The *anti*-social brain: Novel insights from neuroscience and molecular biology

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Abstracts

Human beings are social animals. Life in society requires individuals to modulate their behavior accordingly to the norms that rule social contexts. Despite being generally sanctioned, violence remains a major issue worldwide.

Advances in neuroscience and molecular biology are shedding new light on the biological mechanisms that underlie poor inhibitory control in impulsive aggression and the lack of empathy and emotional resonance in predatory violence. The increase in neuroscientific knowledge on the biological underpinnings of impulse control, moral judgment and social behavior may contribute to a wider understanding of the notion of free-will and responsibility. Here, we briefly discuss novel findings on the neurobiological correlates of aggressive and antisocial behavior and their potential ethical, forensic and political implications.

Keywords

Aggressiveness, psychopathy, neuroimaging, behavioral genetics, free-will.

1. Introduction

The last century has been characterized by amazing achievements in the exploration of the functioning of the human brain *in-vivo*. From the 90s on, the so called *Decade of the Brain*, this field of investigation has shed light on the neuronal underpinnings of the finest aspects of cognition, emotion and behavior, including decision making processes, perspective taking and moral judgment. Topics that have been for a long time the domain of philosophy and psychology and that seemed far beyond the reach of science, such as the distinction between good and bad and the way individuals value moral alternatives, begin to be studied with the scientific approach.

Behavioral genetics has greatly contributed to gain a complete understanding of the way the brain functions by uncovering the influence of genetic factors on complex behavioral traits. This discipline is leading to novel insights on the subtle interplay between nature and nurture in shaping human behavior. The origins of evil and the question as to why people choose bad actions over good ones date back centuries. Plato was among the first philosophers to refer the origins of malevolent actions to the complex interaction between biological and cultural factors. Namely, he stated that «No one is willingly evil, but one can become evil for a bad disposition in his body and for a training without a true education; this is hideous for everyone and happen against his will».[1]

The unprecedented development of neuroscience has opened a window on *the brain in action*[2] and has revitalized the debate on the contribution of the interaction between nature and nurture. Are criminals *bad*, that is, are they individuals who intentionally choose to be wicked even if they could do otherwise or, to what extent are they predisposed to engage in antisocial actions, i.e., are they *mad*?

Clinical observations have revealed that traumatic brain injuries and neurological disorders may dramatically affect behavioral control and impulse inhibition. The study of mirror neurons, a neuronal population which fires when a subject engages in a specific action as well as when s/he

[1] Plato, *Timaeus*, 86e.
[2] P. Pietrini, «Toward a Biochemistry of Mind?», *American Journal of Psychiatry* (2003), 160, pp. 1907-1908.

observes the same action being performed by others, has shed new light on the mechanisms that enable action recognition and on more complex processes involved in decoding others' behavior, namely *theory of mind*. We now know that the emotional experience of a given event, such as the pain of losing a significant other, enables us to fully share the feelings of somebody who is experiencing a similar situation, and feel empathy toward this person. Brain networks that are crucial for understanding the perspective and the needs of others as well as for modulating behavior accordingly to the social constraints have been identified. These novel pieces of knowledge are enabling investigators to clarify more and more the brain underpinnings of selective deficits in emotional and cognitive processing for neurological and psychiatric disturbances. As an example, we now know that specific alterations in brain connectivity, i.e., the way different brain areas are linked together, are observable in autism[3] and that those underpinnings may contribute to explain the social inabilities that characterize this disorder. Current understanding of the causes of a given disorder affects its treatment, as well as the way it is perceived by society and stigmatized. For instance, advancements in medicine have enormously changed the way epilepsy has been considered. Epilepsy was long believed to be due to demoniac possession. Nowadays, it is recognized as a neurological disorder, which can be treated pharmacologically and surgically.

By analogy, discoveries on the neuronal underpinnings of empathy and moral values raise a number of questions as far as deviant behavior is concerned. Will culpability be evaluated differently once we know that the actions of a criminal were severely conditioned by his/her early life experiences and/or genetic predispositions? How will this affect the notion of free-will, which is the fundamental assumption behind our legal system? What will be the social and legal consequences of gaining a more complete scientific knowledge with respect to the manners in which genetics and environment interact in affecting behavior? The more we deepen our understanding of the human brain functioning in healthy and pathological states, the more we

[3] M. Verly, *et al.*, «Altered Functional Connectivity of the Language Network in ASD: Role of Classical Language Areas and Cerebellum», *Neuroimage: Clinical,* n. 4 (2014), pp. 374-82.

increase our ability to dissect the biological basis of individual differences. Ultimately, this will progressively lead to a shift from *bad* to *mad* for individuals who behave with no respect for the rights and needs of others and who show specific alterations in brain networks crucial for empathy and impulse control. Here, we briefly discuss the most recent findings on the neurobiological correlates of aggressive and antisocial behavior also in light of the implications that novel neuroscientific acquisitions may have on the notion of free-will and culpability.

2. The evil inside us: insights from acquired psychopathy

The development of the human brain through evolution has mostly regarded the anterior part of it, namely the prefrontal cortex. The increase in volume and complexity of the human brain has allowed our species to engage in complex social interaction, to organize life in society, to maintain memory of the past by relying on written language. Life in society, however, requires that the individuals learn to modulate their impulsive behavior according to the social norms that rule specific cultural contexts, as norm violations are typically sanctioned. Thus, emotion regulation, i.e., the ability to volitionally control and modify emotional responsiveness according to the constraints imposed by social norms, is very important for the societal integration and success of an individual. Poor emotion regulation skills are common to many psychiatric disorders[4] and can be observed in psychopathy as well. Aggressiveness is ingrained in living beings. The ability to respond with aggressive behavior carries an adaptive role as it increases the chances of survival of an organism in an environment that may potentially be harming. An animal that is under attack and has no possibility to escape typically reacts by initially displaying a freezing response. Afterwards, it attempts to intimidate the aggressor by sending signals that emphasize its physical strength. The animal unsheathes the claws, arches the back with the aim of showing to the predator that an attack may be deadly. When intimidating signals are not enough, aggressive behavior takes place. In

[4] D. Cicchetti, *et al.*, «Emotions and Emotion Regulation in Developmental Psychopathology», *Development and Psychopathology*, (1995), 7, pp. 1-10.

affective aggression, violent behavior is typically conveyed toward an individual that is perceived as a source of threat, or that may have caused frustration in the offender. It is possible to identify a specific event, or an event series that trigger negative emotions, such as anger, hostility or anxiety in the offender[5]. Typically, impulsive aggression is not driven by the aim of attaining goods, such as financial resources or social benefits. Affective aggressive behavior is an appropriate response in the need to attack for personal defense, but it may also occur in the absence of a real threat. An exaggerated perception of threat may play an important role in triggering aggressive attacks[6]. Difficulties in restraining from aggressive behavior may also result as a consequence of poor emotional regulation abilities. The ability to volitionally modulate impulsive aggressive behavior crucially depends on the integrity of the prefrontal cortex, and specifically of the medial prefrontal cortex and orbital frontal regions.[7], [8]

The case of Phineas Gage is well known in the history of medicine as it was among the first accounts on the link between prefrontal lesions and massive changes in personality and behavior. Phineas Gage was a young man who worked at the construction of a railway track in Vermont. While exploding a huge amount of dynamite, an iron bar was accidentally thrown in the air and blasted through the front of his head. The accident was very severe but Gage survived and in a few months he was able to recover almost completely his cognitive functions. John M. Harlow, Gage's physician, followed the patient for months during his recovery and he published a paper on his case that made him worldwide famous.[9] What was remarkable about Gage's case was that he did not display overt impairments in motor, linguistic or memory-related skills. However, many personality changes that affected both his private and professional life occurred after the accident. Gage lost

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[5] M.D. Robinson and B.N. Wilkowski, «Personality Processes in Anger and Reactive Aggression: An Introduction» *Journal of Personality*, n. 78 (2010), pp. 1-8.

[6] R.J.R. Blair, *et al.*, «The Development of Psychopathy», *Journal of Child Psychology and Psychiatry*, n. 47 (2006), pp. 262-275.

[7] P. Pietrini and V. Bambini, «Homo Ferox: The Contribution of Functional Brain Studies to Understanding the Neural Bases of Aggressive and Criminal Behavior», *International Journal of Law and Psychiatry*, n. 32 (2009), 4, pp. 259-65.

[8] A. Raine, *The Anatomy of Violence: The Biological Roots of Crime*, Pantheon Books Publisher, New York 2013.

[9] J. Harlow, «Passage of an Iron Bar Through the Head», *Boston Medical and Surgical Journal*, n. 13 (1848), pp. 389-393.

concern to others' feelings and commitment to the wellbeing of his family. He became shallow, irreverent, capricious, quick-tempered and aggressive. He was not able to commit to his work duties any more. Thus, Harlow documented the loss in foresight planning as well as the indifference for the consequences of one's own actions that typically characterize frontal lobe injuries. A reconstruction of the lesion site, consistently, revealed that the accident had mainly affected the ventro-medial and the orbitofrontal parts of his prefrontal cortex.[10]

Lesion studies, as the case documented by Harlow, have greatly contributed to elucidate the functional role of the different brain areas. A great increase in the understanding of the manner in which our brain functions has been made possible by the great body of evidence accumulated during the First and the Second World War as well as during the Vietnam War. During these military conflicts, physicians had the possibility of gathering information on the modifications in behavior and personality traits that followed perforating brain injuries. They had the opportunity to observe that injuries in circumscribed brain sites where accompanied by specific loss in cognitive and emotional functions. This evidence suggested that those brain areas were to be considered the neuronal underpinnings of those lost affective and cognitive processes.

Vietnam veterans, in particular, had been a source of public concern in the US for the aggressive and often violent behavior that characterized many of them. The Vietnam Head Injury Study monitored for nearly forty years the conduct of over thousand veterans who had suffered from brain injury on the battlefield. Many of them had injuries that were specifically confined to the frontal lobes and exhibited poor reasoning and planning abilities as well as deficits in motivated social behavior.[11] Also, most of them had been experiencing irritable mood as well as a marked deficit in impulse control. In many cases there were radical changes of personality similar to those observed in Gage. In patients with lesions of the ventromedial portion of the prefrontal cortex elevated levels of aggression were often observed. The Vietnam Head Injury Study expanded

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[10] H. Damasio, *et al.*, «The Return of Phineas Gage: Clues About the Brain from the Skull of a Famous Patient», *Science*, n. 264 (1994), pp. 1102-1105.
[11] J. Grafman, *et al.*, «Frontal Lobe Injuries, Violence, and Aggression: A Report of the Vietnam Head Injury Study», *Neurology*, n. 46 (1996), 5, pp. 1231-1238.

current knowledge about the functional role of brain sites affected by cerebral lesions and raised public awareness with regard to the causes of the Veterans' aggressive behavior, which has severely limited their social integration.

In recent years it has become possible to investigate the functioning of the human brain *in vivo*.

Neuroimaging studies have allowed us to gain further insights on the difficulties in emotional regulation that may underline impulsive aggressive behavior. A Positron Emission Tomography (PET) study conducted by our own group[12] was among the first ones to address the neural underpinnings of affective aggression in humans. The participants of this study were young healthy adults who were asked to engage in the imagination of scenarios in which different levels of provocation and restraints were applied. Participants were required to imagine taking an elevator ride together with their own mother and two strangers. In a high provocation condition, they imagined that their mother was the victim of a violent attack while: a) they were restrained and could not react; b) they reacted with aggressiveness to save her. These two conditions were compared with scenarios of emotionally neutral content. By comparing the experimental conditions with the neutral ones it was possible to identify the neural substrate of aggressive ideation. Aggressive responses were associated with a marked reduction of neuronal responses in the medial orbitofrontal cortex. This study identified, with an *in vivo* brain investigation, the substrate for aggressive behavior in healthy and non-violent volunteers. By supporting a role for the orbitofrontal cortex in the inhibition of impulsive aggression, the findings of this study were in line with the clinical literature on brain prefrontal regions.

A number of neuroimaging investigations have found consistent evidence with respect to the dysfunction of prefrontal networks in individuals who display aggressive behavior.[13], [14], [15] The

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[12] P. Pietrini, *et al.*, «Neural Correlates of Imaginal Aggressive Behavior Assessed by Positron Emission Tomography in Healthy Subjects», *American Journal of Psychiatry*, n. 157 (2000), 11, pp. 1772-1781.
[13] H. Soderstrom, *et al.*, «Reduced Regional Cerebral Blood Flow in Non-Psychotic Violent Offenders», *Psychiatry Research*, n. 98 (2000), pp. 29-41.
[14] A. Raine, *et al.*, «Brain Abnormalities in Murderers Indicated by Positron Emission Tomography», *Biological Psychiatry*, n. 42 (1997), pp. 495-508.

cohort of behavioral changes caused by orbitofrontal and ventromedial lesions shows striking similarities to the cognitive and emotional features of antisocial disorders. This observation has led some authors to the use of the term “acquired sociopathy”[16] for the clinical cases produced by brain damage.

A hypersensitivity to emotionally salient social stimuli may contribute to the escalation of impulsive aggressive behavior. Subcortical structures play a very important role to this respect. In the animal model, it is possible to elicit responses of affective aggressiveness by stimulating the amygdala[17]. A similar role seems to be carried out by the amygdala in the human brain. The amygdala is involved in triggering the startle reflex[18] and modulates the probability that an individual will engage in aggressive behavior. Enhanced reactivity of subcortical structures in response to threat has been observed in psychiatric disorders such as Post Traumatic Stress Disorder (PTSD). PTSD patients are very sensitive to stimuli that may be associated with a potential threat, as revealed by their startle reflex responses.[19, 20] Over-reactivity of subcortical structures in response to threat-related stimuli has been documented in other psychiatric disorders such as anxiety and depression.[21, 22] Consistently, these disturbances are typically characterized by a higher level of affective aggression.[23]

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[15] P.F. Goyer, *et al.*, «Positron-Emission Tomography and Oersonality Disorders», *Neuropsychopharmacology*, n. 10 (1994), pp. 21-28; H.D. Critchley, *et al.*, «Prefrontal and Medial Temporal Correlates of Repetitive Violence to Self and Others», *Biological Psychiatry,* n. 47 (2000), pp. 928-934.

[16] A.R. Damasio, «A Neural Basis for Sociopathy», *Archives of General Psychiatry*, n. 57 (2000), pp. 128-129.

[17] T.R. Gregg, and A. Siegel, «Brain structures and neurotransmitters regulating aggression in cats: implications for human aggression» *Prog. Neuropsychopharmacol. Biol. Psychiatry,* (2001), 25, pp. 91-140.

[18] M. Davis, «The Role of the Amygdala in Conditioned and Unconditioned Fear and Anxiety», in J.P. Aggleton (ed.), *The Amygdala: A Functional Analysis*, Oxford University Press, Oxford 2000, pp. 289-310.

[19] C.A. Morgan, *et al.*, «Startle Reflex Abnormalities in Women with Sexual Assault-Related Posttraumatic Stress Disorder» *American Journal of Psychiatry,* n. 154 (1997), pp. 1076-1080.

[20] C.A. Morgan, *et al.*, «Exaggerated Acoustic Startle Reflex in Gulf War Veterans with Posttraumatic Stress Disorder», *American Journal of Psychiatry*, n. 153 (1996), pp. 64-68.

[21] W.C. Drevets, «Neuroimaging and Neuropathological Studies of Depression: Implications for the Cognitive-Emotional Features of Mood Disorders», *Current Opinion in Neurobiology*, n. 11 (2001), pp. 240-249.

[22] K M. Thomas, *et al.*, «Amygdala Response to Fearful Faces in Anxious and Depressed Children», *Archives of General Psychiatry*, n. 58 (2001), pp. 1057-1063.

[23] See for instance the works: T. Galovski, *et al.*, «Intermittent Explosive Disorder and Other Psychiatric Comorbidity Among Court-Referred and Self-Referred Aggressive Drivers», *Behaviour Research and Therapy*, n. 40 (2002), pp. 641-651; M. Knox, *et al.,* «Aggressive Behavior in Clinically Depressed Adolescents», *Journal of the American Academy of Child & Adolescent Psychiatry*, n. 39 (2000), pp. 611-618; in the same journal see also: D.S. Pine, *et al.*, «Social Phobia and the Persistence of Conduct Problems», n. 41 (2000), pp. 657-665.

3. Predatory violence: inside the brain of serial killers

Instrumental predatory behavior is very different from the type of aggressive behaviour that has been considered so far. Cold-blood aggressiveness is typically mediated by the desire to gain a valued outcome, either being economic or social. Raine and colleagues used PET to investigate brain activity in predatory and affective murderers. Interestingly, they found that both types of murderers exhibited an increased activity in sub-cortical brain structures like the right amygdala and hippocampus. However, only the affective murderers showed a reduced response in prefrontal cortical activity[24]. This finding suggests that these subjects may specifically suffer of poor inhibitory control of aggressive impulses. Nevertheless, impulsive affective and instrumental aggressiveness often co-occur, and individuals that engage in instrumental aggressiveness may engage in impulsive aggressiveness as well.[25] Both types of behavior can be observed in individuals that are affected by the antisocial personality disorder. Individuals affected by this disorder show general disregard and lack of concern for the needs and rights of other people. In a case study, described by Cleckley, on a young male adult called Tom, the description of Tom's complete lack of interest and concern for the negative consequences of his actions on the well-being of significant others, is very remarkable.[26]

> Tom's mother had for some years suffered special anxiety and distress because of his unannounced absences. After telling her good-bye, saying he was going downtown for a Coca-Cola or to a movie, he might not appear for several days or even for a couple of weeks. Instead of his returning, a long-distance telephone call might in the middle of the night arouse the father, who would be entreated to come at once to nearby or distant places where the son had encountered unpleasant events or, perhaps, restraint by the police. […]
> During the war Tom maintained over some months an offhand relationship with the wife of a man in combat overseas. When in town he ate at her house, sometimes slept there with her, but was as heedless of her and her feelings as of his parents. She apparently suffered some anxiety when, after making plans and promises to do something special with her, he disappeared and she heard nothing from him until he called her from another city (reversing the charges) to chat casually and sometimes to speak eloquent words of endearment. Sometimes he took precautions to deceive her about his sporadic sex relations with other women; sometimes he forgot or did not bother.[27]

[24] A. Raine, *et al.*, «Reduced Prefrontal and Increased Subcortical Brain Functioning Assessed Using Positron Emission Tomography in Predatory and Affective Murderers», *Behavioral Sciences & the Law*, n. 16 (1998), 3, pp. 319-332.
[25] J.R. Séguin, «Neurocognitive Elements of Antisocial Behavior: Relevance of an Orbitofrontal Cortex Account», *Brain and Cognition*, n. 55 (2004), 1, pp. 185-197.
[26] H.M. Cleckley, *The Mask of Sanity Revised Edition*, fifth edition, Mosby Medical Library, St. Louis, MO 1988.
[27] Ivi, pp. 69 ff.

Recently, Decety and colleagues investigated the ability to feel empathy and emotional concern in a perspective-taking task in psychopaths and healthy volunteers.[28] In this study, volunteers underwent an fMRI scanning while viewing images of wounded body parts. The subjects were asked to assume a perspective focused on themselves or on other people. Specifically, they were requested to imagine being wounded or that another person was injured as depicted in the pictures that were presented to them. While imagining themselves, severe psychopaths showed an increase in neuronal activity in areas of the brain that have been associated to empathy, such as the anterior insula, right amygdala, the anterior cingulate cortex, as well as areas of the inferior prefrontal cortex and in somatosensory regions. Interestingly, this pattern of activation was silent while they imagined others in pain. Furthermore, in severe psychopaths who imagined pain in others, the amygdala and the insula activation were inversely correlated with the level of psychopathy as measured by psychological testing. Finally, the authors found that the level of psychopathy directly correlated with the activation in the striatum. This finding led the authors to suggest that in severe psychopathy the imagination of others in pain may even be a pleasurable experience.

Individuals with the antisocial personality disorder fail to conform to social norms and engage repetitively in behavior that violates others' rights. They may be deceitful to obtain personal advantages. They refuse to take responsibility for their acts and have difficulties to plan in advance and fully commit to work or family obligations. These individuals have no experience of emotions such as shame and guilt, which exert an inhibitory effect on deviant behavior. They are indifferent or they simply rationalize having hurt or mistreated another human being. As a consequence, they endure in behavior that may hurt others' feelings and they lack the ability to develop regret for their actions. Their emotional life is marked by great impulsivity, which partially accounts for their frequent alcohol and substance abuse. These individuals have difficulties in managing frustration, are irritable and become easily aggressive. Finally, individuals with the antisocial personality

[28] J. Decety, *et al.*, «An fMRI Study of Affective Perspective Taking in Individuals with Psychopathy: Imagining Another in Pain does not Evoke Empathy», *Frontiers in Human Neuroscience*, n. 7 (2013), 489, pp. 1-12.

disorder show a complete disregard for the safety of the self or others. There is consistent evidence that psychopaths lack fear-associated responses.[29] The reduced emotional responsiveness of psychopaths to fearful stimuli is also suggested by their reduced startle reflex toward negative stimuli[30, 31]. Furthermore, they lack electrodermal responses during the administration of stimuli that are associated to punishment or that are known to be coupled with aversive items[32, 33]. Consistently with data on peripheral reactivity, brain responsiveness in fear learning paradigms is also reduced in psychopathy. A recent study by Veit and colleagues investigated brain responsiveness in violent criminals, who underwent an aversive learning training based on classical conditioning.[34] Psychopaths, compared with control subjects, showed a reduced activation of the amygdala as they viewed the neutral stimulus that they had learned to precede the administration of the painful one. Deficient fear conditioning mechanisms may thus concur to explain the reckless disregard for the safety of the self and others, as well as their inability to avoid situations that potentially may be harmful.

The extent to which our behavior is conditioned by the anatomical and functional alterations of our brain is well represented by clinical cases in which subjects suddenly engage in very abnormal and deviant behavior. A case of pedophilia, recently described by Burns and Sweldlow,[35] has stirred great interest, as it suggested that sexual deviant behavior may be induced by structural anomalies occurring in areas of the brain that are crucial for the volitional inhibition of impulsive behavior. The man described by the authors, a 40 years old teacher, developed, in a very short time, an

[29] S.C. Herpertz, *et al.*, «Emotion in Criminal Offenders with Psychopathy and Borderline Personality Disorder» *Archives of General Psychiatry*, n. 58 (2001), pp. 737-745.
[30] P.J. Lang, *et al.*, «Emotion and Psychopathology: A Startle Probe Analysis», *Prog Exp Pers Psychopathol Res.*, n. 16 (1993), pp. 163-199.
[31] U. Vaidyanathan, *et al.*, «Startle Reflex Potentiation During Aversive Picture Viewing as an Indicator of Trait Fear», *Psychophysiology*, n. 46 (2009), 1, pp. 75-85.
[32] R. Veit, *et al.*, «Brain Circuits Involved in Emotional Learning in Antisocial Behavior and Social Phobia in Humans», *Neuroscience Letters*, n. 328 (2002), 3, pp. 233-236.
[33] H. Flor, *et al.*, «Aversive Pavlovian Conditioning in Psychopaths: Peripheral and Central Correlates», *Psychophysiology*, n. 39 (2002), 4, pp. 505-518.
[34] R. Veit, *et al.*, «Deficient Fear Conditioning in Psychopathy as a Function of Interpersonal and Affective Disturbances», *Frontiers in Human Neuroscience*, n. 7 (2013), 706, pp. 1-12.
[35] J.M. Burns and R.H. Swerdlow, «Right Orbitofrontal Tumor with Pedophilia Symptom and Constructional Apraxia Sign», *Archives of Neurology*, n. 60 (2003), 3, pp. 437-440.

increasing interest for child pornography. Even though he perceived the inappropriateness of such behavior, «the pleasure principle overrode» and he was not able to restrain himself from collecting massive pornographic material. Finally, he made sexual advances toward his young stepdaughter. His wife sued him and he was found guilty of child harassment, he was put under pharmacological treatment, and he had to enroll in a rehabilitation program for sexual addiction. During the rehabilitation, he could not restrain himself from soliciting sexual favors from other patients, thus exposing himself to the risk of being sent to jail. After the onset of concurrent neurological symptoms he underwent a Magnetic Resonance Imaging (MRI) scan. Physicians found a huge tumor mass located in the orbitofrontal cortex, which extended to the dorsolateral prefrontal cortex. Notably, after tumor resection, all types of deviant sexual behavior disappeared. The patient took part successfully in a rehabilitation program and, as he did not pose further threats to his wife and stepdaughter, he was allowed to go back home. After several months, neurological symptoms appeared again. His activity as a pornography collector had started again and an MRI scan found that the tumor had grown again in the same brain area. As previously, all symptoms vanished after tumor re-resection was carried out.

Neuroimaging advances in visualization methods allow us to investigate subtle anatomical changes in gray matter volume in areas of the brain that are crucial for controlling impulsive aggressive behavior occurring in psychopathy, and to compare them with the brain morphology of healthy volunteers. A recent study by Boccardi and colleagues mapped differences in brain morphology that distinguish violent male offenders from healthy controls. They observed a reduction in gray matter of up to 20% in the orbitofrontal cortex, as well as an increase of around 10-30% of the central and lateral nuclei of the amygdale.[36] This discovery adds an important piece to the understanding of brain anatomy in the antisocial disorder, shedding light on the brain underpinnings of hyperactive emotional responsiveness and poor inhibitory control of aggression.

[36] M. Boccardi, *et al.*, «Cortex and Amygdala Morphology in Psychopathy», *Psychiatry Research*, n. 93 (2011), 2, pp. 85-92.

4. How much is our behavior conditioned by our genes?

Behavioral genetics addresses the role that specific genetic variants may play in predisposing individuals to certain behavioral traits. Thanks to the Human Genome Project we know that human beings possess around 20,000 genes, which codify for about 80,000-100,000 proteins. The number of genes is significantly lower than believed in the past and indicates that each gene may be responsible for the coding of more than one protein. Interestingly, the genome is not identical among all the individuals, but millions of variations have been identified in the DNA sequence. Most of these genetic variants are Single Nucleotide Polymorphisms (SNPs) that are substitutions, deletions or insertions of just one chemical base (A, T, C or G), or Variable Number of Tandem Repeats (VNTRs) that correspond to short sequences repeated a variable number of times. Several of these polymorphic sequences affect the cell phenotype while many others are silent.

How does possessing one or more specific polymorphisms affect the way we behave? A great source of evidence, concerning the genetic influence on behavior, comes from studies on monozygotic twins. Unlike fraternal twins, monozygotic twins are born from the fertilization of the same egg and are genetically identical. Their study allows researchers to isolate the effects of genetics on behavior from those due to the environment. This kind of studies has suggested that the genetic make-up lays the basis for a "neurobiological susceptibility" to aggressive behavior.[37] Genes that codify for neurotransmitters or for molecules connected to them (i.e. enzymes, receptors and transporters), indeed, may mediate the genetic effects on behavior. The serotonin system, for example, plays a very important role in the regulation of emotions, and is affected in the most disabling mood disorders, including major depression.[38] Serotonin enables the behavioral inhibition and, consequently, serotonin-reduced efficiency may result in impulse discontrol. In rodent models,

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[37] L.J. Siever, «Neurobiology of Aggression and Violence», *American Journal of Psychiatry*, n. 165 (2008), 4, pp. 429-42.

[38] K.J. Ressler and C.B. Nemeroff, «Role of Serotonergic and Noradrenergic Systems in the Pathophysiology of Depression and Anxiety Disorders», *Depression and Anxiety*, n. 12 (2000), Suppl. 1, pp. 2-19.

lowering the 5HT signaling produces increased impulsivity and aggression.[39] Studies in humans on the effects of pharmacological therapy with selective serotonin reuptake inhibitors (SSRIs) support the data in animals by showing a reduction in impulsive aggression.[40] Caspi and colleagues studied the effect of possessing a normal functioning (the long version, L) versus a low functioning (the short version, S) allele of a VNTR polymorphism (5HTTLPR) located in the promoter of the 5-HTT gene that codifies for the serotonin transporter. The authors investigated the probability of developing unipolar depression in two groups of individuals who were matched for socio-demographic features but differed for having the L or the S 5HTTLPR allele.[41] They measured the impact of the environment by taking into account the number of traumatic events (e.g. a divorce, the loss of a close relative) that participants had experienced in their life. The authors observed that both groups increased their trend toward depression with the increase of personal traumatic events. However, this trend became significant only for those who possessed the S variant of 5HTTLPR. The study by Caspi and colleagues raised important considerations as far as environmental and genetic influences on behavior are concerned, and partly explains why people differ so much in the way they handle and respond to similar adverse life events. This provide a molecular basis to the great intuition of Freud who in wrote in *Mourning and Melancholia*[42] that psychological processes are grounded on a biological substrate.

Genetic findings have been used in combination with neuroimaging methods to uncover the effect of possessing specific genetic polymorphisms on brain responsiveness to emotionally salient stimuli. A functional Magnetic Resonance Imaging (fMRI) study has shown that individuals with one or two copies of the 5HTTLPR short allele show a higher reactivity of the amygdala in

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[39] S. Chiavegatto, *et al.*, «Brain Serotonin Dysfunction Accounts for Aggression in Male Mice lacking Neuronal Nitric Oxide Synthase», *Proceedings of the National Academy of Sciences of the United States of America*, n. 98 (2001), 3, pp. 1277-1281.

[40] E.F. Coccaro and R.J. Kavoussi, «Fluoxetine and impulsive aggressive behavior in personality-disordered subjects» *Arch Gen Psychiatry*, (1997), 54, pp. 1081-1088.

[41] A. Caspi, *et al.*, «Influence of Life Stress on Depression: Moderation by a Polymorphism in the 5-HTT Gene», *Science*, n. 301 (2003), 5631, pp. 386-389.

[42] S. Freud, «Mourning and Melancholia» [1917], in Id., *The Standard Edition of the Complete Psychological Works of Sigmund Freud*, Volume XIV (1914-1916): *On the History of the Psycho-Analytic Movement, Papers on Metapsychology and Other Works*, Hogarth Press, London 1956–1974, pp. 237-258.

response to fearful stimuli as compared to individuals homozygous for the long variant. It can be hypothesized that an extreme reactivity of the amygdala to social stimuli may trigger aggressive impulsive behavior. Following the one by Caspi and colleagues, several other studies reported an association between the S allele of 5-HTTLPR and impulsive aggression.[43]

Environmental factors also play an important role in determining individual behavior. The most predisposing factors to the development of aggressive behavior include having been the victim of aggression and the witness of acts of violence, especially in childhood.[44, 45, 46] Child mistreatments as well as very punitive and coercive parenting styles are among the factors that may enhance the chances of developing antisocial disorders in adulthood. Factors that might predispose to delinquency in adulthood include growing up in the absence of supportive and caring families, as well as high levels of hostility and maltreatment[47]. Other factors include low socioeconomic status and antisocial peers[48]. The monoamine oxidase A (MAOA) enzyme is involved in the catabolism of neurotransmitters such as norepinefrine, serotonin, and dopamine. Caspi and colleagues studied the effect of possessing a polymorphism that produces an enzyme of reduced efficiency (MAOA Low) in a population of over a thousand individuals.[49] They monitored their behavior for over twenty years. The population sample included children who grew up in violent environments as well as children who grew up in normally caring families. This study showed that, in individuals with a poor and violent background as a child, possessing a low-expression variant of the MAOA enzyme increases the chances of developing antisocial personality in adulthood.

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[43] For a recent review see: C. Iofrida, S. Palumbo, and S. Pellegrini, «Molecular Genetics and Antisocial Behavior: Where do We Stand?» *Experimental Biology and Medicine* (2014) in press.

[44] K. Deater-Deckard, *et al.*, «Multiple Risk Factors in the Development of Externalizing Behavior Problems: Group and Individual Differences», *Development and Psychopathology*, n. 10 (1998), pp. 469-493.

[45] D.M. Fergusson and M.T. Lynskey, «Physical Punishment/Maltreatment During Childhood and Adjustment in Young Adulthood», *Child Abuse & Neglect*, n. 27 (1997), pp. 617-630.

[46] D.M. Fergusson, *et al.*, «Childhood Sexual Abuse and Psychiatric Disorder in Young Adulthood, II: Psychiatric Outcomes of Childhood Sexual Abuse», *Journal of the American Academy of Child and Adolescent Psychiatry*, n. 34 (1996), pp. 1365-1374.

[47] C.A. Smith and S. B. Stern «Delinquency and antisocial behavior: A review of family processes and intervention research», *Social Service Review*, n. 71 (1997), pp. 382–420.

[48] M.W. Lipsey and J.H. Derzon (1998). «Predictors of violent or serious delinquency in adolescence and early adulthood: A synthesis of longitudinal research» In R. Loeber & D. P. Farrington (Eds.), Serious and violent juvenile offenders: Risk factors and successful interventions (pp. 86–105). Thousand Oaks, CA: Sage.

[49] A. Caspi, *et al.*, «Role of Genotype in the Cycle of Violence in Maltreated Children», *Science*, n. 2 (2002), 297(5582), pp. 851-854.

Meyer-Lindenberg and colleagues investigated brain hemodynamic responses in a task of motor inhibition as well as brain anatomy in two groups of volunteers that differed for possessing either a normo-functioning or a hypo-functioning variant of the MAOA enzyme.[50] The authors observed a higher reactivity of the amygdala and a lower response in the prefrontal cortex in subjects with the lower functioning enzyme. In these same subjects they also found anatomical abnormalities in the orbitofrontal cortex, in the amygdala and in the hippocampus.

For the MAOA gene as well, several different authors have confirmed the association with aggressive behavior described firstly by Caspi and colleagues, although others failed to replicate these findings. These conflicting results may be explained by the fact that the environmental contribution, specifically child maltreatment and abuse, is not simple to be evaluated as it has been often assessed by retrospective self-reports that may be characterized by distorted memories.[51] In addition to the 5-HTT and MAOA, other genes have been indicated to have a role in modulating impulsive aggressive behavior, among which the most validated are Catechol-O-methyltransferase (COMT), which is involved in the catabolism of important neurotransmitters (i.e., dopamine, epinephrine, and norepinephrine) and the gene DRD4, which codifies for the dopamine receptor D4.[52, 53]

Hormonal influences on behavior have been also investigated. Sex steroid hormones play an important role not only in modeling physical features during puberty but also in affecting the predisposition to engage in aggressive behavior. Differences in levels of testosterone between males and females seem to account for the higher aggressiveness displayed by men.[54] Other hormones have been investigated as well, such as oxytocin. Oxytocin has been linked to the development of

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[50] A. Meyer-Lindenberg, *et al.*, «Neural Mechanisms of Genetic Risk for Impulsivity and Violence in Humans», *Proceedings of the National Academy of Sciences of the United States of America*, n. 16 (2006), 103, pp. 6269-6274.

[51] For a critical review see: C. Iofrida, S. Palumbo, and S. Pellegrini, «Molecular Genetics and Antisocial Behavior: Where do We Stand?», *Experimental Biology and Medicine*, (2014) in press.

[52] S. Pellegrini, «Il ruolo dei fattori genetici nella modulazione del comportamento: le nuove acquisizione della biologia molecolare genetica», in *Manuale di Neuroscienze Forensi*, Giuffrè editore, Milan 2009, pp. 69-90.

[53] S. Pellegrini and P. Pietrini, «Il comportamento umano tra geni e ambiente: nuove acquisizioni dalla genetica molecolare», *L'esame neuropsicologico dell'adulto*, Giunti O.S. (2013) pp. 25-36.

[54] Y.Z. Yu and J.X. Shi, «Relationship Between Levels of Testosterone and Cortisol in Saliva and Aggressive Behaviors of Adolescents», *Biomedical and Environmental Sciences*, n. 22 (2009), pp. 44-49.

feelings of trust[55] and affiliative behavior[56] as well as to a reduction in amygdala activity in humans.[57] In the animal model, an oxytocin gene knock-out results in extreme aggressive behavior.[58] These data suggest that oxytocin may influence the likelihood of an individual to engage in hostile and aggressive behavior by acting upon his/her levels of mistrust and fear toward the other.

All together these findings bring up the role of multiple influences on volitional behavior, including differences in brain morphological and functional architecture.

5. Concluding remarks: are we really the free agents of our actions?

In this brief overview, we have highlighted the complex interplay between neurobiological and environmental factors in modulating the expression of violent behavior. Finding differences in brain anatomy and function as well as in the genetic profile between criminals and healthy matched controls raises the question as to whether aggressive behavior may be significantly affected by specific neurobiological features. In this case, to what extent may criminal defendants be considered responsible for their actions?

Neuroscientific evidence has recently started to be taken into consideration in psychiatric forensic evaluations as a means to produce an objective and more complete assessment of individuals' ability to exert a volitional control on their own actions. To this respect, Rigoni and colleagues[59] reported a recent case in which multiple neuroscientific investigations were employed in a forensic evaluation. The defendant, J.F., was a young woman accused of smothering her child to death immediately after giving birth to him. J.F. had carried out the labor by alone in the

[55] M. Kosfeld, *et al.*, «Oxytocin Increases Trust in Humans» *Nature*, n. 435 (2005), pp. 673-676.
[56] P.J. Zak, *et al.*, «Oxytocin Increases Generosity in Humans», *PLoS ONE*, n. 2 (2007), pp. e1128.
[57] P. Kirsch, *et al.*, «Oxytocin Modulates Neural Circuitry for Social Cognition and Fear in Humans», *The Journal of Neuroscience*, n. 25 (2005), pp. 11489-11493.
[58] A.K. Ragnauth, *et al.*, «Female Oxytocin Gene-Knockout Mice, in Semi-Natural Environment, Display Exaggerated Aggressive Behavior» *Genes, Brain and Behavior*, n. 4 (2005), pp. 229-239.
[59] D. Rigoni, *et al.*, «How Neuroscience and Behavioral Genetics Improve Psychiatric Assessment: Report on a Violent Murder Case», *Frontiers in Behavioral Neuroscience*, n. 4 (2010), 160, pp. 1-10.

bathroom of her boyfriend's apartment. She denied being able to recover any memory concerning the event for which she was under accusation. The psychiatric and neuropsychological assessments identified a borderline personality disorder with a history of drug and alcohol abuse. Rigoni and colleagues investigated the defendant's brain anatomy with the aim of uncovering anomalies that are known to be associated to pathological impulsivity and deficits in behavioral control. This investigation found a reduction in gray matter volume in the left prefrontal cortex. Moreover, a genetic assessment was carried out. The researchers found five genetic variants that have been consistently linked to impulsive aggressiveness. This cohort of data led support to the psychiatric examination in suggesting that the defendant had a mental disorder that was characterized by high impulsivity, poor impulse control, high sensation-seeking as well as poor ability to understand others' emotional states. Thus, in this case neuroscientific findings were employed to better characterize the level of liability of the defendant. More in general, this approach contributes to reduce uncertainty due to the subjectivity of psychiatric assessments and minimizes the risk of malingering in defendants that may try to fake psychiatric symptoms.[60] Other important areas for the use of cognitive neuroscience in court concern lie detection and autobiographical memory detection. As an instance, the Autobiographical Implicit Association Test has been used to clarify whether traces of autobiographical memories are present in the mind of the respondent[61]. Specifically, researchers use this test to evaluate the veridicity of one among two autobiographical events.

What are the social and legal consequences of using neuroscientific and genetic findings to determine criminal responsibility in court? The notion of free-will is the assumption on which our legal system is based, and plays a central role in the evaluation of criminal responsibility. Consistently, defendants with a psychiatric condition of mental insanity that affects their capacity of discernment are not held responsible for their own actions. Neuroscientific assessments may enable

[60] G. Sartori, S. Pellegrini, and A. Mechelli, «Forensic Neurosciences: From Basic Research to Applications and Pitfalls» *Current Opinion in Neurology* n. 24 (2011), 4 pp. 371-7.
[61] G. Sartori, S. Agosta, C. Zogmaister, S.D. Ferrara, U. Castiello. «How to accurately detect autobiographical events» *Psychol Sci*. n. 19(8) (2008), pp. 772-80.

investigators to elucidate the biological bases that underline subjects' ability to actively and volitionally modulate their own impulsive behavior.[62, 63] This process is crucial to achieve an objective quantification of the individual ability to behave freely and thus establish to which extent s/he may be held criminally responsible for his/her deviant acts. A finer determination of the degree of a defendant's liability is important for justice to be warranted. We are just at the beginning of an amazing scientific journey that will deepen our understanding on the role of multiple biological factors in shaping human behavior. This knowledge may come of use in the future for the implementation of therapeutic rehabilitation programs tailored to each individual's needs and capabilities, greatly benefiting his/her reintegration in society.

[62] S. Pellegrini and P. Pietrini, «Siamo davvero liberi? Il comportamento tra geni e cervello» *Sistemi intelligenti* n. 2 (2010), pp. 281-293.
[63] P. Pietrini and P. S. Pellegrini, «Verso un'etica molecolare» *Giornale italiano di psicologia* n. 4 (2010), pp. 841-846.