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Essay review

A rush of blood to the head: The beginnings of brain imaging

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(Christiane Nockels Fabbri, Trans.), Angelo Mosso's Circulation in the Human Brain, Marcus Raichle and Gordon Shepherd Yale University Press, New Haven (2014). pp. 240 Price $45.00 hardback, ISBN: 9780199358984

A central goal of modern neuroscience is to understand how the brain gives rise to behavior. Advances in neuroscience in the past decade amid great public interest have made this goal closer to being accomplished than ever before. Much less appreciated is the fact that just over a century ago, even the idea that emotions arose from activity in the brain was relatively controversial. The spectre of Cartesian Dualism dominated any discourse on brain and mind (Robinson, 2012). Today, we remember physiologists such as Charles Sherrington and psychologists such as William James as pioneers in the movement away from dualism. The Italian physician Angelo Mosso (1846–1910) is less widely known, despite his relative fame in his own era. This is partly because many of his works have remained untranslated from Italian and German. This new translation of his book *Circulation of blood in the human brain* aims to change this oversight and bring Mosso to the notice of the wider scientific community. Mosso's work has been of interest to researchers studying the brain using various imaging techniques and to those studying cerebral blood flow, but readers of this volume will find that Mosso's writings provide deep general insights into how neuroscience ought to be done. It is a veritable manual on the use of the scientific method and the importance of quantitative techniques.

Several of Mosso's manuscripts have been translated in recent years, without much context or description of the author's life and times. This book aims to change that with a substantial biography of Angelo Mosso followed by an excellent commentary by renowned neuroscientists Marcus Raichle and Gordon Shepherd, who were involved in the translation as well, situating Mosso's contributions within a wider scientific narrative and historical timeline. Raichle and Shepherd provide an excellent foreword with insights into the history of brain imaging and the specific aspects of Mosso's work that make him a pioneer in the field. Several anecdotes discussed in the foreword highlight the special challenges faced by scientists of the past, contrasting them with the advantages of today's technological improvements. From this point in the book, Mosso's manuscript, translated from the original primarily by historian of medicine Christiane Nockels Fabbri, takes over and presents a surprisingly large number of experiments covering several areas of research including studies on cerebral blood flow and it's relation to emotions and sleep. *Circulation of blood* also presents data on blood flow in other organs and includes extensive descriptions of the instrumentation Mosso used. But what strikes one especially is the breadth and depth of ideas in this short manuscript. Some of these are as relevant today as they were a century ago.

The concepts presented in this book seem even more revolutionary and cutting edge given the prevalent philosophical views of the era. By relating changes in cerebral blood flow to changes in emotional and conscious states, Angelo Mosso was trying to prove the hypothesis that mind arose from brain. No wonder, then, that one of his great supporters was William James, who himself espoused this view. In fact, Mosso lived in an era of change for the science of mind, not unlike the past decade, when advances in physiology were coalescing with new ideas in psychology, giving rise to the first mechanistic insights into brain and mind. He was a disciple of such figures as Claude Bernard, who steadfastly defended the use of experimentation in medical science. Bernard's theories of homeostasis (a word coined by Walter Cannon much later (Cannon, 1932)), were essential to the conceptual framework that Mosso and other physiologists used in their experiments.

One of the striking facts highlighted by this book is not how much has changed, but rather, how little has. I mean this more as a compliment to Mosso than as an indictment of current research in neuroscience. However, it is humbling to find that some of the same experimental and conceptual issues that Mosso and his contemporaries grappled with in the 19th century, plague us even today. These issues deal primarily with the sensitivity and resolution of instrumentation to detect and quantify changes in neural activity in

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humans. Indeed, the “new” neuroscience has made more advances in the detection and manipulation of neural activity in non-human experimental systems than it has in humans – a theme I will return to several times in this review with specific examples. To be fair, it probably has a lot to do with the inherent ethical limitations of invasive research in humans. In fact, Raichle and Shepherd commiserate with Mosso’s own challenges in dealing with the institutional review board of his time towards the end of their excellent foreword. The reader will find in this foreword a thorough overview of the history of brain imaging as well as an excellent description of the life and times of Angelo Mosso.

Mosso started with a thorough review and critique of past studies of circulation and blood flow in the brain. He outlined the long history of research on brain circulation tracing the problem’s history to Greco-Roman antiquity including the often-cited passage from Pliny the elder (or Plinius) about the strong pulsations on the forehead of the infant Zoroaster –

> “*enough to lift a hand placed on it*”. (p.7)

No historical overview is of course complete without reference to Galen, whose prescience was perhaps as striking and humbling to Mosso as Mosso’s is to us. The assuredness of Mosso’s prose in this exercise reflects to some extent his confidence in his own abilities and intellect, as well as a disdain for the salesmanship of some of the more famous scientists of the time. One can’t help but speculate that some of this criticism arose form a kind of nationalism and a concerted effort to highlight the existence of good science outside the dominant European schools in Germany, France and England. In a scathing paragraph, Mosso rebuked Francois Magendie thus –

> “… he speaks of the cerebrospinal fluid as his own discovery and does not hesitate, in spite of Cotugno’s research, to designate the aforementioned fluid as a newly recognized element of our organism. His dislike of historic-literary investigations, to which he somewhat cavalierly admitted on this occasion, hardly excuses this disregard for foreign achievements.”(p. 15)

This pet peeve is as prevalent among scientists today as it was then! Mosso made a real effort to highlight the work of Antonio Ravina, another fellow Italian who was the first physiologist to use sophisticated equipment to measure blood flow changes in the brain. Ravina used several instruments to record cerebral pulsations, an approach that Mosso himself favored. In fact, Mosso’s review mostly asserts the theory that the conceptual mistakes of other authors stemmed from a lack of proper recording techniques and proper experimental controls. This position provided a perfect platform for him to segue into the next two chapters, which describe his subjects and apparatus in great detail.

Case studies of individuals with unique injuries have played a vital role throughout the history of the neural sciences. Every student of neuroscience is well aware of Patient H.M. and Phineas Gage. HM or Henry Gustav Molaison received a temporal lobectomy in 1953 for epilepsy and became the totemic test subject for studies on retrograde amnesia. Careful psychological testing by Brenda Milner and others over a span of almost 50 years led to the discoveries that form the basis of all work on the neural mechanisms of memory formation in mammals (Scoville & Milner, 1957; Squire & Wixted, 2011). Similarly, the injuries of Phineas Gage, a railroad worker who survived being impaled by a metal bar through the forehead in 1848, provided clues into the role of the frontal cortex in the executive control of behavior (Damasio, Grabowski, Frank, Galaburda, & Damasio, 1994). One cannot emphasize enough the great service of such test subjects to the cause of neuroscience research. The success of Mosso’s experiments on cerebral pulsations required subjects with brain injuries that left part of the skull damaged and the brain exposed but largely intact. Mosso’s connections at hospitals in Turin made it possible for him to find three subjects suited to his needs. Of these three, Mosso got the most recordings from M. Bertino, who can perhaps now be considered the H.M. of cerebral blood flow and fMRI. Indeed, the manuscript gives an insight into the personality of Bertino and perhaps even some clues into the behavioral effects of the injury he suffered. The interested reader familiar with psychological testing might enjoy speculating if some of the suspiciousness and behavioral affectations in Bertino were related to his injuries.

It seems appropriate at this point to cite a quote attributed to the molecular biologist Sydney Brenner- “Progress in science depends on new techniques, new discoveries and new ideas, probably in that order,” (Robertson, 1980). I have a hunch that Mosso would have wholeheartedly agreed with this assertion. His training in Paris and his admiration for figures such as Ravina probably cemented his belief that new tools were necessary to achieve the precision needed to understand blood flow in the brain in a controlled way. Also worth mentioning is the fact that Mosso relied on several independent devices to make his observations, including interesting modifications unique to his experimental preparations. A good example is the Marey Tambour Explorateur, a simple device widely used at the time to measure and record small changes in pressure on membranous organs, such as skin. Its inventor, Jules-Etienne Marey, was a good friend of both Mosso and Claude Bernard, no doubt influenced Mosso’s own creative inventions. The device consisted of a knob sensitive to small perturbations on the surface it contacted, which then connected to a lever that recorded events on a cylindrical kymograph. After making his first recordings using the explorateur, Mosso found that that the equipment had severe shortcomings, especially in awake subjects who could scarcely be expected to remain still. Mosso proceeded to make modifications deciding to use a warmed gutta percha membrane molded to the surface of the exposed brain surface. This setup was then ingeniously coupled to Mullerian valves connected in series, essentially allowing for small changes in pressure (pp. 45–47). This whole apparatus was ideal for the reliable long-term recording of brain pulsations.

These issues of stability and duration in recording from live subjects are critical factors even today. At one point, the book mentions how this kind of recording would have been difficult in animals where cranial trephination (drilling a hole in the skull) would have inevitably led to inflammation in such a way that the brain would extrude through the opening and lose all pulsations quite rapidly (p. 44). More than a century later, neuroscientists Wen-Biao Gan and Karel Svoboda faced exactly the same kind of challenge, when their laboratories were in a race to use *in vivo* imaging to examine dendritic spine dynamics in a living, behaving mouse (Grutzendler, Kasthuri, & Gan, 2002; Lendvai, Stern, Chen, & Svoboda, 2000). Dendritic spines are the points on a neuron where it makes synaptic connections with other neurons. These units of synaptic communication were hypothesized to change when an animal learned new information, thus providing a correlate of memory storage in the brain (Bailey & Kandel, 1993). Until Gan and Svoboda performed their experiments, it was only possible to examine these changes post mortem, which provided but a weak correlation with actual behavior. The ability to follow the dynamics of spine changes in the same mouse over days would be a huge leap for neuroscience. However, the two groups ran into challenges

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similar to the ones Mosso and his compatriots faced. Svoboda's lab used a technique that involved using a glass coverslip over a hole drilled in the skull to make a cranial window, through which spine dynamics could be observed using a two-photon fluorescence microscope (Lendvai et al., 2000). Gan's group, however, realized that drilling a hole to install a glass coverslip led to inflammation similar to Mosso's description, which changed the dynamics of the endogenous spine changes (Yang, Pan, Parkhurst, Grutzendler, & Gan, 2010). This group decided to use a very delicate, thinned skull preparation, making the skull thin enough for the microscope to capture images and thus avoiding the inflammation associated with trephination-induced damage (Grutzendler et al., 2002). Both these methods have been used widely to directly measure activity related spine dynamics with great precision, although their use is still limited to use in animal model systems.

The gold standard in non-invasive brain activity detection today is functional magnetic resonance imaging (fMRI), which is based on relative local changes in brain blood oxygenation levels or the BOLD (Blood oxygenation level dependent) signal. This is a direct correlate of changes in cerebral blood volume and metabolism, which, in turn, are correlates of changes in neural activity patterns. Mosso's techniques are direct forerunners of this method and indeed, Mosso is most widely remembered today by researchers using fMRI. In fact, recently translated two of Mosso's manuscripts from 1882 and 1884 have brought to light experiments that he conducted with an apparatus he called 'the human circulation balance' (Sandrone et al., 2014). This device was probably invented soon after the publication of *Circulation of Blood in the Human Brain*. It took advantage of the findings reported in this book, on the changes in blood flow in the brain relative to changes in blood pressure in the rest of the body. Mosso realized from his careful recordings of the cranial pulse during emotional effort as well as during other activities that the pulsations and blood pressure in the brain were quite different from those occurring in the arm or the legs. He made sure he performed controlled experiments where hydrosphysmograph – an instrument relying on changes in blood pressure which displaces water placed in a tube encasing the arm or leg – were used to measure blood pressure in the arms and legs at the same time as the brain. This kind of controlled experiment made it clear that an increase in the weight of the body near the head during states of mental activity could be taken as a rough estimate of brain activity. Indeed, modern reenactments of those studies performed by Field and Inman have confirmed Mosso's conclusions as largely correct (Field & Inman, 2014)! Interestingly, the validity of fMRI signals as direct correlates of real neuronal activity patterns have remained controversial (Logothetis, Pauls, Augath, Trinath, & Oeltermann, 2001). Recent studies using the cutting edge tools of optogenetics (a technique that uses the artificial expression of an algal light gated channel to drive action potentials in neurons using laser stimulation *in vivo*) have provided the best evidence that the BOLD signal correlates very specifically with changes in activity patterns of neurons (Lee et al., 2010). However, some researchers in this field have come under attack for incorrect statistical analyses leading to widely exaggerated claims correlating specific brain regions to changes in emotional states (Vul, Harris, Winkielman, & Pashler, 2009).

Mosso's obsession with proper controls and quantitative methods is of great value as a lesson to young researchers today. This obsession led him to make extensive recordings of brain pulsations during the resting state of his subjects, including during sleep. Mosso's shrewd insights into resting state brain activity during his initial observations are especially fascinating. In a prescient piece of writing, Mosso encapsulates this concept in a paragraph at the beginning of chapter 4:

> Since the brain belongs to the organs removed from direct voluntary control … the changes that its blood flow can undergo in the waking state are contingent much more upon fluctuations in the vigorousness of the mental activity than on a true transition of the psychic centers from a state of absolute rest to one of full activity (p.63).

This is not a trivial technicality. In fact, the importance of resting state activity in the brain has only recently come to the fore, owing to the efforts of Dr. Marcus Raichle among others (Raichle, 2015). Moreover, the tracings are strikingly reminiscent of brain oscillations that have been implicated as substrates of cognitive binding and memory retrieval. Changes in the strength of oscillations in the range of 60–90 Hz (Gamma) and 4.5–8.5 Hz (Theta) are strongly correlated with volitional activity in the brain (Buzsaki & Moser, 2013; Osipova et al., 2006). Co-modulation of these has been implicated in successful memory retrieval, and manipulations that disrupt these changes usually result in cognitive impairment (Shirvalkar, Rapp, & Shapiro, 2010). These oscillations appear very strongly correlated with specific neuronal activity patterns and thus with fluctuations of cerebral blood flow. Indeed several studies have also examined correlations in the strength of Gamma and Theta during sleep (Cirelli & Tononi, 2015), a topic that Mosso was very interested in and to which he dedicates a considerable slice of this book (pp. 74–97).

Sleep is an enduring mystery. The reasons for its existence and what it accomplishes remain big questions for neuroscience and psychology. In Mosso's time, it was thought that sleep resulted from a decrease in blood flow to the brain. Mosso, however, included sleep among the functions of the brain and hypothesized neural centers for its regulation. Chapter 5 includes several paragraphs of brilliant observations about the neural substrates of sleep:

> By this time I was convinced that the weaker blood flow to the cerebral hemispheres was not the sole cause of sleep, but rather that, aside from alterations in circulatory condition, there were other and even more substantial changes in the excitability and the nutritional state of the nervous centers, which must be the basis of sleep (p.79).

This has indeed been proven to be absolutely correct! In fact, the neurons regulating sleep were discovered only about two decades ago and progress in identifying the neural circuitry underlying sleep continues to be an active area of current research (Adamantidis & de Lecea, 2008). Moreover, Mosso made observations about the value of sleep research in understanding the neural bases of consciousness. The foreword examines these studies in the context of the different phases of sleep such as slow-wave and REM (rapid eye movement), which seem to have been recognized by Mosso long before their eventual discovery. Mosso also made use of several sleep inducing techniques for his studies including the use of chloral hydrate induced anesthesia. In fact, this again displays the genius of Mosso. The neural basis of anesthesia is poorly understood even today, and several laboratories are actively engaged in research into its mechanisms. A whole chapter is devoted to Mosso's opinions on the basis of sleep and the mental processes associated with the unconscious. The writing reflects his wonder at the phenomenon of sleep and its origins and utility. The conceptualization of sleep as a dynamic process linking the mind and body reflect his tutelage under Claude Bernard and his belief in the unity of mind and body. He heavily cites Herbert Spencer's treatise – the *Principles of Physiology*, which also propounds the idea of sleep as a process promoting homeostasis. Modern neuroscience has revisited the idea that sleep aids the process of memory stabilization,

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even facilitating the incorporation of new information into existing memory traces (Westermann, Lange, Textor, & Born, 2015). fMRI imaging studies of sleeping subjects have demonstrated the activation of brain regions involved in memory retrieval during the presentation of odors associated with the memory, lending support to this theory (Rasch, Buchel, Gais, & Born, 2007).

Mosso also dedicated a few chapters to issues of circulation and its relation to respiration. His experiments using amyl nitrate to dilate blood vessels transiently as well as his chapter on hyperemia and anemia of the brain represent good examples of what one might call experiments in the bidirectional control of cerebral blood flow. This is of course the very definition of a complete study today-one that examines the effects of agonists as well as antagonists to uncover the mechanisms of a physiological process. He also presented an experimental critique of three accounts of pulmonary blood flow using his own apparatus designed to overcome the limitations of earlier methods. The book ends with a reexamination of the question of cerebral blood flow in the intact skull and an examination of the flow of cerebrospinal fluid.

This fascinating manuscript illuminates the thought process of a brilliant scientist and forerunner of modern neuroscience. In rescuing Mosso from oblivion, Fabbri, Raichle and Shepherd have given historians, students and neuroscientists a valuable new resource to fill gaps in the narrative that modern neuroscience was built upon. Moreover, the works of Mosso give us a new perspective on age old questions of the mind and perhaps pause to appreciate the new age of wonder we live in and to attack these questions with renewed vigor and greater humility.

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