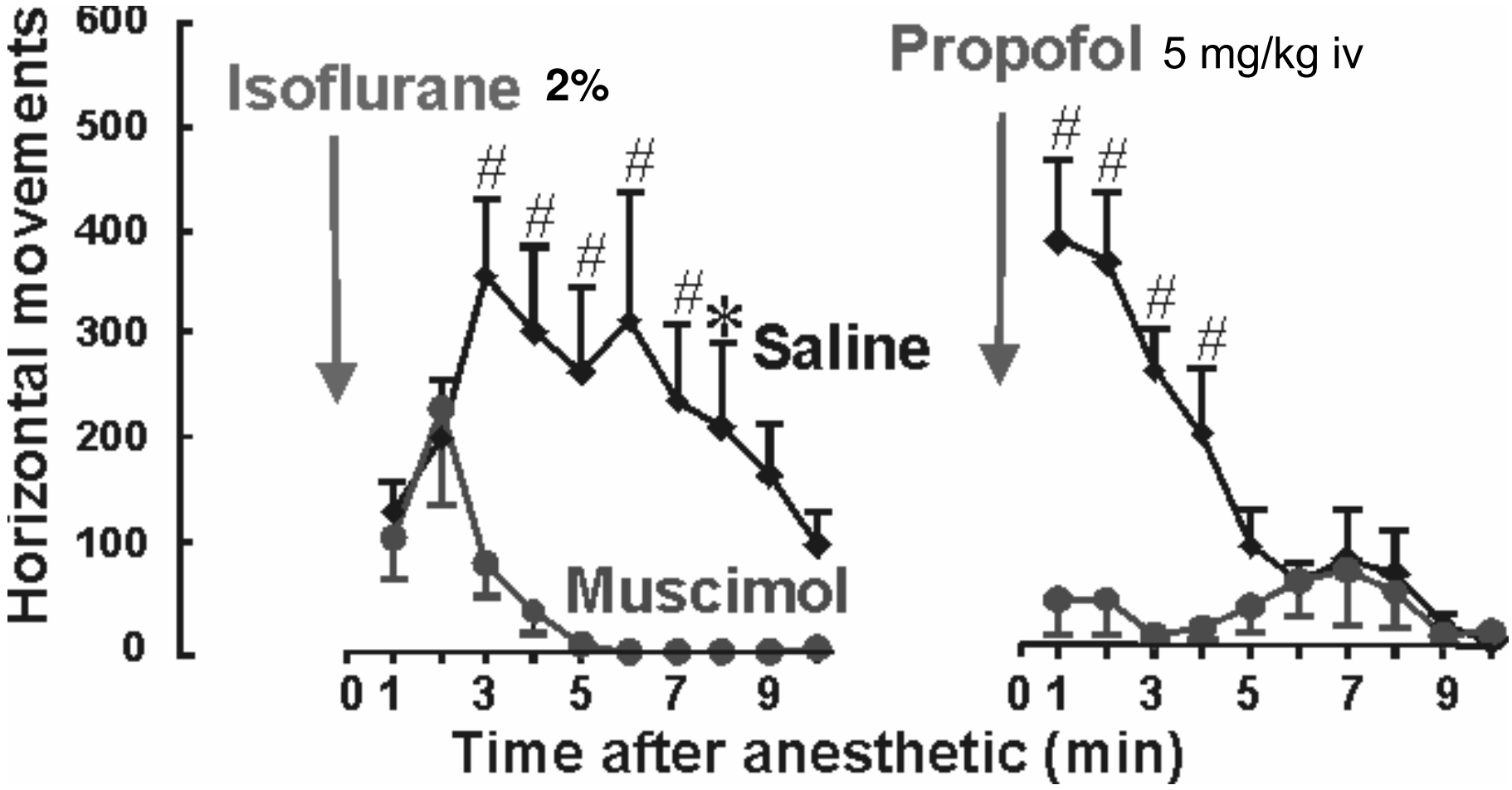
Ma et al., J Neurosci. 22:RC200: 1, 2002

Ketamine induced delirium suppressed by septal inactivation



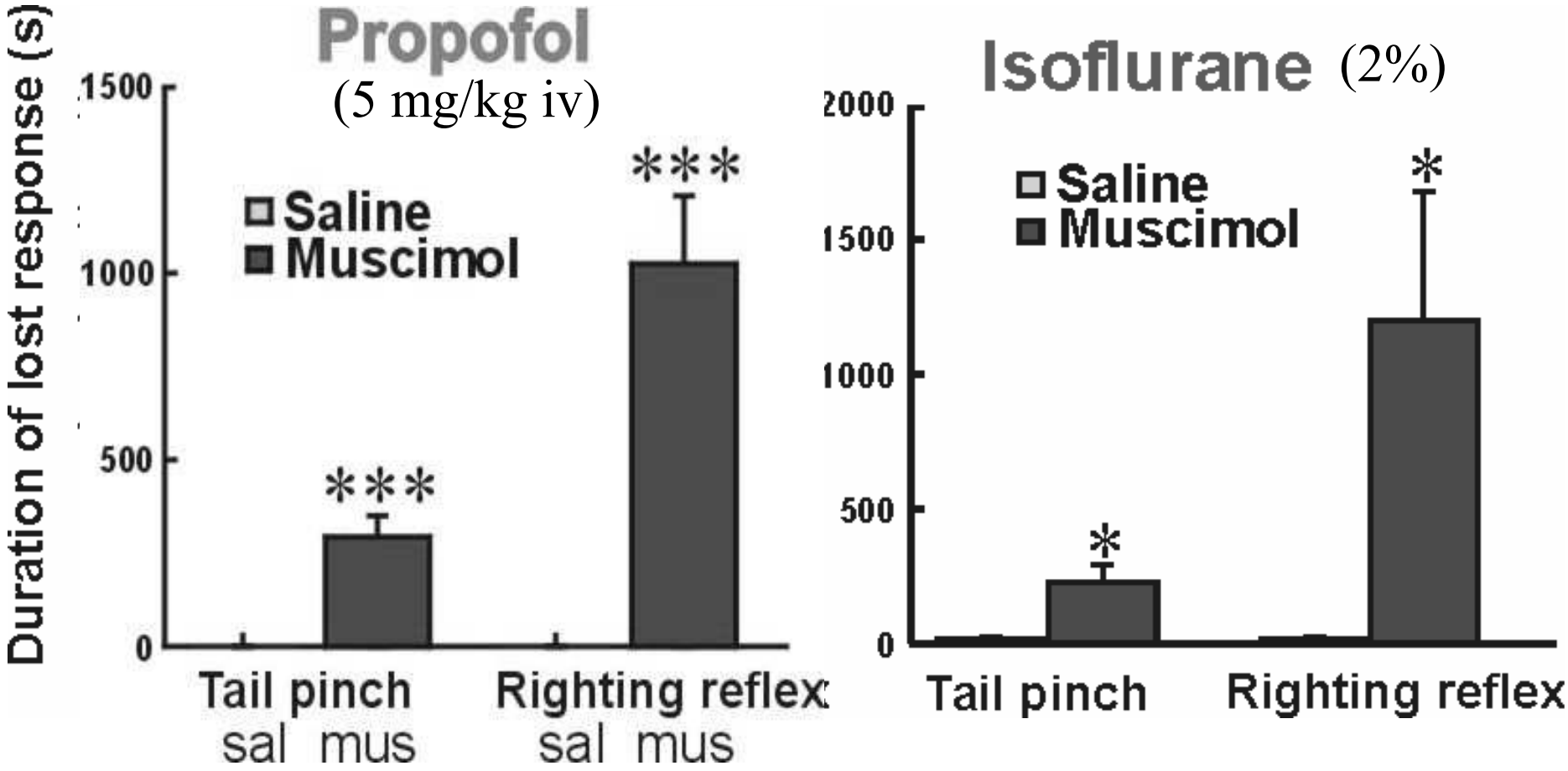
Ma & Leung, Psychopharm, 191:961, 2007

Delirium reduced by hippocampal inactivation (muscimol)



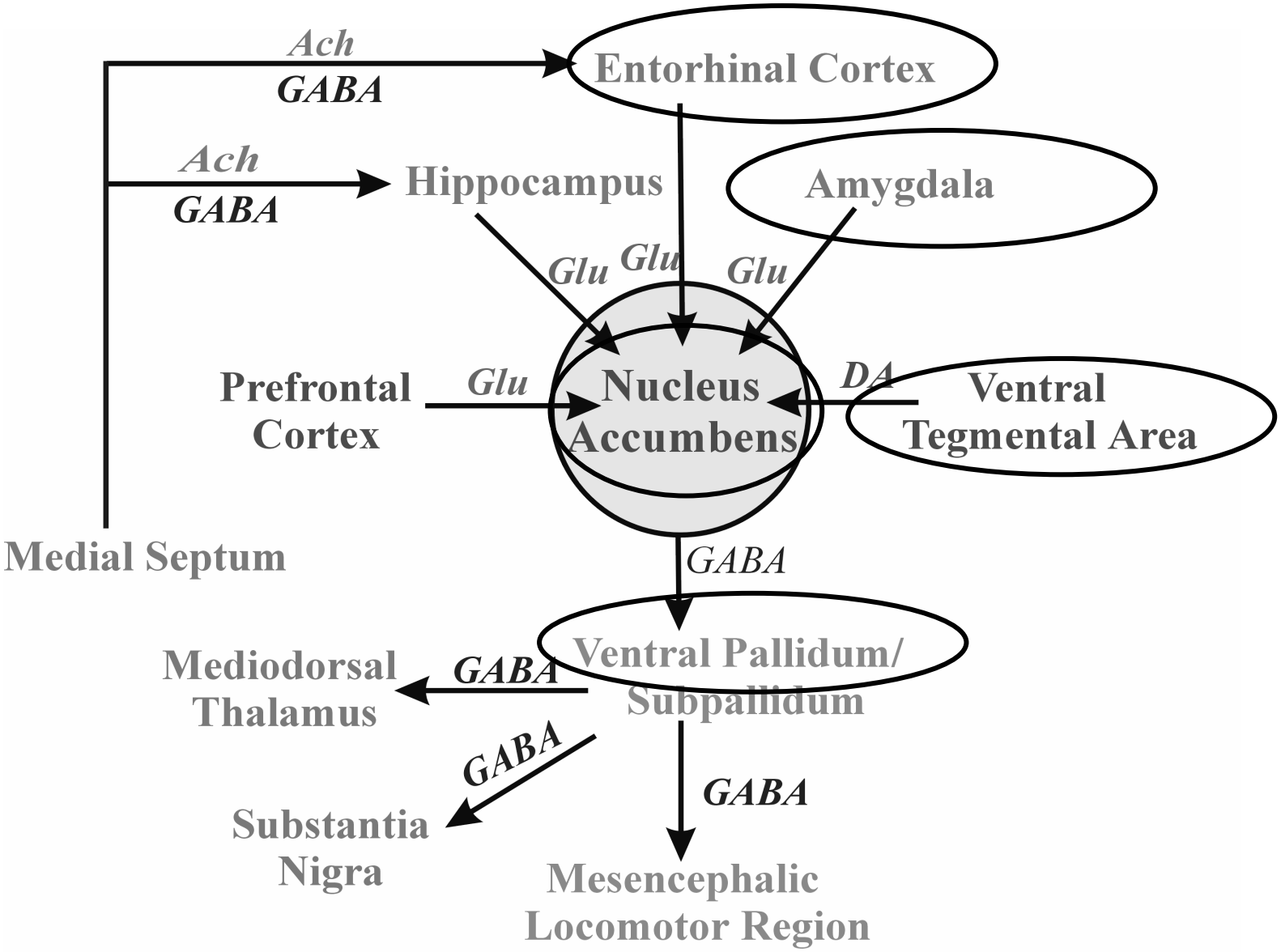
Ma et al., J Neurosci., 2002

Septal inactivation prolongs effects of general anesthesia



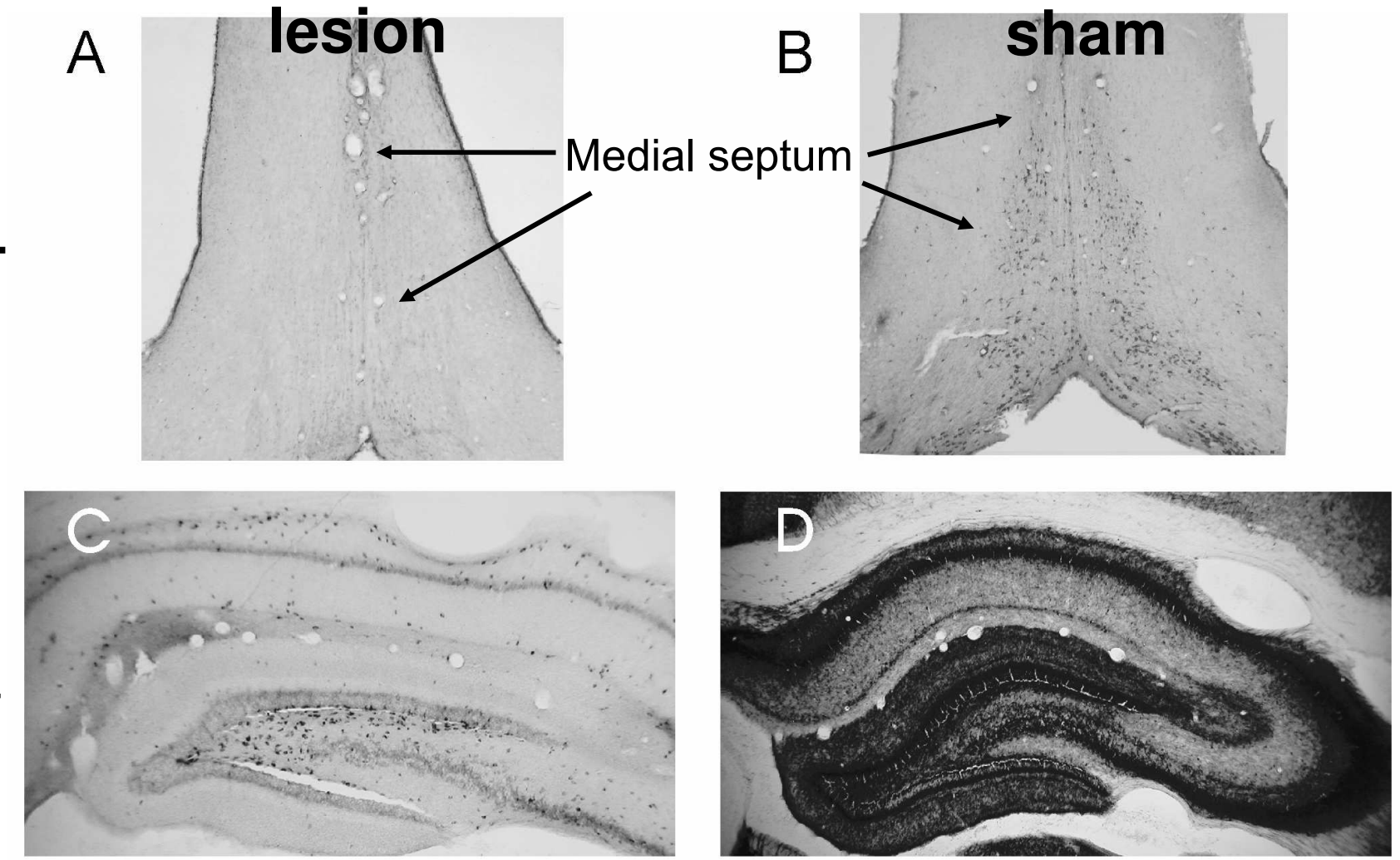
Ma et al. J Neurosci 2002

Limbic circuit involved in anesthesia

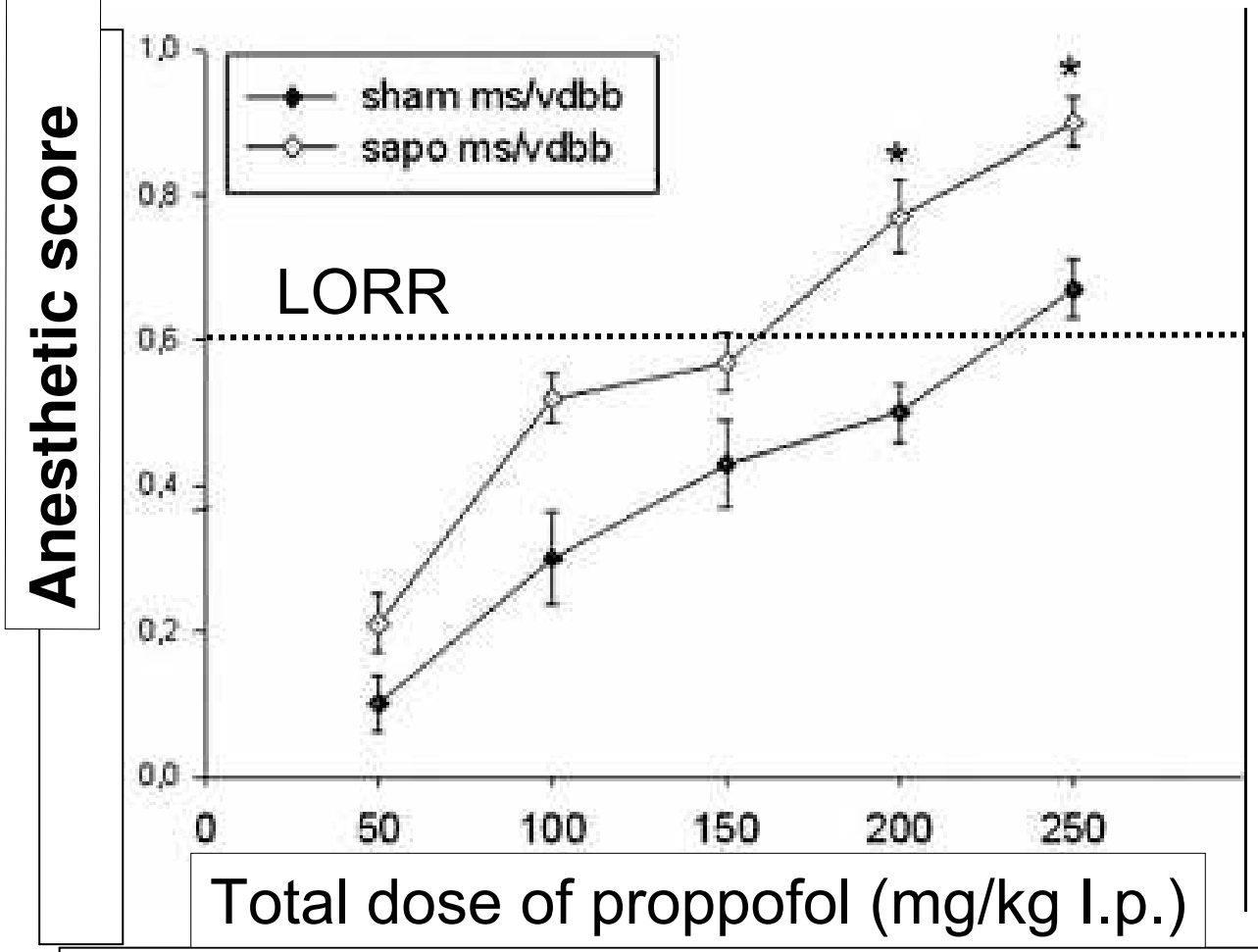


Ma & Leung, Neuropsychopharmacology, 2006

Cholinotoxin (192 IgG-saporin) lesion of medial septum



Septal cholinergic lesion increased propofol sensitivity



Laalou et al. Anesthesiology. 108:888, 2008.

Septal cholinergic lesion increased isoflurane sensitivity

Sensitivity to equilibrium level of isoflurane increased
In septal cholinergic lesion rats as compared to sham lesion

Both induction and emergence from anesthetic were affected

Induction measured by the time to the loss of righting reflex in 1.375% isoflurane
and emergence measured by the time to recover righting after 30 min in isoflurane

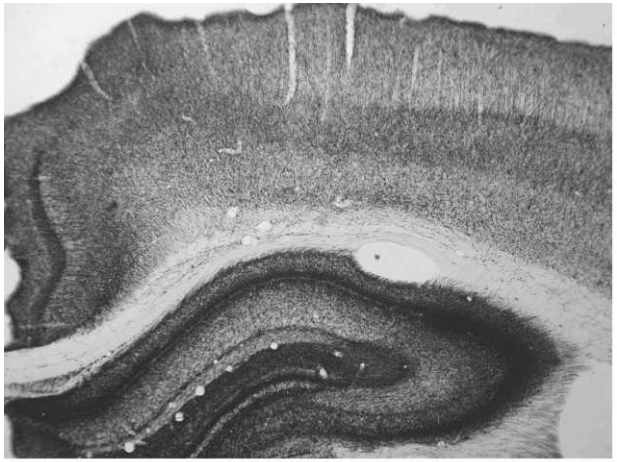
Tai SK and Leung, unpublished

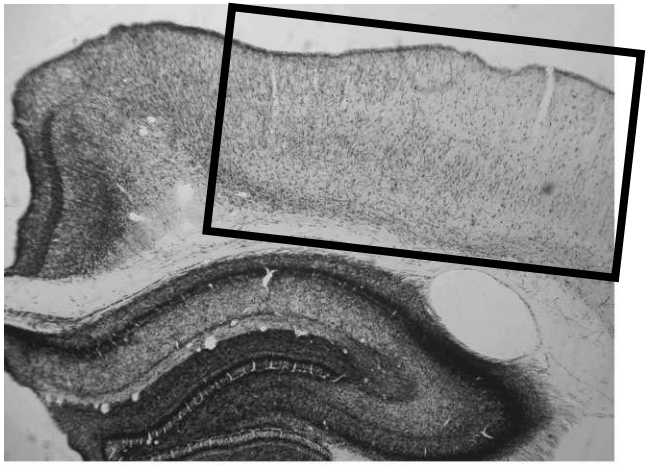
Nucleus basalis Cholinergic Lesion

Saline in NB

192 IgG-saporin in NB

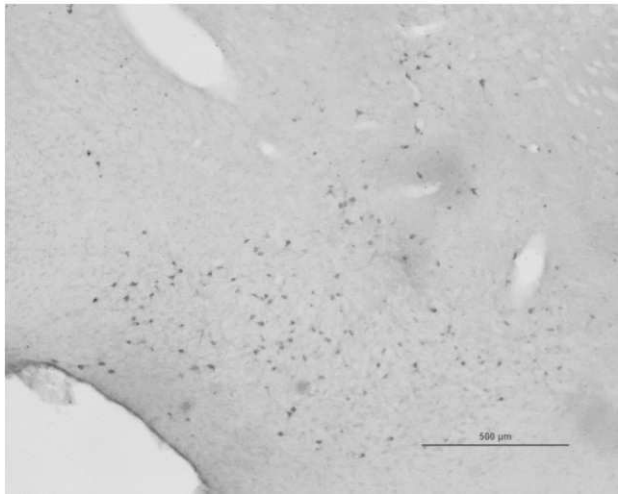
AchE

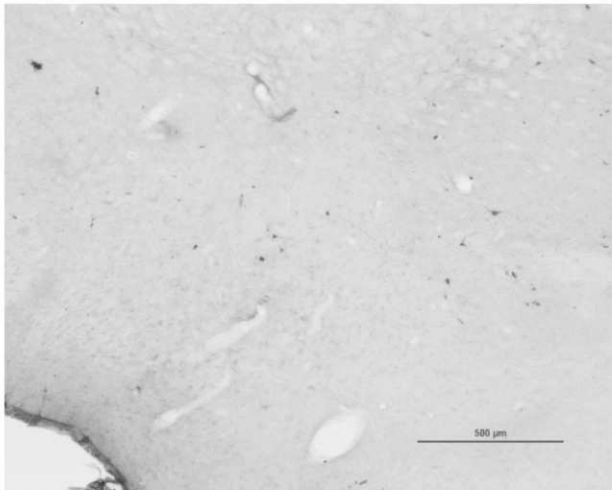




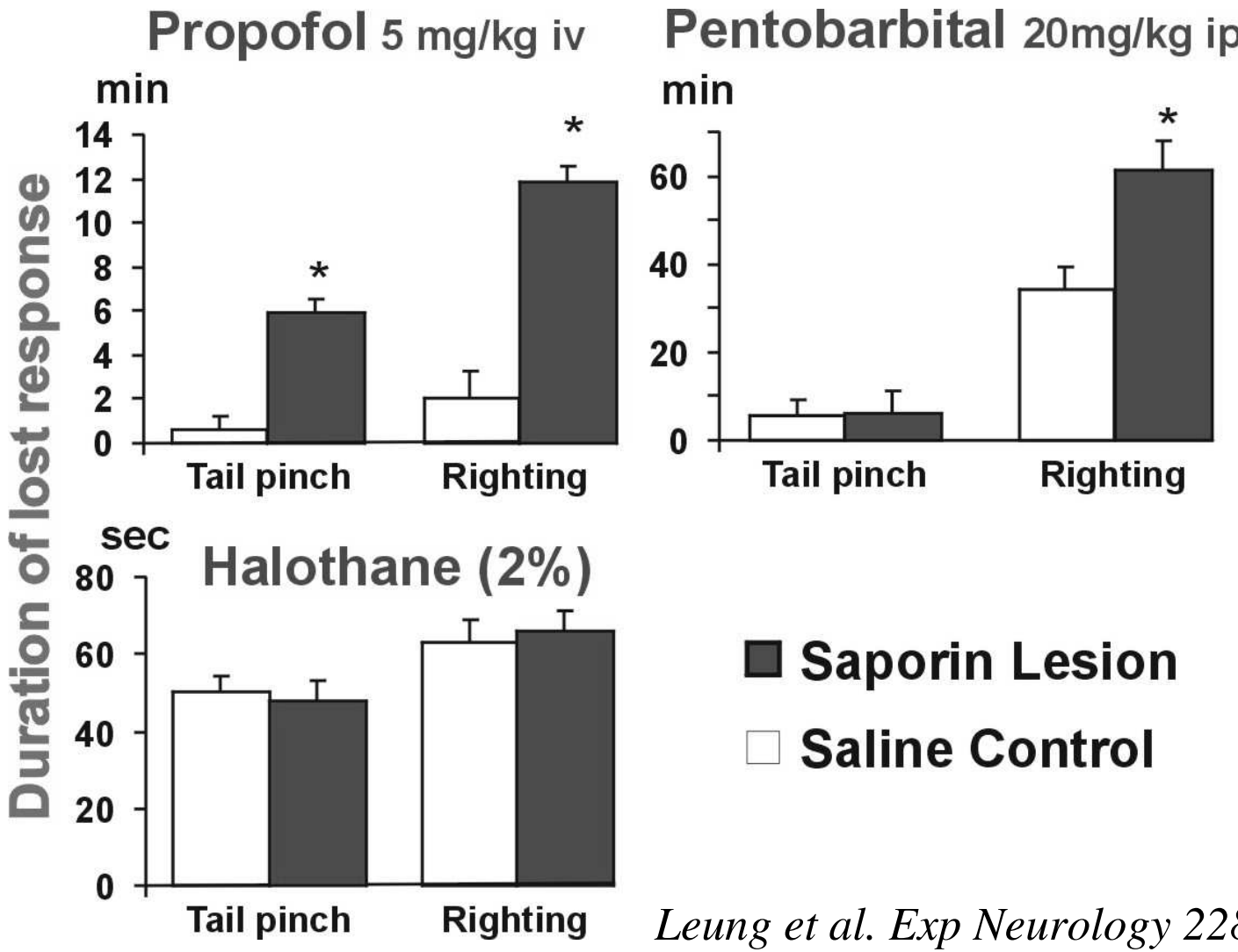
0.5 mm

ChAT in NB



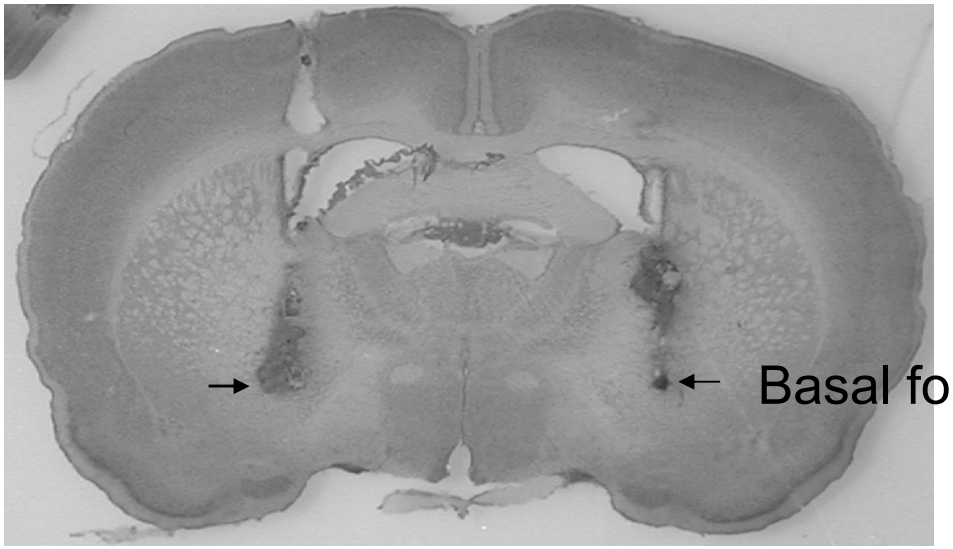


Nucleus Basalis Cholinergic Lesion prolongs some anesthetic effect

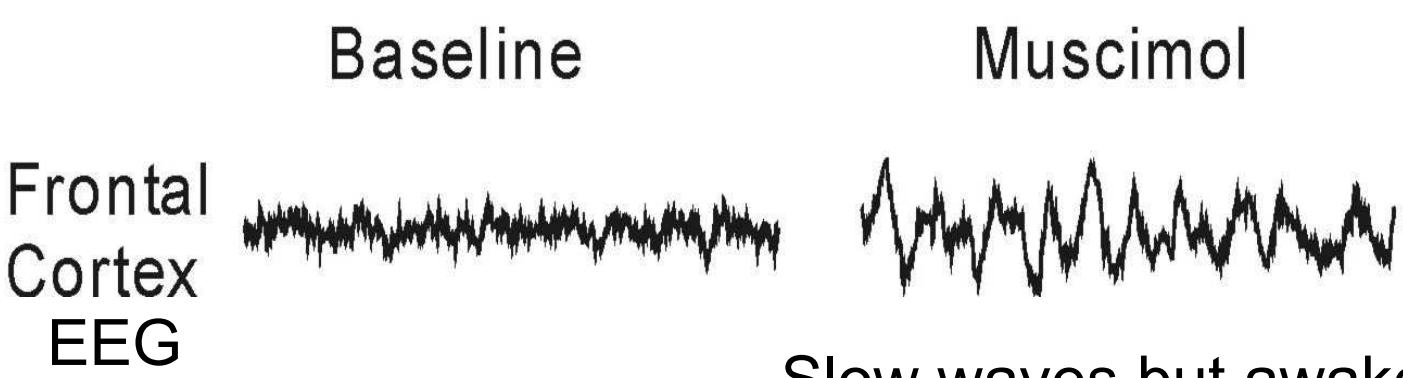


Leung et al. Exp Neurology 228: 259, 2011

Inactivation of nucleus basalis induces paradoxical slow waves during waking



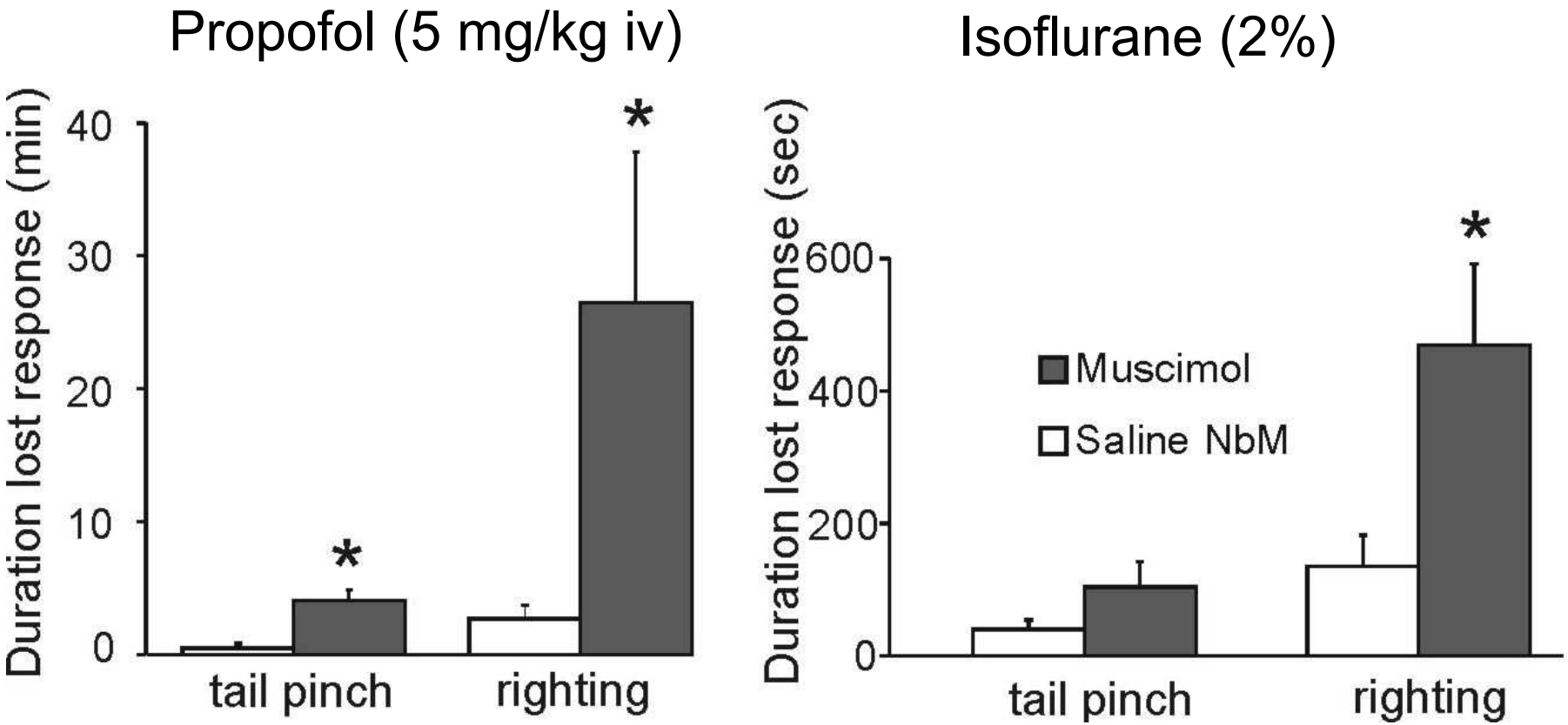
Basal forebrain (n. basalis)



Slow waves but awake,
with righting and pain responses intact

Leung, Luo, et al. Exp Neurology 228: 259, 2011

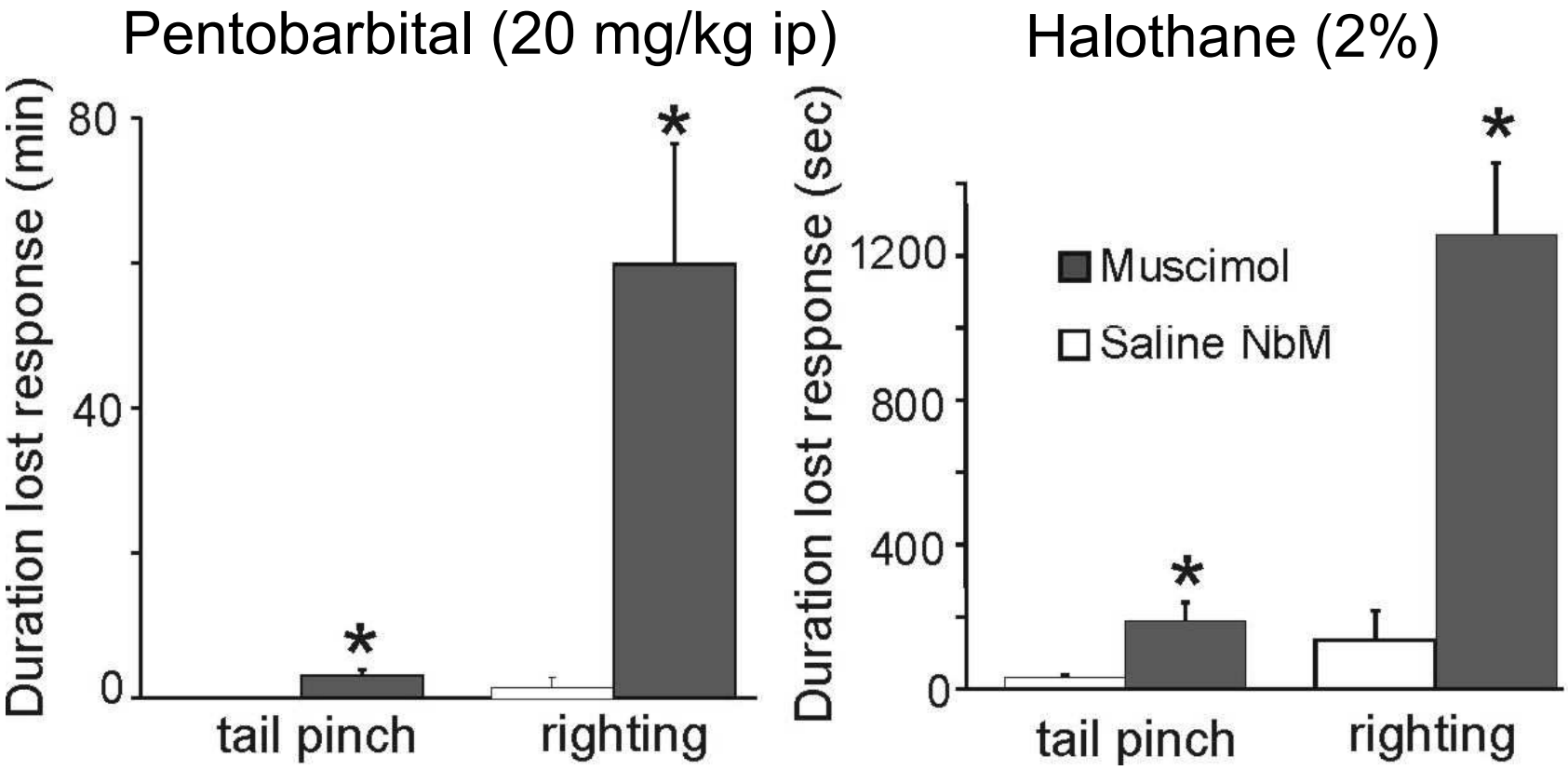
Nucleus Basalis inactivation prolongs effect of general anesthetic



Leung et al. Exp Neurology 2011

Nucleus Basalis inactivation prolongs effect of general anesthetic

Duration of lost response



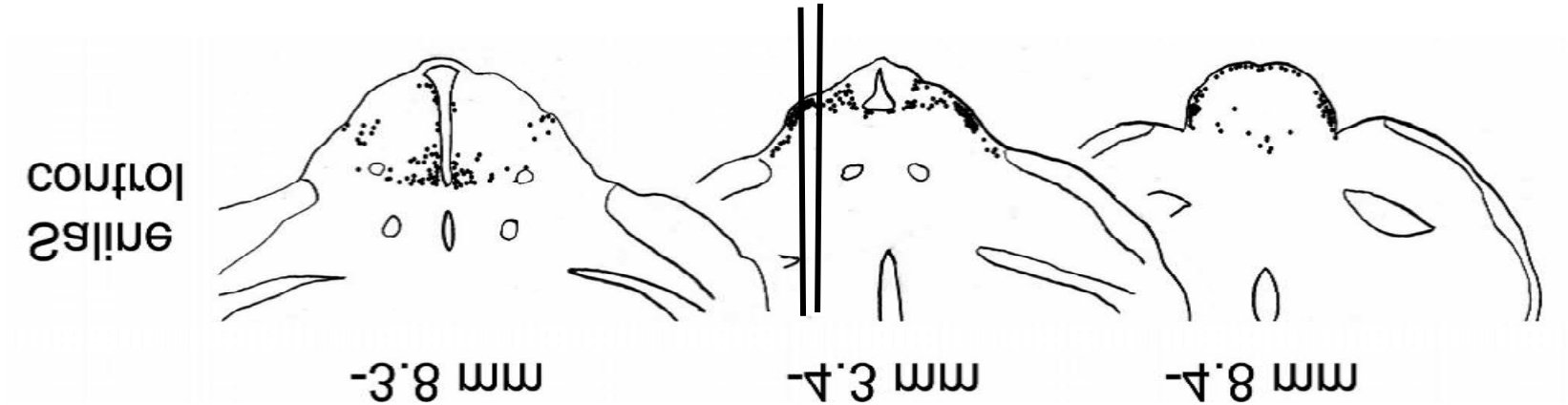
Leung et al. Exp Neurology 2011

Neurochemical correlates of behavioral states

	SWS	REMS	quiet awake	active awake
Acetyl-choline	-	+++	+	+++
Histamine	-	-	+	+++

(similar to other monoamines: serotonin, noradrenaline; orexin)

Histaminergic neurons in hypothalamus: tuberomammillary nucleus (TMN)



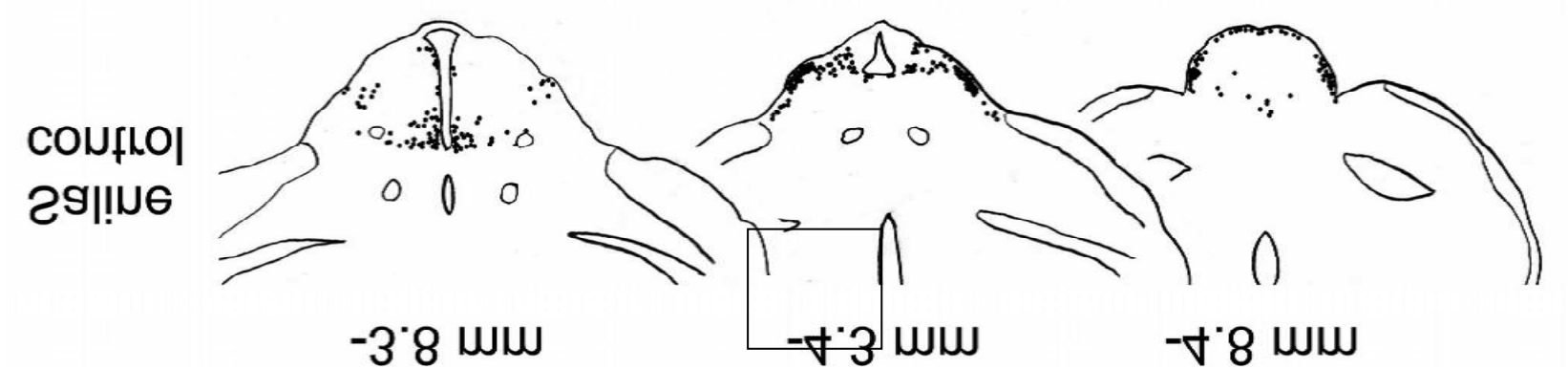
adenosine deaminase stain, Gerashchenko et al. 2004

Nelson et al., Nature Neuroscience 5:979. 2002

GABA-A agonist muscimol in TMN induced sedation
GABAzine, GABA-A antagonist, in TMN reversed GABAergic anesthetic induced sedation

Histaminergic neurons in hypothalamus

Gerashchenko et al. Sleep 2004



Luo and Leung, Anesthesiology 115:36 (2011)

Control (sham) Lesion (orexin2-saporin)