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The parents of neuroscience and the neuroscience of parents

Os pais da neurociência e a neurociência dos pais

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Abstract

Today's burgeoning science of the mind, neuroscience stands on the shoulders of giants, great minds that have made history and still influence present day neurobiology because the strength of their contributions was so widespread and enduring. Our contribution will discuss some of the major forebears of neuroscience, and their continued contribution to the field. We will trace some of the fundamental roots of the field going back thousands of years, showing a logical connection between thinking of the past and ideas today. We next discuss our present day work and modest contributions to the thinking about the brain and its natural malleability owing to the events of pregnancy and care of young. Finally, we will talk about what the future of the field may hold as more advancement in technology and apparatus lead us to new discoveries and insights into our inner universe. Together, we hope to demonstrate that basic ideas and theorizing, first proposed in the vivid imaginations of science giants still hold sway today, influencing thinking and research at the threshold of the 21st century. A good idea remains a good idea, resistant to time and tide, and available to inspire and guide thinking and theorizing long after its source has disappeared.

Keywords: History of neuroscience. Phrenology. Nervous system. Maternal brain.

Resumo

O crescimento expansivo da ciência da mente, a neurociência, se deve aos esforços de grandes cientistas do passado, mentes brilhantes que fizeram história e ainda influenciam os atuais estudos em neurobiologia por conta de suas amplas e duradouras contribuições. O presente ensaio pretende discutir alguns marcos da neurociência e suas contribuições contínuas para a área de estudo. Mostraremos as origens da neurociência e suas raízes há milhares de anos, enfatizando a conexão lógica entre o pensamento científico do passado e as ideias do presente. Em seguida, discutiremos o trabalho atual e as modestas contribuições do nosso laboratório para a compreensão do encéfalo e a sua flexibilidade natural diante dos eventos fisiológicos da gestação e dos cuidados maternais. Finalmente, discutiremos o que o futuro da área pode nos revelar enquanto os avanços tecnológicos cada vez mais propiciam novas ideias e descobertas sobre o nosso universo biológico. Portanto, esperamos demonstrar que as ideias e teorias básicas, inicialmente produzidas vividamente na imaginação de grandes cientistas, ainda perpetuam nos dias atuais, influenciando o pensamento científico e a pesquisa em pleno século XXI. Uma boa ideia permanece sempre uma boa ideia, resiste às mudanças de direções, inspirando e guiando o pensamento científico e suas teorias resultantes, mesmo muito tempo depois do desaparecimento de sua fonte original.

***Palavras-chave**: História da neurociência. Frenologia. Sistema nervoso. Encéfalo materno.*

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A virtuosic brain

The theater is crowded and buzzing with anticipation as hundreds of people are eagerly waiting for the concert to start, eyes fixed straight ahead. The house lights dim. A pianist appears and quickly heads to the majestic instrument, placed strategically center-stage thereby affording good sound to the entire audience. With no hesitation and showing utmost self-confidence, the musician takes the bench and puts the score away; she knows what to do. As if alone in the silence of her music room, the pianist lovingly touches the keys, conjuring a wonderful melody that cascades around the theater. As the melody follows, the virtuosic musician begins to improvise, using practiced creativity, acquired over decades of practice and intense study. Sometimes one hand plays the chords while the other walks through complex scales and arpeggio sequences. Sometimes both execute different phrases simultaneously, although complementary, creating a rich combination of sounds. Occasionally, the improvisation reaches ever-new heights of speed and accuracy, calling upon additional stores of concentration, but producing runs of lightning fast sequences of notes punctuated with calm, peaceful melodies. By way of closing, like a speaker summing-up a speech with a summary of what was stated, the pianist plays the final notes, taking the audience back to the main beginning melody. The musician rises and receives the audience's acclamation; after watching those several minutes of breathtaking performance on the piano, it is rapt. Witnessing this exchange, one question comes to mind: just how did this musician acquire such impressive skills?

Imagine constructing musical improvisation: the above pianist must remember all the chords, scales and arpeggios, and all must match a particular melody. This "musical vocabulary" must be, within a few milliseconds, transformed into fine motor movements, of eyes and hands and fingers all coordinated with near-perfect timing. Further, the musician must be sensitive to the sounds she produces, the auditory feedback, to plan and execute the next sequence of matching notes, a musical sentence with deep and specific meaning. By far, the feats performed by the pianist would not be possible without the precise control of a well-trained, fascinating and complex biological organ: the brain.

Like the skills, talent and training necessary to perform at the high musical level described above, a scientific field has its forebears, teachers and practitioners, its students, its performers, some outstanding, some who labor in the shadows, its "instruments", and its successes and failures. But, like the musician above, a brain studying itself – the ultimate irony – presents many opportunities for appreciating the parallels between art and science, particularly, neuroscience.

Brain, heart and "spirits"

Since ancient times, questions about brain and behavior have intrigued many investigators from distinct areas of knowledge. For instance, preserved Egyptian papyri from 17th century BCE contain medical records with the first mention of the human brain. Interestingly, these descriptions of symptoms, diagnoses, and prognoses of soldiers show that early Egyptian physicians were able to associate movement disorders with head injuries, usually caused by swords and other weapons (Finger, 1994). Nonetheless, Greek thinking brought to light the role of the brain, initially based on the *Corpus Hippocraticum,* a treatise attributed to Hippocrates, which provided perspectives on nervous system diseases, and highlighted the importance of the brain for perception, thinking and acting. We see this as illustrated in a famous passage from *On the sacred disease*:

> Men ought to know that from the brain, and from the brain only, arise our pleasures, joys, laughter and jests, as well as our sorrows, pains, griefs and tears. Through it, in particular, we think, see, hear, and distinguish the ugly from the beautiful, the bad from the good, the pleasant from the unpleasant [...] It is the same thing which makes us mad or delirious, inspires us with dread and fear [...] These things that we suffer all come from the brain, when it is not healthy, but becomes abnormally hot, cold, moist, or dry, or suffers any other unnatural affection to which is was not accustomed (Translated by W. H. S. Jones, 1923).

The idea of a single organ located inside the skull that controls mental functions was quite challenging, and it cast doubt on an unexplored research field. Moreover, not all Greek thinkers were convinced that the brain would be the seat of intellectual functions. The outstanding philosopher-scientist Aristotle (BCE, 384-322) attributed to the heart the functions of movement and sensation. To support his cardiocentric position, he made the argument that the heart was better positioned relative to the body, centrally, allowing the homogeneous distribution of blood. Such a position would be indispensable for sensation; its warmer temperature also would be important, as a characteristic of higher life. Lastly, the heart was connected with all sense organs and muscles through the blood vessels, whereas the brain was not, or had some irrelevant connections (Gross, 1995). The Aristotelian cardiocentric view influenced medical thinking for many centuries, and the origins of higher functions.

Yet, another Greek, the physician Galen (130-200) refused to accept Aristotle's conclusions, arguing for the brain as the source of the intellect. By dissecting the nervous system of several different species, such as cats, monkeys and cattle, Galen made valuable contributions to neuroscience; some of them included the description of cranial nerves, as well as sensory and motor pathways. Curiously, he emphasized that "animal spirits" or "high spirits" conveyed information through the nerves to the muscles, producing movement and sensation. Later on, the philosopher René Descartes (1596-1650) would attribute to the pineal gland the function of controlling the flow of the "animal spirits" through the nervous system. These were early and heuristic attempts to understand nervous function and regulation.

Can specific functions be localized in the brain?

Another key point that intrigued researchers in the late 18th century was the localization of functions in the brain. As a result, two opposite views emerged: some investigators believed that the cerebral cortex had specific areas associated with specific functions (localizationist theory), while others argued that all regions worked together, as whole, i. e., without functionally distinct areas (connectionist theory). The main proponent of the localizationist theory was the German physician Franz Joseph Gall (1758-1828), who became interested in neuroanatomy while still in high school. At that time, he observed that one of his classmates had an excellent verbal memory and associated this skill with a specific physical characteristic: his large and protuberant eyes (Thorne & Henley, 1997). Consequently, Gall assumed that a high-developed mental activity would enlarge its related cortical area in the brain, causing a visible bump in the skull; in this case, he reasoned that verbal memory would be located in the frontal lobes, behind the eyes. During his lifetime, Gall investigated the cranial shape of numerous people with some "special skills", such as writers and poets, suggesting 27 general mental faculties (later on, more were added to this list), which could be localized to the cerebral cortex (e.g. benevolence, destructiveness, hope, creativity). Further, Gall proposed that by measuring the morphology of the skull, it would be possible to predict people's mental abilities, as well as characteristics of their personality. Even a person's propensity for specific professional careers could be mapped onto their skull. This practice, known as Phrenology, received a lot of attention and influenced thinking and theorizing in Europe and the United States for many years.

A French physiologist, Mari-Jean-Pierre Flourens (1794-1867), however, vigorously debated Gall's ideas. Flourens refined the ablation method to investigate the behavior of lesioned animals, finding no correlation between a particular area in the cortex and a specific function. For instance, in some species of birds, removal of specific portions of the cerebral cortex led, in some animals, to recovery of their basic motor functions. These and other experiments lead Flourens to propose the "aggregate field" theory, in which the brain is an integrated organ, working as a whole. As Flourens states here, he holds to a holistic view of brain function: "All sensations, all perceptions and all volition occupy concurrently the same seat in these organs (brain). The faculty of sensation, perception, and volition is then essentially one faculty" (Flourens, 1824).

Nevertheless, at the time, no other observations had a greater impact in favor of the localizationist view than those described by the French neurologist, Pierre Paul Broca (1824-1880). Broca reported a clinical case of an aphasic patient, whose speech was terribly impaired. Although the patient could understand speech, he could utter but the sound "*tan, tan*", a fact that made this case known in the scientific community as "The Tan case". Interestingly, *post mortem* analyses revealed a large lesion on the left side of the patient's frontal lobe, the first widely accepted empirical evidence in favor of cortical localization of function. The German neurologist Carl Wernicke (1848-1905) showed a case of a patient with the opposite symptoms of Broca's: his deficit was language comprehension, although the sentences produced seemed meaningless; in this case, the cerebral lesion was located in a posterior portion of the left hemisphere.

A groundbreaking finding brought to light the critical role of deeper structures in the brain of an epileptic patient, since identified as Henry Molaison, but better known as "H.M." (Scoville & Milner, 1957). H.M., whose bilateral portions of the temporal lobes were removed surgically (mainly involving his hippocampus) recovered, with successful reduction of the localized epileptic seizures. But one serious issue was replaced by another: H.M. now was saddled with a devastating and highly selective memory impairment in which he was unable to form new memories. Through his deficit, and intense subsequent study, it was possible to clarify that some specific functions can also be localized in other brain structures besides the cortex.

In sum, even with vague theories or ambiguous experimental findings, many scientific attempts to understand the brain have placed bricks in the wall of current neuroscience understanding. For instance, Aristotle's and Galen's theories inspired many latter-day researchers to examine the origins of mental faculties, discovering a surfeit of support for the simple proposition that the brain is responsible for all our feelings and actions. Furthermore, that electrical and chemical signals are used by cells to convey information through the nervous system and not "animal spirits" enabled great strides to be made. Albeit Gall was wrong when he assigned abstract faculties such as benevolence and hope to specific areas in the brain, the proposition spurred research into the relationships between developed skills or personality traits and a lack of associated skull deformations or morphology. Further, his presumptions that all behaviors emanated from the brain and that some functions have a specific site were correct (although different brain areas may work coordinately to produce specific behaviors). In addition, Flourens provided major contributions to our understanding of the functions of cerebellum and spinal cord, which emphasized the experimental ablation method – addition-through-subtraction – an approach still widely employed today. Broca's and Wernicke's efforts demonstrated function-related sites in the brain, and simultaneously provided theories about cortical connections associated to the language.

It would be unfair though, not mentioning the brilliant and strongly influential work by the Italian physician Camillo Golgi (1843-1926) and the Spanish neuroanatomist Santiago Ramón y Cajal (1852-1934). Golgi developed a silver nitrate staining technique known at the time as "*La reazione near*" (the black reaction), which allowed a more precisely microscopic analysis of the nervous tissue. By using Golgi's method, Cajal described important properties of individual nervous cells and assigned neurons as the functional unit in the nervous system ("neuron doctrine"). Even with opposite views on the nervous system functioning (neuronal network *versus* neuron doctrine), Golgi and Cajal shared the Nobel Prize, for Physiology, in 1906 because their studies were complementary to each other and contributed significantly to the neuroscience field. Still in use today, the technique has revealed some valuable modifications to the maternal brain, which we discuss below (Keyser, Stafisso-Sandoz, Gerecke, Jasnow, Nightingale, et al. 2001; Kinsley & Lambert, 2006).

Not less important, several others great scientists made valuable contributions and their names must be mentioned: Sir Charles Scott Sherrington (1857-1952; studied the functional properties of the gap between two neurons and named it *Synapse*); Hermann von Helmholtz (1821-1894; described physical properties of the nerve impulse, among other contributions); Donald Olding Hebb (1904-1985; proposed that neurons react together in response to an external stimulus – "Hebbian Learning"); Ivan Petrovich Pavlov (1849-1936; described a simple form of learning by which animals can associate different stimuli – "Classical conditioning" or "Pavlovian conditioning"). Each of these studies and many others, therefore, represents a rich contribution they have made to our current thinking about nervous system regulation.

A case of specialization: the maternal brain

We began this piece with a description of a pianist embarked on an improvisational musical flight. It was an apt metaphor to capture the spirit and conduct of a brain at its peak of creativity, which then lead to a disquisition on the foundations of neuroscience, highlighting some seminal names in the history of the field, each adding his "notes" to the musical score. Next, we discuss an example of a current subfield in neuroscience that has connections to the past that act as a bridge to its attractive future.

A rich model for understanding natural neuroplasticity and adaptation, the maternal brain has begun to elucidate the ways in which a female transitions from virgin to mother. The research has, for the past decade, focused on the manifest and natural neural and behavioral change that accompanies reproductive experience (RE). Such change summates to provide the female with the means to keep herself and her offspring alive and thriving – in the absence of a male parent or partner, who may not be available to contribute to the family (Kinsley & Meyer, 2011). Given such remarkable, but general augmentation, how does one begin to define the maternal brain, a burgeoning model of neural flexibility? Pascual-Leone, Amedi, Fregni e Merabet, (2005, p. 377, grifo nosso) suggests a guiding principle:

> Plasticity is an intrinsic property of the human brain and represents evolution's invention to enable the nervous system to escape the restrictions of its own genome and thus adapt to environmental pressures, physiologic changes, and experiences. Dynamic shifts in the strength of preexisting connections across distributed neural networks, changes in task-related cortico-cortical and cortico-subcortical coherence and modifications of the mapping between behavior and neural activity take place in response to changes in afferent input or efferent demand. **Such rapid, ongoing changes may be followed by the establishment of new connections through dendritic growth and arborization**. […] Plasticity [therefore] is the mechanism for development and learning.

Often, asking "why?", or why something exists, is an informative way to phrase questions about life and its evolution. With regard to reproduction, which every living thing on this planet shares in common, the problem is how to efficiently accomplish it, and perpetuate it. Simply, life must adapt, an aphorism both clear and unforgiving in its simplicity. Whereas the brain is a model and a marvel of change, the maternal brain extends even that degree of plasticity significantly further (by maternal we herein refer primarily to females with one [primiparous or PRIM] or more than one [multiparous or MULT] pregnancies [PREG] and lactations [LACT], compared to zero [nulliparous or NULL females). Why is the maternal brain such a good example of adaptation? It is a model of proximal adaptability that enables the parent to survive, including enhancements to learning and memory that extends even to foster parents (which could have implications for the production and perpetuation of one's genes by non-breeding homosexual or infertile caregivers), thereby allowing the propagation of subsequent generations. That is, the presence of one's genes for many downstream millennia.

In fact, perhaps no other developmental milestone is exemplified by a more sudden and dramatic change in behavior than that observed in the maternal mammal (e.g., in the rat; Kinsley & Lambert, 2006; Nephew, Lovelock & Bridges, 2008), an exemplar of parental care. As pregnancy progresses, the female is literally transformed from an animal that once actively avoided pup-related cues (Kinsley & Bridges, 1988, 1990; Kinsley, 1994; Nephew, et al. 2008; Stafisso-Sandoz, et al. 2008) to one now highly motivated to build nests, and retrieve, group, groom, crouch-over, and protect a set of pups (which we refer to as maternal behavior [MB] or, collectively, full maternal behavior [FMB]), and to do so for these many vulnerable and demanding objects for a long period of time (Consiglio & Bridges, 2009; Nephew & Bridges, 2008a, 2008b). The experiences of pregnancy, too, imprint on the female an enhancement of her recognition of her young that transfers to other offspring, so-called maternal memory (which complements but is different from what we are discussing here; Byrnes & Bridges, 2000; Lee, Li, Watchus & Fleming, 1999; Li & Fleming, 2003; Nephew & Bridges, 2008a, 2008b). Such broad-based maternal behavior, where reproductive females engage in parental care even for non-genetically-related offspring, may point out the importance of generalized maternal behavior: to discriminate and deny maternal care may enhance mechanisms that could go wrong, often jeopardizing one's own genes, leading to a significant loss of a large metabolic and genetic investment. Thus, it makes sense for evolution to err on the side of caution: be maternal toward all comers.

Further, considering that juvenile female rats exhibit shorter latencies to express FMB compared to adult virgin (or nulliparous; NULL) females (Nephew & Bridges, 2008a, 2008b), it is apparent that a significant ontogenetic shift exists in the female rat upon puberty, setting the stage for variations in behavioral plasticity required for successful parenting (Numan & Insel, 2003). We here define neural plasticity as the natural ability of the brain to modify its organization and/or processing to accommodate changing environmental demands, as Pascual-Leone, et al. (2005) above, have written. The maternal brain, then, and the neurobiological landscape that leads to such striking shifts in behavioral responses, appears to be an ideal model of natural neural and behavioral plasticity.

In the vast majority of events, motherhood progresses normally; in a striking subset, however, neither mothers nor their offspring, are likely to benefit from the potential disruptions of the maternal brain-infant interaction, to which we allude above. A better and more fundamental understanding of the maternal brain will shed light on its cognitive, emotional, and plastic nature. Therefore, the more we understand normal behavior, like Gall and Flourens, and Broca and Wernicke above, in our case, maternal, the better we understand those situations when something goes terribly wrong. The pianist hits a series of bad or wrong notes.

Looking beyond the more traditional MBs above, modifications in ***ancillary*** MBs, which draw generally on neuroplastic mechanisms, are also necessary for the pups'/genes' survival. For example, due to increased energy demands, maternal rats benefit from being more efficient foragers; additionally, less time spent away from the nest likely translates directly into decreased vulnerability for the altricial pups. Accordingly, maternal rats exhibit enhanced foraging/spatial ability in an 8-arm radial maze, and in an analog of the Morris Water Maze [*viz*., the dry land maze (DLM; Kesner & Dakis, 1995)] in which they learn the location of a baited food well (Gatewood, Morgan, Eaton, McNamara, Stevens, et al. 2005; Kinsley, Madonia, Gifford, Tureski, Griffin, et al. 1999; Lambert, Berry, Griffin, Amory-Meyer, Madonia-Lomas, et al. 2005; Love, Torrey, McNamara, Morgan, Banks, et al. 2005). Enhanced (and accurate) processing of the social surround (Wartella, Amory, MacBeth, McNamara, Stevens, et al. 2003) is another ancillary MB central to successful parenting; postpartum rats performed better than NULL subjects in social learning tasks that were independent of pup or maternal cues (Fleming, Kuchera, Lee & Winocur, 1994). Mothers also display intense aggression against intruders, and increased exploration (Consiglio & Bridges, 2009; Gammie, Negron, Newman & Rhodes, 2004; Neumann, 2001; Nephew, Bridges, Lovelock & Byrnes, 2009; Svare, 1990). Recent work has shown dramatic improvements in predation (Kinsley, et al. 2004, 2005, 2006, in preparation), a summary behavior that may be an exemplar of the marked changes in the maternal female.

Overall, the maternal brain encompasses elements of the past, present and future, in theorizing, research, technical tools available, and significance. The vast array of data suggests strongly that mothers are made, not born (Gonzalez-Mariscal & Kinsley, 2009; Kinsley, 1994; Kinsley & Lambert, 2006; Kinsley, 2008; Kinsley & Lambert, 2008; Kinsley, Bardi, Karelina, Rima, Christon, Friedenberg, et al. 2008; Lambert, Tu, Everette, Love, McNamara, et al. 2007; Lambert & Kinsley, 2009; Numan & Insel, 2003; Rima, Bardi, Friedenberg, Christon, Karelina, Lambert, et al. 2009; Tomizawa, Iga, Lu, Moriwaki, Matsushita, et al. 2003). Virtually all female mammals examined, from rats to monkeys to humans, undergo fundamental behavioral changes during pregnancy and motherhood. What was once a largely self-directed organism devoted to its own needs and survival becomes one focused on the care and well-being of its offspring (there are suggestions, too, that other organisms, for example, invertebrates, may undergo some significant change related to reproduction-related events that ensure survival of offspring [mosquitoes: Beach, 1979; wolf spiders: Choi & Kinsley, unpublished]). Although scientists have long observed and marveled at this transition, only now they are beginning to understand what causes it (Byrnes & Bridges, 2000; Byrnes, Babb & Bridges, 2009; Lee, et al. 1999; Li & Fleming, 2003; Nephew, et al. 2008), even in humans (Kim, Leckman, Mayes, Feldman, Wang, Swain, et al. 2010; Kinsley & Meyer, 2010).

New research indicates that the dramatic hormonal fluctuations that occur during pregnancy, birth and lactation may remodel the female brain (Keyser, Stafisso-Sandoz, Gerecke, Jasnow, Nightingale, Lambert, et al. 2001; Kinsley, Trainer, Stafisso-Sandoz, Quadros, Keyser-Marcus, Hearon, et al. 2006), increasing the size of neurons in some regions and producing structural changes in others. Some of these sites are involved in regulating MBs such as building nests, grooming young, and protecting them from predators and rogue males (Byrnes & Bridges, 2007; Byrnes, Lee & Bridges, 2007; Febo, Stolberg, Numan, Bridges, Kulkarni, et al. 2008; Kinsley, et al. 2008; Kinsley & Lambert, 2008; Lambert & Kinsley, 2009; Nephew, Byrnes & Bridges, 2010). Other affected regions, though, control memory, learning and responses to fear and stress. Recent experiments from our lab have shown that mother rats outperform virgins in navigating mazes and capturing prey. In addition to motivating females toward caring for their offspring, the hormone-induced brain changes may enhance a mother rat's foraging abilities, giving her pups a better chance of survival. What is more, the cognitive benefits appear to be long-lasting, persisting until the mother rats enter old age, maintaining brain health (Gatewood, et al. 2005; Kinsley, Franssen & Meyer, 2012). Although studies of this phenomenon have so far focused on rodents, it is likely that human females also gain long-lasting mental benefits from motherhood. Most mammals share similar MBs, likely controlled by the same brain regions in both humans and rats. In fact, some researchers have suggested that the development of MB was one of the main drivers for the evolution of the mammalian brain. As mammals arose from their reptile forebears, their reproductive strategy shifted from drop-the-eggs-and-flee to defend-the-nest, and the selective advantages of the latter approach may have favored the emergence of hormonal brain changes and the resulting beneficial behaviors (MacLean, 1990). Therefore, the hand – or paw – that rocks the cradle indeed rules the world.

A new brain science

A changeable controller, adaptable mechanisms, evolution of the latter principle all of it suggests a marvelous synergy in service to Life. In other words, the brain is the antithesis of stasis. Like the brain itself, the field of study devoted to its understanding is, fittingly, likewise nimble and creative. Although its history can be traced as far back as the earliest philosophers, neuroscience has only just recently culminated into a new field of science of revolutionary proportion. Presently, an average of 30 thousand neuroscientists from around the world attends the Society for Neuroscience yearly conference. Over the course of one week, a coliseum sized conference center is filled with lectures and symposiums from all aspects of neuroscience: from molecular, behavioral, cognitive, to computational emphasizing the wide breadth of approaches. This is an amazing fact seeing as the field was founded only within the last 50 years or so. The foundations were laid throughout neuroscience's history; technological advances made more recently, however, have propelled neuroscience forward as a new frontier in science that is growing increasingly more equipped to unravel one of the greatest mysteries of humankind, the brain (SFN, 2012).

From understanding the molecular bases that lead to behavioral changes to mind-reading machines and brain-computer interfaces that seem to come straight from science fiction, the advances in neuroscience highlight a promising future that offers hope for enhancing/restoring cognitive function, and healing mental diseases like autism, Alzheimer's disease, and schizophrenia; and even offering hope for healing paraplegia.

A time of significant improvements in research methods and breakthroughs in technology, the 1990's were thought of as the decade of the brain. It is, however, the dawn of the new millennia that may prove to be the age where the thread that weaves through the history of neuroscience is tied to the various approaches currently active in neuroscience; to, finally, yield a cohesive representation of the brain. Through understanding how regions in the brain, or neural networks, are connected and organized, neuroscientists will be better equipped to find treatments for mental diseases and to even answer the age old question of consciousness that plagued philosophers for thousands of years. Neuroscience is not just scientific inquiry; it explores and seeks to understand the very meaning of human existence and experience (Kandel, 2007).

Much of the recent advancement in neuroscience is indebted to refinements of brain imaging techniques. For example, the advent of functional magnetic resonance imaging (fMRI), which measures changes in blood flow in the brain, has revolutionized the field of neuroscience. fMRI and other brain imaging techniques such as electroencephalography (EEG), magnetic resonance imagining (MRI), and diffusion tensor imaging (DTI) also allow researchers to non-invasively peer into the human brain or to measure brain activity during resting states and while subjects perform varied behavioral and cognitive tasks. The combination of imaging techniques with single and multi-neuronal recording can also be utilized to give a more specific and nuanced understanding of brain processes and their correlation to specific behaviors (Hasson & Honey, 2012).

High-tech advances in neuroimaging are not the only means through which neuroscience advances its ability to quantify neurobiological changes. Staining techniques such as immunohistochemistry and immunocytochemistry have long been used, but the ever-increasing knowledge base of neurochemistry enables a subsequent advancement in staining techniques. With more specified antibodies, neuroscientists using animal models are able to collect more unambiguous and precise results of neural activation. Recently, a team at Harvard Medical School developed a fluorescent staining procedure that is able to stain individual neurons in different colors (Weissman, Sanes, Lichtman & Livet, 2011). This allows researchers to distinguish different types of neurons from one to another (Livet, Weissman, Kang, Draft, Lu, Bennis, et al. 2007) and has become a powerful tool in studies of neurogenesis within the human hippocampus (Eriksson, Perfilieva, Bjork-Eriksson, Alborn, Nordborg, Peterson, et al. 1998) and non-human animal models (Eriksson, et al. 1998; Ming, & Song, 2011). It is also useful in mapping the connections of neural networks (Lichtman, Livet & Sanes, 2008).

Neuroscience, focusing on how behaviors and cognitions emerge from underlying neurobiological and neurochemical processes, has made great strides in the last decade alone in unraveling the connection matrix of the brain (Sporns, Tononi & Kötter, 2005). There had not been a collaborative research effort, however, to collect and analyze the interconnectivity of the brain until just recently. Launched in 2009, the goal of the National Institute of Health's Human Connectome Project is to build a network map of the human brain using cutting-edge brain imaging technology. This is a massive undertaking, spread out over several institutions, through several years of data collection from over a thousand subjects. DTI, fMRI, and resting state and task MRI, as well as powerful super computers will be utilized to first acquire data from brain scans during resting states and during specific behavioral tasks, and secondly to analyze all recorded data. Starting this summer, 2012, the five-year journey will begin: 1,200 healthy adult participants, as well as 300 twin pairs, will have their brains scanned in a resting state, and then will be given a series of behavioral tasks to assess sensory-motor and cognitive function. This dual scanning process will enable researchers to see the associativity between neural networks and specific tasks; twin studies will further enable researchers to assess brain function and heritability. This project will be invaluable for future clinical use in diagnosing and understanding mental diseases like those mentioned above, as well as neurodegenerative disorders. Though the Human Connectome Project will provide an unprecedented amount of information on the connectivity of the human brain at fine detail, it will only look at the brain at the macro-level, i.e., the interactions between brain regions. There is still finer detailing at the micro-level, i.e. the molecular and cellular level, which will need to be analyzed and disseminated (NIH, 2012; Van Essen, Ugurbil, Auerbach, Barch, Behrens, Bucholz, et al. 2012).

One of the forthcoming approaches in neuroscience further merges with computer science to produce the subfield of neuroengineering. Thus far, the use of brain stimulators such as cochlear implants for restoration of auditory function, and deep brain stimulations for pain management and control for motor disorders like Parkinson's disease have paved the way for more advanced brain-computer interfaces. In just the past five years, research has indicated the feasibility of building better devices that would aid in restoring functions from vision and audition, to motor function (Nicolelis, 2003).

Recently, researchers at the Massachusetts Institute of Technology (MIT) have designed a computer chip made of silicon that mimics neurons (Poon & Zhou, 2011). Brain activity at the neuronal level is a very subtle and complex activity, and computer models that had previously been used to mimic brain function were limited to binary code type signals: yes/no and on/off. Signal transmission via neurons in the brain however work more along a gradient scale by integration and summation of signals (Carlson, 2009). These new and improved artificial neurons will enable researchers to have a clearer understanding of the processes of learning and memory, for example. Furthermore, the creation of silicon chips that are more integrated with biological systems (like the human brain) provide researchers hope for use in prosthetic devices and limbs (Poon & Zhou, 2011; Rachmuth, Shouval, Bear & Poon, 2011).

It may have been thought of as a far-fetched idea from a science fiction movie, but the future of neuroscience brings humankind one step closer to "mind-reading machines". Brain-machine interfaces, or BMIs, have been used in studies of both humans and non-human primates to reconstruct previously seen and unseen images (Schwartz, 2011). Using fMRI technology, researchers associated certain blood flow patterns with various photographs of people, objects, food, etc. as they were viewed by subjects. Later, the subjects viewed a separate set of photographs and the computer-brain model was able to reconstruct the image being viewed with 90 percent accuracy (Kay, Naselaris, Prenger & Gallant, 2008; Kay & Gallant, 2009). Researchers are hopeful that BMIs such as this brain imaging decoder could be useful for studies in attention, dream states, and consciousness.

BMIs are also proving to be useful for individuals with motor deficits: they once again can regain control of their actions and movements. Though originally begun in the 1970's, only recently have technological limitations been lifted. Neuroscientists are now developing implantable devices (like silicon chips) to transpose brain signals into a computer signal to help restore limb mobility in paralyzed subjects and enable prosthetic limbs to act like real human arms (Nicolelis & Lebedev, 2009). Studies with both humans and primates have shown the initial stages of this research to be successful: both primates and humans were able to control a robotic arm via neural activity to allow them to drink from a cup (Schwartz, 2004; Donoghue, 2002; Hochberg, Bacher, Jarosiewicz, Masse, Simeral, Vogel, et al. 2012).

The advent of BMIs in neuroscience research not only provide hope to restoring lost motor and cognitive abilities, but also add to the fundamental knowledge of the interconnectivity of the brain and how it functions at the neuronal level (Lebedev & Nicolelis, 2006; Nicolelis & Lebedev, 2009).

It is not, however solely through impressive neuroengineering that individuals suffering from paralysis may find the chance to walk once again. Researchers have discovered a support cell to neurons (radial glial) that acts like a stem cell (Decimo, Bifari, Rodriguez, Malpeli, Dolci, Lavarini, et al. 2011). Ogawa and colleagues (2002) showed that after implanting these cells into the spinal cord of rats, the animals showed function recovery and neurogenesis within the spinal cord in only five weeks.

Within the last decade, neuroscientists have discovered a rather special neuron within the motor cortex. Rizzolatti and colleagues (2004) found that when a primate actively reached for and grabbed an object or performed a specific action, certain areas or networks of neurons fired. This, by itself, is not necessarily anything groundbreaking, however when the same animal watched another primate perform a similar action, the pattern of neuronal firing was mirrored. Research with human subjects also expressed a similar result (Chong, Cunnington, Williams, Kanwisher & Mattingley, 2008; Gazzola, Rizzolatti, Wicker & Keysers, 2007; Kilner, Neal, Weiskopf, Friston & Frith, 2009). Justly named, "mirror neurons" may perhaps be one of the most important discoveries in Neuroscience within the last decade: The mirror neuronal system offers insight into learning through imitation, empathy, the human acquisition of language, and overall brain evolution. Neuroscientists also aim to examine the extent to which mirror neurons play in social behaviors and autism, a disorder associated with deficits in empathy, language learning, and mimicry and pretend play (Ramachandran, 2011).

Further studies by neuroscientist V.S. Ramanchandran shed light on how understanding the mirror neuronal system could be used for clinical applications. A phenomenon known as phantom limb syndrome leaves some individuals with an amputated limb still suffering various degrees of pain or sensation in that limb that no longer exists. By using a mirror in a box, patients suffering from phantom arm pain, watch the actions of their other (real) arm in the mirror, thereby tricking their brain into thinking that the actions seen in the mirror are being made by the phantom limb. This "brain trick", utilizing the contextual implications of the mirror neuronal system, has been useful to help alleviate certain types of pain felt in Phantom Limbs (Ramachandran & Rogers-Ramachandran, 1996; Ramachandran & Altschuler, 2009). Furthermore, researchers speculate that mirror neurons allow individuals to see the world from other visual and conceptual vantage points allowing for self-reflection and perhaps, by extension, self-awareness (Ramachandran, 2011).

Both the present and the future present of neuroscience prove to be well equipped to tackle the outstanding questions about the functionality of the brain. However, as an integrative field, neuroscience is not insulated to simply seeking answers to how the brain is connected; it also aims to understand how and why brain processes lead to particular behaviors, thoughts, and also how these, in turn, give rise to the notion of experience, meaning, and "being" or self.

Once a problem for the philosophers, the question of consciousness is now in the hands of neuroscientists (Crick & Koch, 1998). Consciousness studies had long been avoided by scientists, but the recent advances in neuroscience now enable researchers to assert the possibility of a biological basis of subjective human experience (Crick & Koch, 2008; Edelman, Gally & Baars, 2011).

Some of the most promising avenues in neuroscience studies of consciousness are those in visual attention and memory. Researchers are looking towards the connection of attention, focused and unfocused, to the neural feedback loops that occur in the brain between regions responsible for basic life-sustaining functions and those regions responsible for higher, executive cognitive functions (Crick & Koch, 2008). Through visual attention, we are able to selectively attend to relevant stimuli in the environment and create mental representations of the world around us. It also allows for a sort of "filter" that enables us to disregard and ignore those stimuli that are irrelevant. The act of attending and creating symbols or representations in our internal world (brain), elicit the use of memory creation and storage. Attention works to amplify consciousness: the more or longer a stimulus is attended to, the stronger the associations and representations of it become through a joint effort with memory (Posner, 2012; Tallon-Baudry, 2012). The means by which these two systems (the attentional system and the memory system) interact, and the extent of their interconnectivity provide neuroscientists with a fertile ground to study awareness and thus consciousness (Crick & Koch, 2008). However, to be conscious does not always imply awareness. Studies of a particular mental phenomena of cortical blindness known as blindsight proves that sensory perception and behavioral guidance can be accomplished without an individual being aware of why he or she has reached a certain conclusion or produces a certain motor output (Carlson, 2009). People with blindsight have no visual impairments but, depending on the location of the brain damage within the visual areas, remain unaware of certain perceived visual information. Blindsight studies suggest that consciousness is not an inherent property of all brain areas, but that it emerges from the interactions of different regions (Crick & Koch, 2008).

Qualia, or the essence of being for subjective conscious experience, may best be examined through the advances in brain imaging technology to highlight the similarities between different people attending to the same stimuli. For example, if two subjects are shown the color blue, fMRI output has shown that similar pathways and neural activity is shown across subjects. The "blueness of blue" is not as subjective as philosophers once suggested, but instead a very real and quantifiable perceptual experience (Crick & Koch, 2008).

Future directions for neuroscience studies of consciousness rest on further development of brain imaging technology, BMI's, and cognitive and behavior tests in attention and memory. The utilization of advances in neuropsychopharmacology for drug studies, and altered states of consciousness via anesthesia, meditation, and brain injury are a viable open door of research of consciousness and unraveling the biological basis of meaning and subjective experience in not just humans, but other animals of varying nervous system complexity (Crick & Koch, 2008; Edelman, et al. 2011).

The female reproductive system has long been thought to have a relatively short "shelf-life" as it is the first organ to fail with increasing age. Several studies, however, have not just suggested but have successfully shown that mammalian female fertility can be prolonged (Selesniemi, Lee, Niikura & Tilly, 2009; Tilly & Telfer, 2009). Researchers found a population of germ cells in mice that, if implanted to a younger host environment, were able to form oocytes. Exposing the dormant germ cells to the younger host environment produced viable offspring (Niikura, Niikura, & Tilly, 2009). Similar studies shown similar effects in humans (White, Woods, Takai, Ishihara, Seki & Tilly, 2012). Moreover, Selesniemi and colleagues (2009) found that transplantation of bone marrow into adult female mice also prolonged fertility and thus the reproductive lifespan.

With such a diverse range of subfields coupled with exponential growth and advancement in technology, neuroscience is quickly becoming not only a popular field in science, but also one that appears to have revolutionary-sized discoveries waiting around every corner. The tools and techniques of neuroscience enable this expanding field to face some of the greatest mysteries in life head on.

In closing, we have here attempted to present the field of neuroscience from its early origins, to a current research field, and through its present and future directions. It goes without saying, the future is bright because the past has provided us with such a strong foundation. Historians believe that Ludwig von Beethoven composed his *Moonlight Sonata*, in 1801. For over 200 years, musicians and pianists, like the one with which we began our article, have found the melody and its tempo alluring and seductive. They all play it today, still adding their unique signatures to its performance. As we said before, a good idea will continue to inspire. Thus, the musicians of the brain, neuroscientists, add their notes to the score of our understanding, bringing forth ever new and creative interpretations.

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