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Alteration of Consciousness by Anesthetics:

a multi-scale modulation from the molecular to the systems level

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Author Contributions

MAD, MC, SD, JAT and EAZ designed the work, supervised the study and contributed to the writing of the manuscript. EAZ, MC, SD collected and rationalized literature data. MAD and JT were responsible for critical revision of the manuscript. All authors read and approved the final manuscript.

26 **Abstract**

27 General anesthesia has been used in medical practice since mid-nineteenth century but its
28 pharmacological mechanism of action is still not entirely clear. In a top-down approach,
29 investigations probe smaller and smaller scales to shed light on how anesthetics disrupt or alter
30 neural activity, ultimately resulting in loss of consciousness. In the past few decades, advances
31 in neuroscience and molecular biology allowed for investigations on the brain structure and
32 function from the behavioral level to the systems, cellular and molecular level. This multiscale
33 approach implicates the molecular domain as a fundamental link between general anesthesia
34 and consciousness, which also sheds light on how anesthetic agents affect the pathogenesis of
35 postoperative behavioral changes. This review discusses the current state of knowledge about
36 the relationship between consciousness and General Anesthesia determined using
37 pharmacokinetics, molecular biology, and advanced medical imaging, including EEG, fMRI,
38 PET, MEG. It is hoped that the mechanisms of action of anesthetic gases may help solve the
39 mystery of consciousness. Conversely, understanding the cellular and molecular mechanisms
40 of consciousness could lead to the design and development of new anesthetic agents and
41 technologies to controllably turn off and on consciousness. It could also generate new concepts
42 in neurocognitive pathophysiology disorders.

43

44 **Keywords:** General Anesthesia, Consciousness, Cytoskeleton, Orch OR, Quantum
45 mobility theory, POCD

46

47

48

49 **Introduction**

50 The very definition of human consciousness has baffled philosophers, spiritualists, and modern
51 scientific scholars alike for a long time, but is yet to be found with consensus. The underlying
52 issue is the lack of understanding of where and how consciousness arises in the brain. A first,
53 pragmatic step toward understanding consciousness is to inspect the role of general anesthesia
54 (GA), whose mechanism is still an enigma in spite of the fact that its discovery dates back to
55 1860. Indeed, GA is routinely used for reversibly extinguishing consciousness prior to and
56 during surgery, but without a clear knowledge of its mechanisms of action, especially at the
57 cellular and molecular levels. Scientific inquiries aimed at defining the neural correlates of

58 consciousness, and hence the susceptibility thereof to general anesthetics, have been conducted
59 at all investigative levels, from molecular/genetic to systems biology, but with inconclusive
60 results. From a molecular point of view, this type of investigation is complicated by the fact
61 that in spite of their diverse molecular structures and different putative molecular targets, all
62 general anesthetics consistently induce reversible loss of consciousness and memory
63 (Craddock *et al.*, 2015). Indeed, GA represents an extraordinary clinical procedure that allows
64 for a temporary and reversible manipulation of the person's consciousness level in a dose-
65 dependent manner and with only minor variations among subjects and a similar mode of action
66 in humans as well as animals. Thus, exploring the relationship between general anesthesia and
67 the associated fields of neuroscience becomes intriguing. Understanding the mechanisms
68 underlying anesthesia may help to resolve the mysteries surrounding consciousness. At the
69 same time, understanding the cellular and molecular mechanisms involved in consciousness
70 could help the design and development of new anesthetic agents and psychoactive mood-
71 altering drugs. It may also explain what mechanism of neuronal processing mediates the
72 qualitative feeling associated with subjective experience. What exactly is measured or
73 monitored during general anesthesia? Could there be a more reliable measure of consciousness
74 when patients are under the influence of general anesthesia? The so-called Hard Problem in
75 answering any question related to consciousness is the nature of reality that one experiences
76 (Chalmers, 2007). The complexity of brain structure, function, and behavior further explains
77 the broad spectrum of neuroscience research, ranging from philosophy to quantum physics
78 (Baijpai, 2015). While consciousness at present is not known to be directly measurable or even
79 observed, modern science continues to seek quantitative measurements of its possible neural
80 correlates. Current neuroscience research related to the investigations of general anesthetics, is
81 being conducted at different biological levels, from the whole organism (to determine clinical
82 effects such as changes in the cardiac and respiratory rhythms, blood pressure, sweat
83 production, tears or pupil dilation), to the cellular level (to identify cortical/neural mechanisms
84 and pathways), and deeper to the molecular level (in order to identify and characterize both the
85 sites and microscopic mechanisms of action of anesthetic molecules). Thus, the present work
86 provides a review of the current state of knowledge regarding the targets, mechanisms and
87 effects of general anesthesia at different time- and length-scales, and its contribution so far to
88 the overall understanding of the biology of human consciousness.

89
90 This review is organized as follows. After a brief introduction of the different classes and uses
91 of general anesthetics, as well as their specific pharmacokinetic properties, we focus on the

92 experimental and computational evidence regarding known and putative targets of general
93 anesthetics at the molecular scale. Subsequently, an in-depth review of higher-scale studies is
94 provided, bridging the gap between molecular knowledge and clinical practice. Lastly, we will
95 discuss current hypotheses regarding the basis of human consciousness stemming from such
96 multi-scale evidence of the mechanisms of action of GA.

97

98 **General Anesthetics**

99 General anesthetics are divided into two major classes: (1) intravenous anesthetic agents, which
100 induce anesthesia and are usually administered in combination with sedatives or narcotics; and
101 (2) volatile anesthetic agents, which are typically utilized to maintain anesthesia (Alkire,
102 Hudetz and Tononi, 2008).

103 Interestingly, inhalational anesthetics act on suppressing bodily functions in a systemic way
104 allowing for loss of awareness, yet physiological functions are preserved, explaining further
105 why this area of science is so challenging to study. General anesthetics are stereoisomers, a-
106 polar, hydrophobic (lipophilic) molecules, with atomic structures ranging from steroids to the
107 elemental atom Xenon. Their anesthetic concentrations in the phospholipid neural membranes
108 during general anesthesia are high (10–100 mM), without any apparent relationship between
109 their molecular structure and physiological effect they elicit (Herold *et al.*, 2017). This suggests
110 that there might be several possible molecular mechanisms of action of anesthetics on different
111 targets rather than a single unitary theory (Franks, 2008). In the case of volatile agents, their
112 ability to selectively prevent consciousness while sparing non-conscious brain activities
113 depends on achieving therapeutic tissue concentrations in the central nervous system (CNS).
114 These compounds are unique compared to other pharmacological agents, having their main
115 route of administration through the lungs and multiple physical properties determining the
116 bioavailability.

117

118 The Meyer-Overton correlation between GA lipid solubility and their minimum alveolar
119 concentration (MAC) suggests that inhalational anesthetic agents have one or more
120 hydrophobic sites of action and may bind to both membrane lipids and to hydrophobic pockets
121 in proteins. To quantify the GA potencies, Eger *et al.* (1965) introduced the concept of MAC,
122 which defines the alveolar fraction of an anesthetic gas that prevents movement in response to
123 a surgical skin incision in 50% of patients (half-maximal effective concentration values, EC₅₀)
124 (Urban and Bleckwenn, 2002). The MAC concept negated the variability by measuring a single

125 quantitative endpoint: immobility. Moreover, MAC expresses the end-tidal anesthetic as a
126 measure of the anesthetic level within the alveoli and, in turn, assumed as the level in the CNS
127 (Aranake, Mashour and Avidan, 2013). In other words, the required efficacious site
128 concentrations depend on the partial pressure of these agents in the CNS and at equilibrium
129 (between alveoli, blood, and brain) are given in terms of the alveolar concentration (5). This is
130 a multi-factorial process that principally depends on factors that:

- 131 i) determine the alveolar concentration of the drug, such as the inspired concentration,
132 the alveolar ventilation and the lung functional residual capacity,
- 133 ii) influence the uptake in the lungs, including the compound's solubility, the
134 pulmonary blood flow and the alveolar-venous partial pressure gradient.

135 Overall, the biophysical properties of inhaled anesthetics influence both uptake from the lungs
136 and distribution through the body. Inhaled anesthetics enter the body *via* trans-alveolar
137 exchange from gas to blood and their clearance is *via* the same route. Thus, inhaled anesthetic
138 delivery is dependent on pulmonary ventilation, whereas uptake and clearance are dependent
139 on pulmonary perfusion.

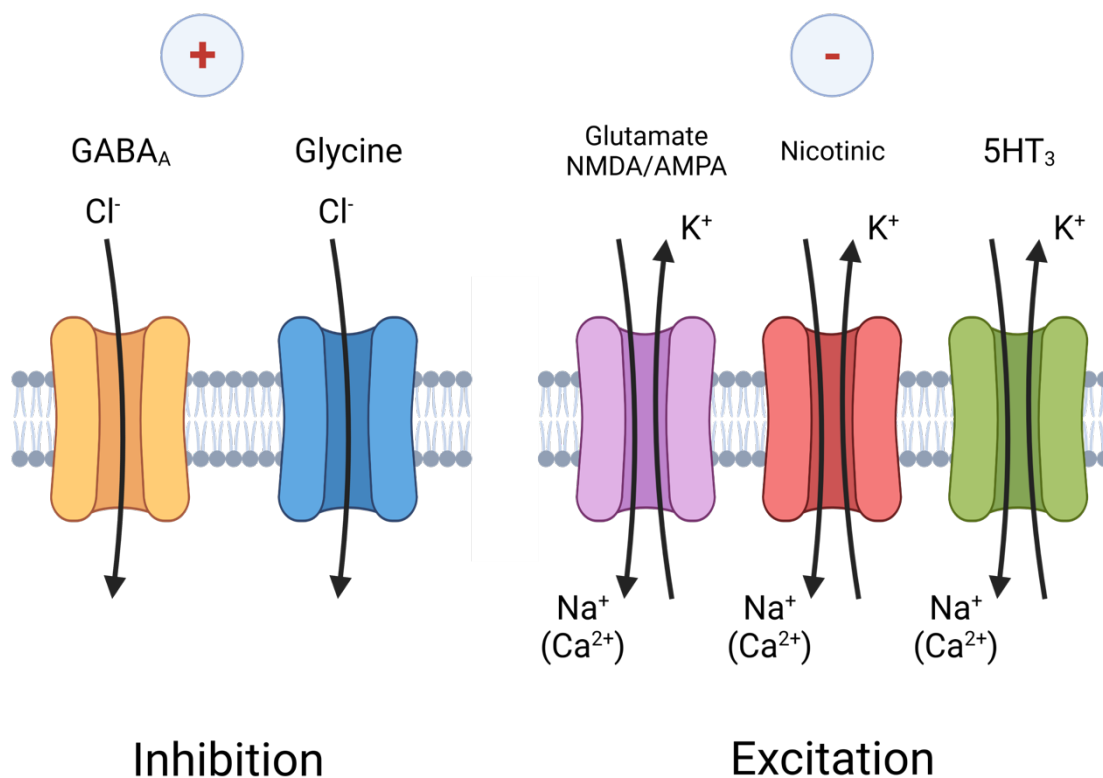
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141 **Molecular targets and driving mechanisms of anesthesia**

142 The concept of general anesthetic action involving specific neuronal pathways implies they
143 might behave selectively at the molecular level. The exposure to general anesthetics shares a
144 common response from bacteria to human neurons, namely the abolishment of cytoplasmatic
145 motility (Goldstein and van de Meent, 2015; Kelz and Mashour, 2019). The organized
146 movement of cytoplasm within all cells is mediated by cytoskeletal proteins, which have
147 recently been implicated as an invariant anesthetic target. The first attempt to explain the effect
148 of general anesthetics on the neuronal membrane came more than a century ago when Meyer
149 and Overton correlated the hydrophobicity of an anesthetic molecule to its efficacy (Urban and
150 Bleckwenn, 2002). Neuronal cell membranes are mainly composed of phospholipids. Since
151 neuronal signals are governed by the structural organization of these membranes, it was
152 concluded that the Meyer-Overton effect implies a unitary action of anesthetics in lipid regions
153 of the neuronal membranes of the brain. Decades later, Johnson and Flagler (1950) discovered
154 that when ambient pressure is increased to 130 atm, the anesthetic effect of ethanol can be
155 reversed. Although the site where pressure reversal occurred appeared to be the membrane, it
156 was not clear which location in the body was involved in this phenomenon (Miller and Wilson,
157 1978).

158

159 Despite the persistent presence of some still-unresolved issues, such theories imply that a
160 profound physical basis of anesthesia must exist, explaining the effects of anesthetics on
161 cellular and subcellular targets, i.e. membranes and proteins. In fact, it is widely known that
162 the tertiary structures of proteins, fundamental for their functional activity, are easily affected
163 by physical factors (Baluška *et al.*, 2016). Indeed, later the molecular mechanisms responsible
164 for neuronal membrane excitability were found to depend on ion channels and membrane
165 receptor proteins. In the 1980s, Franks and Lieb discovered that anesthetic molecules act
166 directly within hydrophobic regions of these proteins (Franks and Lieb, 1994). These findings
167 provided evidence that the effect of general anesthetics on membranes was also stereospecific
168 (Harris, Moody and Skolnick, 1992). Recently, numerous diverse groups of ion channels,
169 receptors, enzymes, and even cytoplasmic proteins have been identified as putative targets of
170 anesthetic agents. However, there is still no direct experimental evidence linking these findings
171 to a mechanism of action. More recently, Herold (2014) investigated a wide range of
172 chemically diverse general anesthetics and structurally related non-anesthetics with the aim of
173 characterizing their neuronal properties employing a standard fluorescence assay, which
174 detects drug-induced changes in the affected lipid bilayer. These investigators established that
175 the lipid bilayers exposed to general anesthetics exhibit only an insignificant change in their
176 properties at clinically relevant concentrations. This would indicate that the effects of
177 anesthetic agents on the function of ion channels are not lipid bilayer-mediated but rather
178 surprisingly directly engage in protein interactions (Herold *et al.*, 2017). Thus, it may be agreed
179 that general anesthetics interact with many proteins through non-specific activity (binding to
180 more than one receptor site) with half-maximal effective concentration (EC₅₀) values, most of
181 which are the order of 1 mM (Chau, 2010). Thus far, sufficiently strong evidence is only
182 available for two ligand-gated ion channels, namely the γ -aminobutyric acid (GABA) type A
183 receptor and the *N*-methyl-D-aspartic acid (NMDA) receptor, as the most probable sites of
184 action (Solt, Johansson and Raines, 2006) (see Figure 1).



185

186 *Figure 1. Inhalational anesthetics modulatory activity on transmitter-gated ion channels.*
 187 *Anesthetics can modulate both pre- and postsynaptic synaptic activity. Presynaptic, by*
 188 *interacting with a variety of proteins, that regulate resting membrane potential and calcium*
 189 *dynamics, thus modulating the neurotransmitter release. Postsynaptic, by binding to targets*
 190 *such as extra-synaptic GABA_A receptors will also affect signaling. Anesthetic agents alter*
 191 *synaptic function through their inhibition of excitatory synapses and through enhancement of*
 192 *the activities of inhibitory synapses*

193 The family of GABA_A receptors has been dissected for each subunit composition. Interestingly
 194 GABA_A receptor subunits are differently distributed among brain regions, according to their
 195 pharmacology, cell-type expression, and subcellular localization (Baldassarre, Scarpati and
 196 Piazza, 2020a). The GABA_A receptor activation is responsible for evoking two forms of
 197 inhibitory currents (modulatory inhibition). Understanding how the different GABA_A subunit
 198 modulates the inhibitory transmission under clinical conditions could be essential for the
 199 recognition of disease conditions (Herold *et al.*, 2017). There is evidence that the GABA_A
 200 receptor may be involved in GA effects since haloalkanes, etomidate, and the barbiturates
 201 interact with different domains of the α - and β -subunits, while propofol binds to the β -subunit
 202 (Tang and Eckenhoff, 2018). Propofol has not been shown to bind to the α -subunit of the
 203 GABA_A receptor.

204

205 Glutamate is an excitatory neurotransmitter found in the CNS whose effects have been seen on
 206 three classes of receptors: NMDA, AMPA, and kainate. NMDA receptor seems to reduce

207 activated current in the presence of nitrous oxide and haloalkanes. However, their effects are
208 not as significant as those exerted on the GABA_A receptor (Hollmann, 1999; Baldassarre,
209 Scarpati and Piazza, 2020b). Many excitatory or inhibitory postsynaptic receptors, once
210 activated, initiate a cascade of metabolic steps that involve cytoskeletal protein conformational
211 changes to modulate cell activity.

212

213 To act as a general anesthetic agent in the CNS, a drug must be able to cross the blood-brain
214 barrier (BBB) and diffuse through the brain parenchyma in order to interact with its designated
215 target. Therefore, anesthetic agents must have apolar characteristics. The interactions between
216 two apolar gas molecules are referred to as van der Waals forces and are relatively weak since
217 they are due to induced polarization in the electron cloud around the nucleus of each of the
218 interacting molecules. For the same reason, GAs typically interact with their targets through
219 weak polarization forces (mostly London dispersion forces) and to a lesser degree by hydrogen
220 bonding (Abraham, Lieb and Franks, 1991). This explains the absence of large conformational
221 changes in the target protein following anesthetic binding. Consequently, anesthetics do not
222 possess the common functional groups that endow most pharmacological agents with their
223 specificity.

224 Furthermore, the binding sites of anesthetic agents on protein surfaces are also expected to be
225 non-polar, pre-formed cavities where the anesthetic displaces water (Bertaccini, 2010). These
226 non-polar intra-protein regions were found to be composed of highly polarizable aromatic
227 amino acids, such as tryptophan, tyrosine, and phenylalanine, and can provide a chiral
228 environment. As a result, the orientation of the anesthetic molecule in its binding pocket is
229 determined by its chemical structure. These findings suggest that anesthetics do not act by
230 inducing new conformational states of proteins instead they bind to pre-existing
231 conformational states. At present, there are only two viable methods to identify the general
232 anesthetic's binding site at this biological level of investigation by direct measurements. The
233 first method involves a mutation of an amino acid at the putative binding site. The second
234 method uses a photo-affinity analog of the anesthetic in order to be able to observe and image
235 its binding location. Eckenhoff et al. used radiolabeled halothane in mice and was able to show
236 that at clinically relevant concentrations, anesthetics bind to roughly 70 different neuronal
237 proteins. About half of them are cellular membrane components, and the other half are
238 cytoplasmatic proteins, particularly tubulin. Proteomic analysis conducted after halothane,
239 isoflurane, desflurane, and sevoflurane exposure shows that tubulin expression levels change
240 even several days after treatment while the membrane protein expression does not modify

241 (Kalenka *et al.*, 2007; Elsevier, 2014). More recently some authors presented a new model for
242 the anesthetic mechanism of action based on experimental findings, which may involve some
243 form of electron transfer processes in protein. Experiments showed (Turin, Skoulakis and
244 Horsfield, 2014) that *Drosophila* exposed to an external magnetic field generates spontaneous
245 radio frequency emission that is abolished by chloroform (Cukras and Sadlej, 2021). Similar
246 results were found using Xe, N₂O, CH₃Cl, further corroborating the hypothesis that anesthetics
247 may affect electron spin degrees of freedom as shown in specific electron spin resonance
248 signals (ESR) (Pavel *et al.*, 2020). These findings appear to open a new avenue for the study
249 of the physical mechanism of anesthesia and consciousness since they include electronic
250 properties of proteins, possibly embedded in the membranes of excitable cells resulting in free-
251 electron transfer and possibly interactions with nuclear spin. The involvement of anesthetics in
252 the electronic properties of a neurological systems also allows important progress in
253 understanding how quantum effects contribute to information transfer processes in biological
254 systems (Smith *et al.*, 2021). In this regard, low light intensity pulses have been demonstrated
255 to trigger neuronal action potential in vivo showing the neurons are susceptible to light and
256 thus hypothesizing a possible role in information transfer (Bouche *et al.*, 2001) including
257 quantum electromagnetic interaction (Burdick *et al.*, 2019).

258 The link between anesthesia, consciousness and biophysical phenomena involving neuronal
259 tubulin was already proposed in the mid- and late 1990s by Hameroff and Penrose (Hameroff,
260 1998). They formulated the Orchestrated Objective Reduction (Orch OR) theory, a paradigm
261 linking together biology and quantum physics, still a matter of lively debate and controversy
262 to this day. The theory states that the site of action of anesthetics is a distributed phase of non-
263 polar, hydrophobic medium composed of discrete pockets inside microtubules throughout the
264 brain. In the hydrophobic regions, the theory states that quantum mechanical forces direct the
265 functions responsible for consciousness, which is postulated to occur due to 'orchestrated'
266 ('Orch') objective reduction ('OR'), i.e. quantum collapse of quantum states in microtubules,
267 which resonate through a multiscale vibrational hierarchy to the membrane and synaptic
268 activities in the low frequency range (below 100 Hz) (Hameroff and Penrose, 2014). Others
269 have also investigated the relationship between microtubule activity and cognitive function. It
270 has been shown how during brain development, a period associated with the formation of
271 synapses and visual learning at the highest rates, the visual cortex of the brain produces
272 extremely large quantities of tubulin (see The Human Protein Atlas
273 <https://www.proteinatlas.org/>).

274 What is interesting in the context of quantum consciousness is that neurons contain structures
275 such as microtubules, mitochondria and dendritic spines that might support coherent energy
276 transfer. Furthermore, living organisms tend to be favorably affected by coherent patterns of
277 electromagnetic (EM) waves, which may induce a “biological order”. Pribram pioneered the
278 notion that brain activity at the level of neural web patches involves EM interactions in terms
279 of local field potentials leading to holographic phenomena (Xu et al. 2018). These would
280 represent interference patterns that form images due to constructive and destructive
281 interference effects of the overlapping waves. This hypothesis is referred to as the Holonomic
282 Brain Theory (Pribram, 1986; Pribram *et al.*, 2013). Holonomic processes have subsequently
283 been termed “Quantum Holography” by Schempp (Schempp, 1992) and applied to image
284 processing in brain tomography including PET scans and functional Magnetic Resonance .
285 Dolgoff instead of looking at the effects of EM waves on biological structures, hypothesized
286 that biological structures such as synapses generate electromagnetic waves for ultra-efficient
287 storage, processing, retrieval of data and performing biological functions (Dolgoff, 1973). The
288 study of the brain’s EM properties has added valuable information on neuronal physiology and
289 could shed light on the role of anesthetics in the interference patterns of electromagnetic waves.
290 The idea is that if holographic images are formed due to conscious activities in the brain, then
291 anesthetics may act to extinguish or scramble such images. Obviously, experimental studies
292 are needed to validate the holographic brain hypothesis and its consequences for anesthesia.
293
294 In summary, it is clear now that anesthetics at their MAC values preferentially bind to
295 membrane receptors and ion channels as well as phospholipids. However, we now know that
296 they also bind to tubulin in microtubules. Although the molecular mechanisms and locations
297 of the action of anesthetic molecules are unknown, it is generally accepted that the potency of
298 the effects of anesthetics is correlated to their hydrophobicity, electrostatic polarity,
299 polarizability, and ability to affect hydrogen-bonds (Davies, Bagnall and Jones, 1974; Urban,
300 2008). As mentioned above, the Meyer-Overton relationship most directly exemplifies the link
301 between the potency of an anesthetic and its lipid solubility (Urban, 2008) and hence represents
302 a quantitative structure-activity relationship (QSAR). Craddock et al. further proposed that
303 anesthetics can alter London force-mediated oscillations acting in non-polar, hydrophobic
304 regions of tubulin dimers in neuronal microtubules, particularly in dendrites, since they exhibit
305 a high level of polarizability (Craddock *et al.*, 2015). These hydrophobic regions are mainly
306 composed of the aromatic amino acid residues, namely tryptophan, tyrosine and phenylalanine.
307 They all are highly polarizable and hence susceptible to interactions with anesthetics *via* their

308 induced dipoles. However, without more accurate and precise information, the proportions of
309 anesthetic binding to these different cellular locations listed above and the strengths of these
310 interactions, it is not possible to determine the molecular mechanism of action at the subcellular
311 level. As this requires the most precise biological resolution (nano-level) of investigation to
312 date, the development of new technologies (i.e., X-ray free-electron laser and crystallography)
313 could provide a better determination of membrane protein structures in general anesthesia.

314

315 **Insights from in silico modelling**

316 In recent years, thanks to the dramatic increase of computational power and to the refinement
317 of the underlying methodologies, the computational investigation of biomolecules, including
318 lipids and proteins, has proven a valuable tool for shedding light on molecular events taking
319 place at the sub-nanometer and sub-millisecond time- and length scales (Lu *et al.*, 2006;
320 Apicella *et al.*, 2013; Deriu *et al.*, 2014; Bernardi, Melo and Schulten, 2015; Grasso *et al.*,
321 2015, 2016, 2018; Hollingsworth and Dror, 2018). As a matter of fact, thanks to the computing
322 power available in current days, atomistic Molecular Dynamics simulations of protein-ligand
323 complexes embedded in lipid membranes can be performed, with simulated systems reaching
324 sizes in the order of hundreds of thousands of atoms and simulation timescales close to or even
325 beyond the microsecond (Priel, Tuszynski and Woolf, 2010).

326 In the context of anesthesia, a significant obstacle towards its further understanding is the lack
327 of conclusive evidence for a single, putative receptor at the atomic level, so different putative
328 functional mechanisms have been investigated computationally to this date, including (a) the
329 structural effects of anesthetics on the cell membrane and (b) direct effects of anesthetics on
330 ion channels and cytoskeleton proteins. As for the effects on the lipid bilayer, anesthetics have
331 been shown to alter bilayer properties through Molecular Dynamics simulations in 1994 by
332 Huang and coworkers (Huang and Bertaccini, 1995), who reported among others an increase
333 in membrane fluidity and lipid diffusion caused by the presence of trichloroethylene. Early
334 computational predictions carried out by Tu and colleagues (Tu *et al.*, 1998) suggested no
335 significant effects of halothane on local membrane structure, but later investigations by Koubi
336 *et al.* highlighted how the anesthetic induced significant alterations of membrane electrostatics
337 (Koubi *et al.*, 2001). A similar effect has been predicted more recently by Mojumdar and
338 Lyubartsev (Mojumdar and Lyubartsev, 2010), who highlighted how the local anesthetic
339 articaine behaves differently depending on its charge, with the neutral form altering the local
340 electrostatic properties of the membrane. This behavior was later confirmed by the findings of

341 Saeedi and coworkers (Saeedi, Lyubartsev and Jalili, 2017), who also provided quantitative
342 estimates of the binding free energies of arcticaine and lidocaine within the membrane. The
343 pressure reversal phenomenon has also been the focus of computational predictions:
344 Yamamoto et al. (Yamamoto *et al.*, 2012) employed molecular dynamics simulations to
345 investigate the pressure reversal mechanism for Xenon at the atomistic scale, providing
346 computational evidence for the alteration of Xenon diffusivity inside the membrane caused by
347 the increase in pressure. With similar methodologies, different computational studies have
348 investigated the interaction between anesthetics and ion channels: in 2002, Tang and Xu
349 provided early evidence supporting the theory that volatile anesthetics may significantly alter
350 the dynamics of ion channels at the nanosecond time scale (Tang and Xu, 2002). More
351 importantly, these findings underlined the physical validity of the assumption that anesthetics
352 might defy the lock-and-key paradigm of drug-target interaction, and might instead exhibit
353 global effects on protein functional motions even without the need of a single, well-defined
354 binding site. In 2008, the work of Vemparala and colleagues (Vemparala, Domene and Klein,
355 2008) employed Molecular Dynamics to directly investigate the effects of halothane on the
356 open and closed states of the KirBac1.1 channel, and later simulations carried out by Cheng et
357 al. in 2010 (Cheng, Coalson and Tang, 2010) suggested an effect of halothane on the GLIC
358 channel, in the form of a destabilization of the open conformation.

359 The subsequent availability of experimentally solved atomic structures of anesthetic-bound
360 GLICs (Nury *et al.*, 2011; Pan *et al.*, 2012) further supported this idea. Interestingly, other
361 protein targets have also been considered by atomistic simulations, as a consequence of a
362 progressive shift of interest from ion channels and membrane proteins alone towards other
363 classes of proteins. An example is represented by cytoskeleton proteins, in the light of genomic
364 and proteomic studies pointing specifically to microtubules as a putative functional target of
365 anesthetics (Pan *et al.*, 2008). Indeed, there is increasing experimental evidence of the
366 interaction of tubulin, the main building block of microtubules, with anesthetics (Livingston
367 and Vergara, 1979; Eckenhoff and Johansson, 1997; Pan *et al.*, 2006; Sahni, 2016), but the
368 exact consequences of said interaction remain to be elucidated. In this regard, some works have
369 suggested a pivotal role of the specific microtubule architecture and topology, both in axons
370 and in dendrites, in the signaling process across the neuronal network (Kapitein and
371 Hoogenraad, 2015). Further, the clinical relevance of microtubules in the context of anesthesia
372 has been underlined in the light of the already discussed role of cytoskeleton reorganization in
373 learning, cognition and memory, resulting in a selective tuning of both the activity and the
374 firing intensity of synapses (Janke and Kneussel, 2010). Moreover, extended exposure to

375 anesthetics has been related, together with low temperature, to depolymerization of neuronal
376 cytoskeletal proteins, which is thought to mediate postoperative cognitive dysfunction
377 (Hameroff, 2018). Thus, the role of tubulin might also be of significance in the light of potential
378 side effects of anesthesia such as POCD, as well as in the context of anesthesia with
379 simultaneous chemotherapy or neurodegenerative disorder. In this context, the investigations
380 of Craddock et al. predicted putative binding sites of anesthetics on tubulin and postulate the
381 ability of anesthetic gases to alter dipole oscillations along the tubulin dimer (Craddock *et al.*,
382 2017). More specifically, they found that the presence of an anesthetic agent (acting as a
383 potential alteration on the network of aromatic residues within microtubules) creates a shift of
384 the normal oscillatory modes of the dipoles and resulting in the addition of a further normal
385 mode of the dipolar oscillations, according to their anesthetic potency. The addition of an
386 anesthetic slows down the normal oscillatory modes of the dipoles by orders of 1 to 100 GHz,
387 whereas non-anesthetics did not. A recent computational investigation of ours further mapped
388 the interaction between volatile anesthetics and human tubulin, finding transient hydrophobic
389 binding sites on the dimer surface and quantitative estimates of tubulin-anesthetic binding
390 energies (Zizzi *et al.*, 2021). These results obtained through computational modeling
391 demonstrated that binding of anesthetics to microtubules may be involved in the mode of action
392 of anesthetics, or at least in some of their side effects, by altering the polymerization and
393 function of microtubules.

394

395 **From Molecules to Organs**

396 Experimental data point to GA action on synaptic transmission at both pre-and postsynaptic
397 nerve terminals. Also, direct interaction with plasma membranes seems possible, and also
398 indirect action through second messenger systems. Clinical signs of anesthetic effectiveness
399 (i.e., depth) have been reported since early 1900 and have been associated with specific targeted
400 neural pathways. ~~Arthur Ernest~~ Guedel (1937) described a classification of clinical anesthetic
401 states using the inhaled anesthetic agent, diethyl ether. The classical signs of Guedel's
402 classification were based upon clinical observations such as eyelash reflex, respiration, blood
403 pressure, heart rate, eyeball movements, pupillary size, and muscular movements, among
404 others. This clinical evidence suggests that anesthetics might act on different brain regions (i.e.,
405 cortex, midbrain, and spinal cord) at different times and durations (early/acute vs.
406 late/sustainable) (Devika Rani and Harsoor, 2012). This heterogeneity of neurophysiologic
407 effects, shown by general anesthetics, in extinguishing awareness, supports the consideration

408 that consciousness is intrinsically a *multiscale* phenomenon, emerging through very complex
409 interactions of both spatially and temporally localized functions of the human brain.

410

411 **a) Pathway and Cell Level**

412 Moving from the molecular to the cellular scale, elegant electrophysiology and connectivity
413 studies support the hypothesis of feedforward and feedback processing in the brain. Thalamo-
414 cortical projections are shown to terminate in granular layer IV. Feedforward cortico-cortical
415 projections arise mostly from upper layers II-III, containing the cellular bodies of large
416 pyramidal neurons, and terminate primarily in deep layers V-VI and some in layer III.
417 Feedback cortico-cortical projections originate mostly from deep layers V-VI (fewer from layer
418 III) and end in the upper layers II-II (and some in layers I and IV) (Mejias *et al.*, 2016).
419 Collectively, low field potentials (LFP), which are generated by the apical dendrites within the
420 cortex, are the primary source of electroencephalogram (EEG) signals (Koht, Sloan and
421 Toleikis, 2017; Phillips, Bachmann and Storm, 2018). EEG recording during general
422 anesthesia shows a transition from wakefulness high-frequency pattern to the low-frequency
423 EEG of deep NREM sleep, and finally to a burst-suppression pattern (Voss and Sleight, 2007).
424 EEG recording during the normal transition from the state of wakefulness to sleep, shows
425 characteristic 'spindle waves' (7 to 14 Hz occurring every few seconds), produced by the
426 thalamus. Spindling reveals the deactivation of pathway between the thalamus the cortex and
427 the inhibitory GABAergic reticular neurons. The deactivation of sensory input and output to
428 the cortex during the progression from the state of wakefulness to deep sleep in human, has
429 been observed during brain imaging studies and it correlates strongly with the EEG spindle (Le
430 Masson *et al.*, 2002).

431 During both sleep and general anesthesia, the disruption of cortical connectivity is likely to be
432 related to loss of consciousness. It is still not known to what extent cortical inhibition causes
433 anesthetic-induced loss of consciousness, which remains an open research issue (Franks, 2008).

434

435 Investigations on the anesthesia effects have often involved the brain's connectome,
436 specifically, interactions among functionally distinct neural networks, which may be
437 suppressed by general anesthetic agents. However, the molecular mechanism responsible for
438 these effects may have a more integrated spatio-temporal dimension that extends beyond
439 current neuroimaging or neurorecording resolution limitations. The activity received or
440 transmitted by neurons is generated from a cellular electrical potential that can be recorded

441 locally, by microelectrodes, in experimental conditions, or during selected brain surgery
442 procedures (Buzsáki, Anastassiou and Koch, 2012). Charges in brain cells, including neurons
443 and glial cells, generate detectable electric currents (i.e., Local Field Potential, LFP) (Einevoll
444 *et al.*, 2013). LFPs have attracted renewed interest in the past decade as a potentially useful
445 signal, which lends itself to studying the aggregate activity behavior of small populations of
446 neurons.

447 LFP represents a continuous voltage signal with a variation in its amplitude and frequency.
448 Similarly, to the EEG, LFP can be decomposed into their power spectrum (Fourier
449 transformation) containing a wide range of frequencies shifting from delta waves (<1 Hz), theta
450 waves (4–8 Hz) and alpha (8–12 Hz), beta (12–30 Hz), gamma (30–80 Hz), and high-gamma
451 or high-frequency activity (>80 Hz) (Jia and Kohn, 2011).

452 Importantly, neural circuits often exhibit patterns of oscillatory activity, and temporally
453 coordinated input can enable both the transmission and integration of information within
454 neurons. This is consistent with the functional significance of synchronized oscillations
455 (Pereda *et al.*, 2013). Investigations of gamma oscillations are aimed at establishing a link
456 between changes in synchrony and/or coherence across different brain regions between signals
457 in the frequency range centered at 40 Hz with perceptual, behavioral, and cognitive processes.
458 These processes are hypothesized to involve long-distance network coordination and reflect
459 the LFP gamma power in a neural population of two or more connected interneurons (Hu and
460 Agmon, 2015). Gap junctions have been reported in thalamocortical neurons in the thalamus
461 and cortical interneurons' dendrites, which might be responsible for gamma synchrony
462 oscillations in the 30-80 Hz band (Traub *et al.*, 2001).

463 In general, gamma oscillation periodicity reflects the integrative excitatory and inhibitory
464 synaptic processes at the level of neural population activity. The LFP is sensitive to
465 subthreshold dendritic processes therefore serving as an indicator of engaged cortical networks
466 (Buzsáki, Anastassiou and Koch, 2012). Gamma synchrony has been observed in cortex areas
467 and in subcortical structures, and it is associated to a broad range of cognitive phenomena (Liu
468 and Newsome, 2006). In the higher cortex, gamma signals have been found to be elevated
469 during functional activation cortex such as working memory and learning activities (Bauer,
470 Paz and Paré, 2007). The range of time scales available in LFPs offers the possibility to
471 investigate whether or not the neuronal information processing is spread throughout the many
472 dimensions. Indeed, recent studies determined that bundles of brain microtubules are

473 electrically active and can generate electrical oscillations that might correlate with the
474 oscillatory neuronal activity (Cantero and Cantiello, 2020). It is worth noting that irregular
475 gamma signature has been associated with such neurodegenerative disorders as Alzheimer's
476 disease, Parkinson's disease, schizophrenia, and epilepsy (Uhlhaas and Singer, 2006).

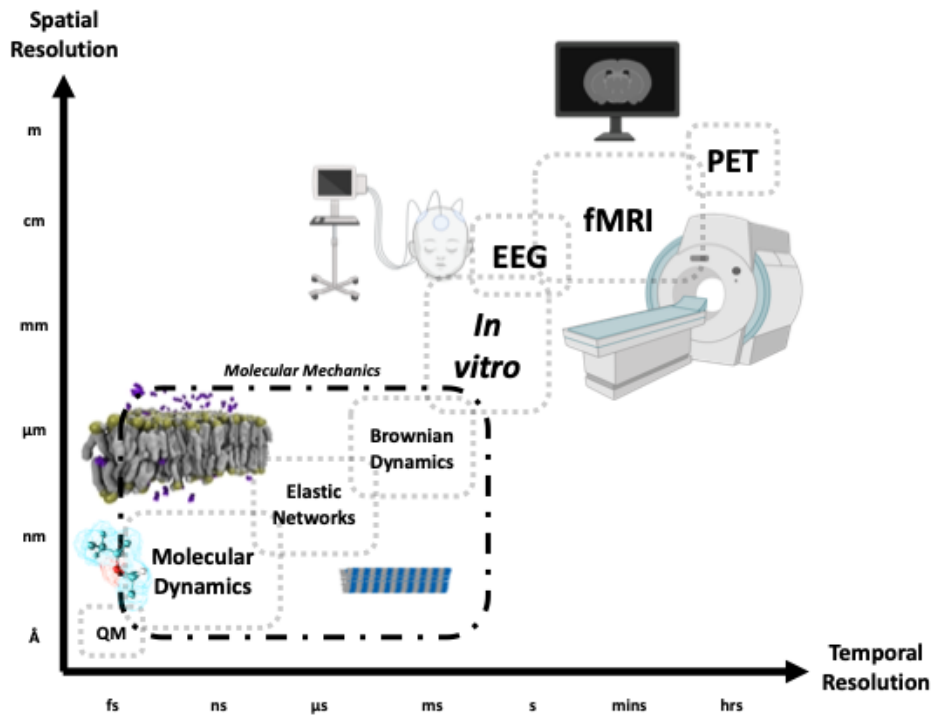
477

478 It has been also demonstrated that gamma activity correlates with activated neuronal networks,
479 but it is much less clear whether it is just a byproduct of fast-spiking GABAergic inhibitory
480 interneurons or has an important functional role. In this context, literature studies have provided
481 a metaphorical description of the synaptic neurocomputational activity as the "conscious pilot,"
482 expressed as a mobile gamma synchronized gap junctions dendritic web which prevails over
483 the otherwise non-conscious autopilot (Hameroff, 2010). Further investigations are still needed
484 to address the underlying molecular mechanism of these signals and how they modulate spiking
485 activity to comprehend the correlation between the frequencies and patterns of these rhythms
486 and any corresponding brain states.

487

488 **b) Tissue and System Level**

489 Neuroimaging enables the extension of the investigations of the brain from the cellular to the
490 system level, which allows a better understanding of how the brain network dynamics works.
491 Through advanced imaging and electrical signaling technologies, we are now able to
492 interrogate the brain for different temporal and spatial patterns: examples include positron
493 emission tomography (PET), functional magnetic resonance imaging (fMRI);
494 magnetoencephalography (MEG); electroencephalography (EEG) (see Figure 2).



495

496 *Figure 2. Diagram comparing different techniques to investigate the effect of anesthetics, from*
 497 *the all-atom molecular level (bottom left corner) towards the cellular, tissue and whole organ*
 498 *level (top right corner). The myriad of modalities employed by researchers in exploring the*
 499 *brain functionality are characterised by a specific spatial and temporal resolution. Techniques*
 500 *positioned near the bottom of the figure have a higher spatial resolution than those at the top.*
 501 *Modalities situated at the left show better temporal resolution.*

502 [18 F]-fluorodeoxyglucose positron emission tomography (FDG-PET) allow for neuronal
 503 activity quantization since it reveals the cerebral glucose uptake at the synaptic level. Early
 504 PET research indicated that both very low and high brain activity patterns are typically
 505 associated with unconscious states (Chiaravalloti *et al.*, 2019).

506

507 Blood oxygen level-dependent (BOLD)-fMRI provides a hemodynamic reflector of neuronal
 508 activity becoming a useful tool to identify structured patterns of slow neuronal oscillations in
 509 the human brain at rest (Hermes, Nguyen and Winawer, 2017). However, these neuroimaging
 510 relationship findings are far from absolute, and a specific connection between brain metabolism
 511 and awareness remains unclear. For consciousness or perception of the external world, sensory
 512 inputs (e.g., visual, auditory, etc.) enter the CNS and converge within the thalamus and are then
 513 relayed onto primary sensory cortices. From there, secondary feedforward mechanisms project
 514 to frontal, temporal, and parietal association areas of the brain before converging onto the pre-
 515 frontal 'executive' cortex. There is evidence suggesting that a third wave exists involving
 516 feedback from frontal areas to more posterior cortical regions responsible for conscious

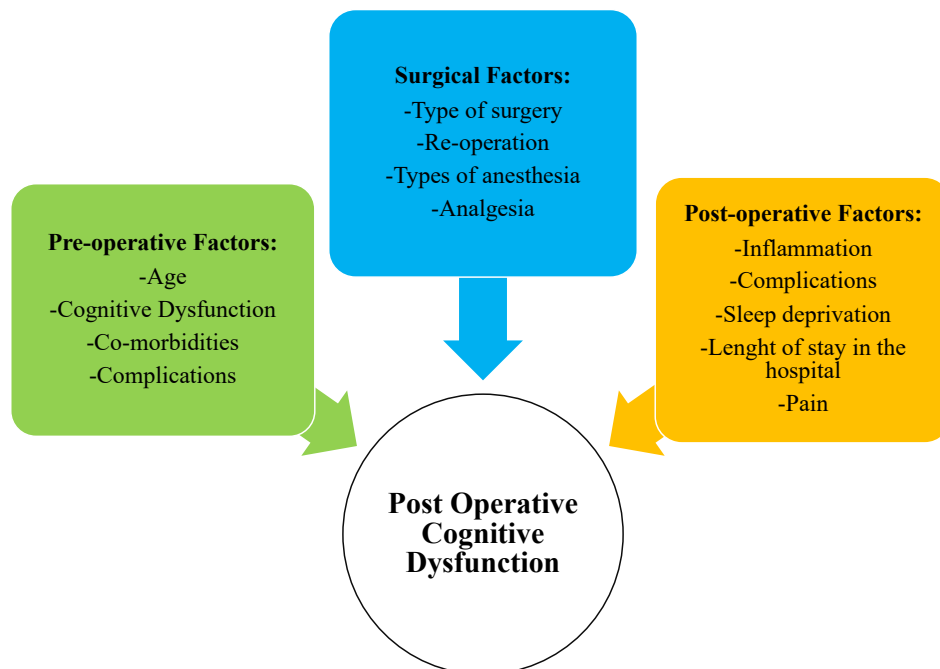
517 experience. This third wave, which represents a higher-order neuro-circuit that integrates
518 sensory information from the first two waves, is specifically sensitive to anesthesia (Craddock,
519 Priel and Tuszynski, 2014). Feedforward projections provide the sensory input about the
520 external world entering the brain/body, while feedback projections are reverberant circuits
521 letting ignition and persistent neuronal firing.
522 Cortex's areas connected by feedforward projections exhibit an equal or greater density of
523 feedback pathways connecting higher order to lower-order regions, dominant in the awake
524 state. Frontoparietal connectivity interruption due to feedback processing inhibition, has been
525 reported during general anesthesia, while feedforward connectivity may generally persist
526 (Uhrig, Dehaene and Jarraya, 2014).

527

528 **c) Bridging the scales: Consciousness as an integrated multiscale property**

529 The modulation effect on consciousness states exerted by general anesthesia has been used as
530 an extraordinary means to explore the molecular mechanisms at the root of neural information
531 processing. Indeed, a chemical compound such as an anesthetic may produce clinically
532 different states of consciousness depending on the chemical structure as well as its dose: at low
533 doses anesthetics cause depersonalization, sedation, analgesia, amnesia, and distorted time
534 perception. At meager higher doses, a patient becomes unresponsive to a verbal command and
535 is considered unconscious (Thomas, Martin and Pollard, 2020). This peculiar pharmacology
536 has manifestations which span from the molecular to the whole-organism scale: at higher
537 scales, the ability of anesthetics to modulate consciousness has been highlighted directly by
538 neuroimaging and EEG recordings during general anesthesia, providing quantitative measures
539 of changes in the brain network topology, and spatio-temporal neuronal firing dynamics.
540 Unfortunately, though, it is still impossible to describe a comprehensive and precise cascade
541 of molecular events ultimately leading to these observable phenomena. It is even more difficult
542 to precisely predict the process of recovery from anesthesia. This is crucial since at the end of
543 a surgical procedure an adequate recovery is expected, with an individual being awake again
544 and aware of its surroundings and identity (Bonhomme *et al.*, 2019). Unexpected delayed
545 awakening and failure to arouse are the most common early neurologic problems following
546 general anesthesia (Rabinstein, 2014). These complications have been reported since the early
547 1900s (Bedford, 1955). These effects are yet another aspect of the interference of general
548 anesthetics with the conscious state and are well worth investigating further. In more general
549 terms, anesthesia-related mental disorders are broadly classified into i) postoperative delirium

550 (POD) and ii) postoperative cognitive dysfunction (POCD). POD is a clinical situation,
551 sometimes occurring after general anesthesia and lasting a few hours. Patients are disoriented,
552 think, and speak incoherently, and show impairment of memory and attention, not explained
553 by a previous medical history of dementia, and an impaired ability to focus (Jellish and
554 Edelstein, 2014). POCD is defined by a range of changes in mental condition and behavior,
555 such as memory loss and inability to perform complex intellectual tasks. These impairments
556 can last for weeks or even months after general anesthesia and surgery (Pappa *et al.*, 2017),
557 with a number of possible trajectories during that time. Currently, the only univocal risk factors
558 seem to be extremes of age and extent of surgical trauma (Figure 3) (Krenk, Rasmussen and
559 Kehlet, 2010).



560

561 *Figure 3. Risk Factors for the Development of POCD. The causes of POCD are multifactorial*
562 *and may include the preoperative health conditions of the patient, periprocedural accidents*
563 *related to the surgical set up, possible neurotoxic reactions to anesthetic agents, and*
564 *environmental factors.*

565 Some concern that general anesthetics may be implicated in POCD has come from animal
566 studies utilizing long exposure to inhalational agents showing neurodegenerative changes such
567 as cell damage and apoptosis (Brambrink *et al.*, 2010). While many studies have attempted to
568 investigate POCD; however, the pathophysiology is not entirely elucidated. There is growing
569 evidence in regard the neuroinflammatory etiology of POCD.

570 It has been reported that subclinical inflammatory states activate the neuronal tissue, including
571 both microglia and astrocytes that if exposed to noxious stimuli, for example, major surgery

572 under general anesthesia, release a cascade of inflammatory cytokines and mediators, leading
573 to neuronal damage and blood-brain barrier dysfunction (Ji, Su and Yang, 2017).

574 Although some experimental findings suggest a possible correlation, the evidence available is
575 sometimes conflicting and may not be readily translated or observed in clinical practice.

576 In the aging brain the multifactorial pathogenesis of post-anesthetic cognitive dysfunction
577 might modify the phenotypic trajectory of a patient's cognitive decline with age (Avidan and
578 Evers, 2016). For instance, in patients with Alzheimer's disease has been observed an impaired
579 axonal transport (Sahni, 2016). Many neurodegenerative diseases, at molecular level display a
580 common dysfunctional neuronal cytoskeleton (e.g., Alzheimer's, Parkinson's, etc.).
581 Cytoskeletal proteins are responsible for neuron morphology and intracellular transport, and
582 the interaction of anesthetics with microtubules and their constitutive protein, tubulin, might
583 play an important role in the pathophysiology of anesthesia-induced postoperative cognitive
584 dysfunction (POCD) (Craddock *et al.*, 2017).

585 In this broad context of diverse clinical manifestations, the scientific challenge of elucidating
586 the precise mechanisms of volatile anesthetic-induced unconsciousness (or altered
587 consciousness) has been tackled both by *bottom-up* and *top-down* approaches. Bottom-up
588 investigations are pointing to the modulatory effects exerted by anesthetic gases which
589 selectively depress arousal-promoting nuclei in the brain stem and diencephalon. This can be
590 regarded as a putative action on the *level* of consciousness (Brown, Purdon and Van Dort, 2011;
591 Leung *et al.*, 2014). On the other hand, most current theories of consciousness rely on *top-*
592 *down* approaches, arguing that anesthetics suppress consciousness by modulating areas of the
593 brain involved in the subjective qualities that define individual experience. In particular
594 anesthetic gases depress brain functions in cortical and thalamocortical circuits involved in the
595 integration of neural information (Franks, 2008; Sleight, 2016). This can be seen as a putative
596 action on the *content* of consciousness.

597

598 Such a multidimensional framework for the mechanisms of anesthesia suggests the hypothesis
599 that consciousness is dual in nature, possessing both a *level* and a *content*. Simultaneous
600 alterations of both aspects, in different forms and strengths, ultimately manifest clinically in a
601 broad spectrum of outcomes, from slight euphoria to unconsciousness and POD/POCD.

602

603 **Conclusions**

604 General anesthetics are the sole class of drugs routinely used by physicians to manipulate
605 consciousness of their patients. The underlying mechanisms by which anesthetic agents control

606 wakefulness are fundamental questions in both anesthesiology and neuroscience, with links to
607 the neurobiology of consciousness itself. From quantum and molecular modelling to
608 neuroimaging-based approaches, an emerging body of evidence suggests that a complex
609 network of processes occurring at different scales (of both time and space) mediate both
610 consciousness and anesthesia in the brain. The multiscale investigative methods on neural
611 activity point to the molecular domain as fundamental in understanding the link between
612 general anesthesia and consciousness. While a conclusive integrative theory of anesthetic
613 action is still missing, the ever-increasing resolution of both experimental and computational
614 investigative techniques is progressively shedding light on important actors involved in neural
615 information processing, with conclusive evidence of anesthetic action on GABA_A and NMDA
616 receptors, as well as a plethora of theoretical and computational studies suggesting the
617 alteration of membrane properties and protein structure within cells. Also, on a higher level,
618 refined neuroimaging investigations are unveiling the neural connections and topology
619 underlying conscious brain activity, and how anesthetics disturb the integration of information
620 in neuronal circuits during anesthesia. The starting point for understanding the complex
621 phenomenon of anesthesia might reside in acknowledging its multi-scale nature, where actions
622 at the molecular, and possibly even quantum level progressively integrate and unfold at
623 increasingly higher scales, disrupting the complex information exchange network within the
624 brain. It is clear that understanding the effects of general anesthetics on consciousness will help
625 science take a further step towards uncovering one of the greatest mysteries in nature.

626

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