The historical role anaesthesia has played in discovering the nature of consciousness

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1/1/2013

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Introduction

The ability to explain conscious perception remains one of the great unsolved mysteries of the twenty first century. It is a fundamental resource every human being takes for granted, which few have questioned and none have fully answered. The subjective experience of the "redness of a rose" or the "smell of fresh coffee" are concepts we can all relate to but find difficult to explain in terms of neural activity. An answer to this enigma has attracted suitors from philosophy, neuroscience, physics and mathematics which have advanced our understanding, but it appears that us anaesthetists have the crucial keys to unlock the secret truth [1]. Anaesthesia not only provides a tool for controlling and therefore investigating consciousness, but also gives insight to the neural correlates of consciousness through exploration of its mechanism and site of action. History is abundant with daring individuals who have explored how anaesthesia breeches this elusive conscious boundary, and pioneers attempting to discover the core of consciousness itself. The following is an attempt to retrace our historical struggles to understand consciousness and to highlight the unsung role which anaesthesia has played in this pursuit.

The Question

"All glory comes from daring to begin" – Eugene Ware, poet

Our unfinished journey to discovering the very nature of consciousness begins in 17th century France during the Age of Enlightenment where the mathematician and father of modern philosophy Rene Descartes explored the human mind. According to Descartes, the conscious mind was of existential importance and proclaimed his famous quote "Cogito, ergo sum" (I think therefore I am) to argue that only through personal consciousness can you be certain of your actual existence. Descartes also made tentative steps in understanding consciousness by introducing the idea of *dualism* in his treatise "Meditations on First Philosophy" [2] in 1641. Cartesian dualism reasons that the mind is a distinct non-physical and independent entity which interacts with the physical body (via the pineal gland!) to make up the person.

Although most scientists now do not accept dualism, believing that thought and consciousness will eventually be explained through physical processes within the brain alone, Descartes' contribution is still significant since it provided the original platform from which knowledge and ideas grew.

In the aftermath of Descartes' mind-body declaration, two opposing theories on conscious experience slowly emerged either side of a religious partition. In one camp, the 18th century Irish bishop George Berkeley promoted *immaterialism* and proposed that conscious perception of material objects was nothing more than images within the mind and that these ultimately depend on the mind of God [3]. Diametrically opposed to this concept were the *materialists* who attempted to explain the mind in purely material terms, showing that the brain was solely responsible for thought and conscious perception [4].

A champion of materialism and perhaps the first doctor to seriously tackle the problem of consciousness was the 18th century French libertine Julien Offray de la Mettrie. Like many controversial thinkers who went against popular opinion at the time, he was forced into exile and ostracised by the medical and ecclesiastical institutions, only for the full importance of his work to be recognised after death. Influenced by his experience as a physician in the War of Austrian Succession in 1743 and his own transient delirium due to illness, Julien concluded that consciousness can be explained entirely by physical processes [5]. He argued that complex biological mechanisms can give rise to conscious perception without the need for divine intervention or an immortal soul, a belief shared by many twenty first century reductionists working on the same problem.

Philosophical scepticism

"The path of sound credence is through the thick forest of scepticism" – George Jean Nathan, essayist

During the18th century, the study of consciousness was restricted to philosophical ideas and thought experiments since neuroscientific research was in its infancy, and anaesthetic agents were not yet discovered. The absence of a clear framework to investigate consciousness fostered a wave of early scepticism to its validity, epitomised by Immanuel Kants now-called

impossibility claim [6]. The famous German lecturer and philosopher argued that private mental phenomena will never be amenable to mathematical modelling thus robust analysis, rendering them impossible for science to explain. His influential ideas were far reaching and still resonated with the behaviourist movement in the early 20th century. Behaviourists reject the direct study of internal mental states and instead believe that the mind should be reduced to and objectively examined solely via observed behaviours [7] (Pavlovs' dogs).

Fortunately a few defiant scientists swam against the tide and started to slowly piece together the fundamental components of our nervous system, crucial to current consciousness research. In 1891, the German anatomist Wilhelm Waldeyer proposed the neuron doctrine [8] which identified the nerve cell as the functional unit of the nervous system. The concept of nerve impulses and their electrical basis was also eloquently demonstrated by Du Bois-Reymond in 1843 using amphibian nerves [9]. A more global appreciation of the brain came from Broca [10] and Wernicke [11] who in the late nineteenth century identified discrete brain regions necessary for speech which bear their names to this day. The physician and physicist Hermann von Helmholtz embraced these principles to produce his revolutionary theory of conscious perception which has startling similarities to current cutting edge ideas. Von Helmholtz believed that sensory input provided signs of reality which importantly needed to be integrated by higher brain regions to allow conscious perception [12]. Interestingly, a lack of cortical integrative power of sensory information is a current competing theory attempting to explain the mechanism of anaesthesia and altered states of consciousness[13].

Early experimentation

"If you don't risk anything you risk even more" – Erica Jong, author

Whilst neurobiological academia was flourishing in nineteenth century Germany, the 18 year old entertainer Samuel Colt who would later on invent the first revolver was touring the United States with his laughing gas show [14]. It is fascinating to observe that branches from these two very different origins are now converging in an attempt to explain the difficult problem of conscious perception.

The laughing gas experience offered by Samuel Colt came courtesy of nitrous oxide, which was first isolated by Joseph Priestley in 1772 by exposing nitrous air to iron and brimstone [15]. Its powerful effect on consciousness however was only fully appreciated twenty seven years later by the young and adventurous Cornish chemist Humphrey Davy. Through inhaling nitrous oxide in various formats, some of which would have left him hypoxic and exposed to carbon monoxide [15], he recorded the first example that modern anaesthetic agents provide access to different levels of consciousness [16].

> "I lost all connection with external things; trains of vivid visible images rapidly passed through my mind and even connected with words in such a manner, as to produce perceptions perfectly novel. I existed in a world of newly connected and newly modified ideas." Humphry Davy 1799[16]

Although Sir Davy didn't fully realise the future potential of similar agents in investigating consciousness itself, he did remark that knowledge could be gained from analysing his altered state.

> "As I recovered my former state of mind, I felt an inclination to communicate the discoveries I had made during the experiment." Humphry Davy 1799[16]

In these early days, Davy was the subject, observer and analyst of his anaesthetic induced altered mental state with no robust mental measuring tools, which makes his contribution even more remarkable. A historical lack of such tools has impeded attempts to scientifically explain consciousness since early evidence was limited to poetic and philosophical descriptions, (just like Kant foresaw in his impossibility claim). Mathematical "information theory", introduced by Shannon [17] and Hartley [18] in the early twentieth century however found a neat way around this tricky obstacle. Through researching the telegraph and signals through noisy channels during World War II, a mathematical tool to quantify the amount of

information in different signals was developed. By viewing the brain as an information processing unit [19] and information as nerve impulses, this new theory allowed mental processes to be physically quantified and researched. Current brain function monitors such as the bispectral index and auditory evoked potentials owe much of their development to this paradigm shift.

Anaesthetic window of opportunity

"One doesn't discover new lands without consenting to lose sight of the shore for a very long time" – Andre Gide, novelist

Anaesthetic agents entered the fray in the mid nineteenth century and have fascinated the public, scientific community and poets alike due to their unique influence on consciousness. The very term "anaesthetic" pays tribute to this powerful effect, originating from the Greek word "anaisthesis" meaning insensibility. Coined by the poet and physician Oliver Holmes [20] in 1846 after witnessing ethers impressive control of consciousness during William Mortons famous first public demonstration in Boston, it is something all anaesthetists can relate to.

Anaesthetists are also familiar with the twilight period between the conscious and unconscious state as the anaesthetic begins to work (or wear off). Many scientists believe that this twilight period provides the perfect window to look for clues to explain just exactly what consciousness is.

The young New Yorker, Benjamin Blood in 1860 became obsessed with this "window" and devoted 14 years of experimentation on himself and his colleagues before publishing "The anaesthetic revelation". In his publication, Blood boldly claimed that on recovering from anaesthesia, the "genius of being" is revealed [21] and he spent the rest of his life trying to find it. Benjamin Blood left us a challenge to understand what happens during this twilight period which may ultimately help us explain consciousness, and we are creeping towards an answer.

Arthur Guedel, famous for later developing the oropharyngeal airway was one such anaesthetist who observed how patients behaved when in this halfway house. Like many advances in anaesthesia, Guedel was not driven by trying to find the "genius of being" or the "nature of consciousness", but instead wanted to improve its' practical application and

wartime safety. As a driven young anaesthetist who had originally left school at the age of 13 and lost the first three fingers of his dominant hand in an accident, he was used to overcoming adversity [22]. Whilst serving for the American forces in World War I, he was given the responsibility of overseeing the heavily understaffed anaesthetic services for the US Army in Vosges, France. Due to a shortage of doctors, ether anaesthesia was frequently delivered by non-professionals forcing Guedel to commute between hospitals via motorcycle to provide supervision and support. To improve safety and help map out the clinical landscape between the awake, anaesthetised and dead state, Guedel devised and later published his famous "Signs and Stages of Ether Anaesthesia" [23] which every anaesthetic trainee to this day learns. His stages of anaesthesia are based on the observed respiratory pattern, muscle tone, pupil activity, and eye lid reflexes as the patient becomes unconscious and accurately correlates with modern BIS indices [24] and ether MAC values [25].

Loss of consciousness defined as an inability to respond to verbal commands is believed to occur at the stage I/II interface and there are marked pupillary changes, cranial nerve reflex and respiratory activity during this transition point [23]. These clinical signs give clues to the underlying neural processes which may influence consciousness, but to get a more detailed understanding, doctors started to investigate how exactly anaesthetics exerted their effects.

Correlation with mechanism of anaesthesia ?

Since various anaesthetic agents reliably guide us past the conscious boundary, it seems intuitive that research into their mechanism of action can help us understand what forms consciousness in the first place. However, caution needs to be observed since this line of enquiry can sometimes confuse causation with harmless association. Different interpretations as to what "consciousness" means can also muddy the waters, but nevertheless, anaesthetic agents and their mechanism of action represents a powerful and unique research edge.

The historical efforts in exploring how anaesthetics work were ingenious and initially driven by curiosity as opposed to an "understanding consciousness" agenda. At the start of the twentieth century Hans Meyer and Charles Overton independently published findings which correlated the solubility of anaesthetic agents in olive oil with their effects on the swimming ability of tadpoles! The Meyer –Overton hypothesis was born and argued that anaesthesia

occurs when a critical number of anaesthetic molecules are integrated with the neuronal lipid cell membrane [26]. Several lipid based theories of anaesthesia evolved from this startling correlation including potential cell membrane volume expansion, increased fluidity and lateral surface pressure disrupting normal neuronal cell functioning and consciousness [27, 28]. Despite being only based upon tadpole behaviour and olive oil solubility, the lipid based hypothesis became the dogma and dominated popular opinion for nearly a century. It unfortunately gave very little insight into the specific neural correlates or mechanisms of consciousness other than the prerequisite of functioning neurons with their lipid membranes unspoiled.

However, just as the swimming prowess of tadpoles helped launch the lipid theory, it was the luminescence of the firefly which so elegantly shattered it. The enzyme luciferase is integral to the generation of firefly light and after purifying the enzyme completely from lipids, Franks and Lieb in the early 1980s showed beautifully that the intensity of the flash generated in the presence of various anaesthetic agents was impaired according to anaesthetic potency [29]. They literally saw the light and realised that anaesthetics can interact with proteins directly which unleashed the global hunt for potential receptor targets.

With such a tantalising prize at stake, the hunt became frantic with some labs suggesting that potentiation of proteins involved with neuronal membrane inhibition such as potassium channels, or GABA and glycine receptors could finally explain anaesthesia. Alternatively, others proposed that the suppression of proteins contributing to excitatory neuronal phenomena such as voltage gated sodium channels, NMDA and glutamate receptors were more relevant. As growing amounts of evidence poured in regarding potential anaesthetic binding sites, the more complex the molecular world became. The existence of a universal single site to explain where general anaesthetics worked became a distant dream and in its wake, the “multiple target hypothesis” gathered pace [30].

Entangled mysteries of anaesthesia and consciousness

"There is no scientific study more vital to man than the study of his own brain. Our entire view of the universe depends on it." – Sir Francis Crick, Nobel laureate.

As the anaesthesia and consciousness dance became increasingly complex on the molecular level, certain neuroscientists and anaesthetists started to focus on the global picture instead. One such scientist was the renowned and charismatic Sir Francis Crick. Famous for his co-discovery of DNA and subsequent Nobel Prize receipt, less is known about his passion for neuroscience and consciousness research. In fact, during his later years, Dr Crick devoted his time in California entirely to investigating this problem, even editing a manuscript on the potential role of the claustrum on conscious sensation the day he died [31]. His "Astonishing Hypothesis" in the early 1990s suggested that sentience could be reduced to neural mechanisms associated with attention and short term memory which needed reverbratory circuits particularly between the thalamus and cortex [32].

Dr Crick also acknowledged the intriguing "cognitive binding problem" [33] which questions how the brain manages to combine visual, tactile, affective and cognitive inputs to create a "unity of experience". For instance, the *experience* of "running" comes in one package, not as separate and independent feelings of changing light, wind, temperature, touch or proprioception. Somehow the brain integrates all of this information and remarkably generates a single conscious percept, but how?

Like many discoveries, one leading hypothesis to explain this binding problem was stumbled upon by accident. In a 1980s German lab whilst analysing EEG activity in kittens, Gray and Singer [34] noticed that *separate* neuronal aggregates engaged in *synchronous* oscillatory (gamma) activity when activated by visual stimuli. This paved the way for research which hinted that different parts of the brain (inputs) could be linked by synchronous neuronal activity: "Binding by Synchrony".

The currently active Harvard academic anaesthetist George Mashour compares this binding hypothesis to an orchestra where the conductor (brain) directs the individual musicians

(sensory inputs), in synchrony (gamma oscillations) to produce a piece of coherent music (unity of consciousness) as opposed to meaningless noise [35].

During the last twenty years there have been other competing theories of conscious perception and the leading ones have involved some form of higher communication and information processing [36] particularly involving the cortex and thalamus. The beauty of general anaesthetic agents is that they now provide the perfect research tool to support or refute these theories and the answers also provide clues to how anaesthetics work.

The entanglement between anaesthesia and consciousness is now exploited and its fruitful application in research is a testament to how far we have got. For example, in the same city where Benjamin Blood recklessly used ether in vain to find "the genius of being " in the 1860s , Dr Johns' lab recently showed that both volatile and intravenous anaesthetic agents reduced cortical oscillatory synchrony upon anaesthetic induction supporting the binding theory of consciousness and also suggesting the "unbinding theory "of anaesthesia [37]. Since the various anaesthetic agents with known different mechanisms had the same disruptive "desynchronising" effect, the results also lend themselves nicely to an ultimately final common anaesthetic mechanism.

The second power of anaesthesia

Difficult problems often require collaborations between numerous sources to solve and this problem is no exception. The historical path in understanding consciousness and anaesthesia is often not a well acknowledged one but represents an unfinished multi-faceted battle against adversity, scepticism and ridicule. Cartesian dualism started our journey, which has since weaved through philosophical scepticism and religious resistance through the help of the materialists and early neuroscientists. Due to the magnitude of the question, tools from mathematics, physics and physiology have been needed along the way. Arguably though, it is the Davys and Bloods of this world who bravely risked their health to try and understand the curious dance between anaesthesia and consciousness who deserve special credit for furthering the cause and keeping the question in the public and scientific minds. The meticulous observations of Guedel during the Great War, and experiments on tadpoles and

fireflies alongside accidental stumbles have now edged us tantalisingly close to a reputable answer.

I wish to conclude with a reflection on the address which the grandfather of anaesthetic research, Professor Henry Beecher gave to a crowd in 1946 during the centennial celebration of Mortons ether demonstration [16].

Anaesthesia's second power.

"With anaesthetic agents we seem to have a tool for producing and holding at will, and at little risk, different levels of consciousness, a tool that promises to be of great help in studies of mental phenomena. . . . The potentialities for future discoveries in this field seem scarcely to have been tapped." Henry Beecher 1946

This was highly prescient and we have never been in a better position to use anaesthesia to attack the most fundamental question of all: "What makes us conscious?" Beecher predicted but didn't live to fully witness this evolution of anaesthesia from a crude adjunct to surgery, to a sophisticated research tool half a century later. However, he would have been proud of the future benefits which application of his thinking will bring. Cleaner drugs, reduced "awareness", improved monitoring and comprehension of brain injured states and a deeper understanding of ourselves are to name but a few.

The psychologist Steven Pinker goes even further, taking the audacious step of predicting that through discovering the biology of consciousness, we may even help bridge science and morality [38]. In proving and acknowledging that all humans are made from the same nerves with the same biological capacity to "feel" and "suffer" to such a fundamental and profound level, we will be compelled to recognize and respect the interests of one another - the essence of morality.

References

1. Mashour G. Integrating the Science of Consciousness and Anaesthesia. *AnesthAnalg 2006;***103:** (4) p 975-82

2. Rene Descartes. Meditations on First Philosophy.(Translation by John Cottingham).Cambridge University Press, 1996. ISBN 0521558182

3. Matthews E. Berkeley: The Philosophy of Immaterialism. *Analytical Philosophy* 1974; **15**(2) p 26-8

4. Churchland P. Matter and Consciousness (Revised Edition): MIT Press, 1999, ISBN: 0-262-03135-3

5. Smith C. JulienOffray de la Mettrie (1709-1751). *Journal of the History of the Neurosciences: Basic and Clinical Perspectives* 2000; **11**(2) p110-124

6. Nayak A et al. Kant on the Impossibility of the "Soft Sciences".*Philosophy and Phenomenological Research* 1995; **55** (1) p133-151.

7. Watrin J et al. On behaviourism in the cognitive revolution: Myth and reactions. *Review of General Psychology* 2012; **16** (3) p269-82

8. Jones E. The neuron doctrine 1891.*J HistNeurosci* 1994; **3** (1) p3-20

9. Finkelstein G. M.du Bois-Reymond goes to Paris.*Br J HistSci*2003;**36**(3) p261-300

10. Lazar R et al. Revisiting the contributions of Paul Broca to the study of aphasia.*Neuropsychol Rev* 2011; **21**(3) p236-9

11. Ardila A. A Review of Conduction Aphasia.*CurrNeurolNeurosci Rep* 2010; **10** p 499-503

12. Turner R. Hermann von Helmholtz and the empiricist vision. *J HistBehavSci* 1977; **13**(1) p48-58

13. Baars et al. Brain, conscious experience and the observing self. *Trends Neurosci* 2003; **26**(12) p671-5

14. Smith W. A history of nitrous oxide and oxygen anaesthesia part II: Davy's researchers in relation to inhalation anaesthesia. *Br J Anaesth* 1965; **37**(11) p871-82

15. Smith W. A history of nitrous oxide and oxygen anaesthesia part I: Joseph Priestley to Humphry Davy. *Br J Anaesth* 1965; **65**(10)p790-8.

16. Beecher H. Anaesthesia's second power: Probing the mind. *Science*1947; **105**(2720) p164-6

17. Shannon C. Communication in the presence of noise. *Proc. Institute of Radio Engineers* **37**(1) p10-21

18. Hartley R. Transmission of Information. *Bell Systems Technical Journal* 1928; **7**(3) p535-563

19. McCulloch et al. A logical calculus of the ideas immanent in nervous activity.*Bulletin of Mathematical Biophysics* 1943; **5** p115-133

20. Keys T. Oliver Wendell Holmes (1809-1894). *AnesthAnalg* 1973; **52**(1): p141

21. James W. Review of "The Anaesthetic Revelation and the Gist of Philosophy"*Atlantic Monthly* 1874;**33**(205) p 627-8

22. Calmes S. American Society of Anaesthesiologists Newsletter2002;**6**(9) p17-19

23. Guedel A. Third-stage ether anesthesia: A sub-classification regarding the significance of the position and movements of the eyeball. *Am J Surg* 1920;**34**(suppl) p53-7

24. Bhargava A. Correlation of Bispectral Index and Guedel's Stages of Ether Anesthesia. *AnesthAnalg* 2004; **98**(1) p132-4

25. Cullen D et al. Clinical signs of anaesthesia. *Anesthesiology* 1972; **36**(1) p21-36

26. Meyer K. Contributions to the theory of narcosis. *Trans Faraday Soc* 1937; **33** p1062-8

27. Mori T. Membrane expansion and inhalation anesthetics. Mean excess volume hypothesis. *MolPharmacol*1984; **25**(1) p123-30

28. Cantor R. The lateral pressure profile in membranes: a physical mechanism of general anesthesia. *Biochemistry* 1997; **36**(9) p2339-44

29. Franks N et al. Do general anaesthetics act by competitive binding to specific receptors? *Nature* 1984; **310** p599-601

30. Lugli A et al. Anaesthetic mechanisms: update on the challenge of unravelling the mystery of anaesthesia. *Eur J Anaesthesiol* 2009; **26**(10) p 807-820

31. Crick F et al. What is the function of the claustrum? *Philos Trans R SocLond B BiolSci* 2005; **360** (1458) p1271-1279

32. Crick F. The Astonishing Hypothesis: The Scientific Search for the Soul. New York. Charles Scribner's Sons p1-317. ISBN: 0684801582

33. Von der Marlsberg C. The Correlation Theory of Brain Function. Internal Report 81-2, Dept of Neurobiology, Max-Planck-Institute for Biophysical Chemistry

34. Gray C et al. Stimulus-specific neuronal oscillations in orientation columns of cat visual cortex. *ProcNatlAcadSci U S A* 1989;**86**(5): 1698-702

35. Mashour G. Consciousness unbound: toward a paradigm of general anaesthesia. *Anaesthesiology* 2004;**100**(2) p428-33

36. Flohr H. An information processing theory of anaesthesia.*Neuropsychologia*1995 **33**(9) p1169-80

37. John E. The neurophysics of consciousness.*Brain Res Brain Res Rev* 2002; **39**(1) p1-28

38. Pinker S. The Mystery of Consciousness.Time Magazine. 2007; January 29.