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STRUCTURAL AND FUNCTIONAL MRI STUDY IN MENTALLY ILL PERSONS CONSIDERED SOCIALLY DANGEROUS WITH DIMINISHED PENAL RESPONSIBILITY

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ABBREVIATIONS

BOLD: Blood Oxygen Level-Dependent

BPRS: Brief Psychiatric Rating Scale

CG: Control Group

EG: Experimental Group

GM: Grey Matter

MRI: Magnetic Resonance Imaging

NGRI: Not Guilty by Reason of Insanity

REMS: Residences for Execution of Security Measures

ROI: Regions Of Interest

Rs-fMRI: Resting-state functional Magnetic Resonance Imaging

VBM: Voxel Based Morphometry

SUMMARY

The relation between mental illness and criminality is a relevant social issue that has been debated over the years. Socially dangerous actions committed by mentally ill patients often have severe consequences, which is why much public attention is directed toward the prevention of these actions by these individuals. Modern neuroimaging investigations support the joint efforts of psychiatrists and lawyers to study the relationship between psychiatric illness and criminality.

The overall aim of this PhD project was to investigate differences in cortical GM volumes of this population, compared to a control group of healthy non-offender participants, using a VBM analysis of structural MRI. We also decided to investigate brain networks underpinning moral behaviour, salience attribution and reward processes performing a functional MRI at resting-state.

Experimental Group (EG) included 13 right-handed individuals (mean age: 44 ± 7 yrs) who committed violent crimes (homicides, attempted homicides, aggressions, and domestic violence), had a diagnosis included in the psychotic spectrum (schizophrenia, bipolar disorder with psychotic features, schizoaffective disorder, delusional disorders) and were declared socially dangerous by the judicial authority due to a high risk of criminal recidivism.
All subjects of the EG were institutionalized in the REMS psychiatric unit of ASL RM5 (Rome, Italy) for no longer than two years.
Thirteen healthy right-handed men, who had never received a

psychiatric diagnosis, undergone any psychiatric treatment, or been convicted of any crime were included in the control group (CG) (mean age: 38 ± 11yrs).

MRI data were acquired using a 3 Tesla Siemens imaging system (Siemens, Verio, Erlangen, Germany) equipped with a 12-channel head coil. Structural scans of the brain were acquired for each participant using a T1-weighted three dimensionals sagittal magnetization-prepared rapid gradient echo sequence. Resting state functional (rs-fMRI) data were collected while participants lay still and awake, with eyes closed using T2*-weighted gradient-echo echo-planar functional images (EPIs).

In study I we performed a voxel-based morphometry (VBM) analyses on participants' T1-weighted structural images using Computational Anatomy Toolbox (CAT12), which runs within SPM12. We found that total cerebral GM volume was significantly reduced in EG in specific regions within the bilateral insular cortex compared to controls. We also found a reduced GM volume in the superior temporal gyrus (STG) of left hemisphere and in the fusiform gyrus of the right hemisphere. We finally performed a correlation analyses between psychiatric symptoms and regions with reduced GM volume. The clusters in STG and insula of left hemisphere significantly correlated with the gravity of symptoms expressed by the BPRS (Brief Psychiatric Rating Scale).

In study II, temporal correlations of the resting-state BOLD signal time series were examined between nineteen seed regions that we selected "a priori" among those known to be involved in moral judgment salience attribution and reward processes. Analysis was performed using the software CONN v. 18a, running in Matlab.
Our results documented reduced connectivity in limbic regions like the nucleus accumbens and the amiygdala and augmented connectivity within the dorsal striatum, between nucleus accumbens and the posterior cingulate cortex, between fronto-orbitalis cortex and basal ganglia and anterior cingulate cortex and amygdala. We suggest that dysregulation in these areas reflects the maladaptive behavior of socially dangerous subjects in terms of an altered emotional response to their own moral violations and a lack of empathy for others when making personal desire-oriented decisions.

While the small sample size does not allow definitive conclusions to be reached, the present study sheds some light on the neural correlates of this specific population, which deserves further attention due to their theoretical and clinical implications.
A further understanding of the neural basis of risk evaluation in mentally ill persons with a history of violence who are judged not criminally responsible could aid in forensic assessment and treatment development.

SUMMARY IN ITALIAN

La complessa relazione tra malattia mentale e criminalità rappresenta un tema di concreta rilevanza sociale, dibattuto da anni ma sempre di grande attualità.

Secondo il codice penale, è considerato "socialmente pericoloso" il soggetto autore di reato, anche se non imputabile per vizio totale o parziale di mente, che abbia una elevata probabilità di recidiva del reato. Per questo motivo la prevenzione delle azioni socialmente pericolose riveste un ruolo di fondamentale importanza giuridica e sociale. In questo contesto la psichiatria forense si occupa delle questioni che sorgono all'interfaccia tra psichiatria e giurisprudenza, con l'obiettivo principale di evidenziare lo stato di salute mentale dei soggetti che commettono un reato attraverso una perizia psichiatrica.

La disciplina neuroradiologica, grazie anche all'utilizzo di tecniche avanzate di analisi delle immagini, si pone oggi come strumento di valido ausilio nella valutazione clinica dei pazienti psichiatrici e può supportare gli sforzi congiunti di psichiatri e giuristi per studiare la relazione tra malattia mentale e criminalità.

L'obiettivo di questo progetto di dottorato è stato quello di effettuare uno studio volumetrico della sostanza grigia cerebrale attraverso un esame di Risonanza Magnetica (RM) su un gruppo di soggetti autori di reato, considerati non imputabili al momento del fatto per vizio totale o parziale di mente, detenuti nella REMS dell'ASL Rm5 e considerati socialmente pericolosi.

I risultati dell'analisi volumetrica sono stati confrontati con un gruppo di controllo, comparabile per età e sesso. E'stata inoltre effettuata un'analisi della connettività funzionale cerebrale a riposo (resting-state functional MRI) con l'intento di indagare i network cerebrali alla base del comportamento morale, dell'attribuzione della salienza e dei processi di ricompensa, confrontando sempre i risultati con un gruppo di controllo.

Nel gruppo sperimentale sono stati inclusi 13 individui destrorsi (età media: 44 ± 7 anni) detenuti nella REMS dell'ASL Rm5 con disturbo dello spettro psicotico (schizofrenia, disturbo bipolare con caratteristiche psicotiche, disturbo schizo-affettivo, disturbi deliranti), che hanno commesso crimini violenti (omicidi, tentati omicidi, aggressioni e violenze domestiche) e che sono stati dichiarati socialmente pericolosi dall'autorità giudiziaria a causa dell' alto rischio di recidiva criminale.

I dati di RM sono stati acquisiti su un magnete 3 Tesla (Verio, Siemens) dotato di una bobina a 12 canali, utilizzando sequenze volumetriche T13D e sequenze BOLD eco-planari (EPI).

Nello studio I abbiamo eseguito un'analisi della volumetria cerebrale con tecnica VBM (Voxel-based morphometry) utilizzando il Computational Anatomy Toolbox (CAT12) del software Statistical Parametric Mapping (SPM12). Abbiamo riscontrato come il volume della sostanza grigia cerebrale del gruppo sperimentale fosse significativamente ridotto, rispetto ai controlli, a livello della corteccia insulare bilaterale, nel giro temporale superiore (STG) dell'emisfero sinistro e nel giro fusiforme dell'emisfero destro. Abbiamo infine eseguito un'analisi di correlazione tra la gravità dei sintomi psichiatrici e le regioni con volume corticale ridotto. I cluster di volume a livello di STG e insula sinistra sono risultati essere significativamente correlati alla gravità dei sintomi espressa dalla scala di valutazione BPRS (Brief Psychiatric Rating Scale).

Nello studio II abbiamo esaminato la connettività cerebrale a riposo nelle 19 regioni selezionate "a priori" sulla base della letteratura che risultassero coinvolte nella morale, nell' attribuzione della salienza e nei processi di ricompensa. L'analisi è stata effettuata utilizzando il software CONN v. 18a, sulla piattaforma Matlab. Abbiamo documentato una ridotta connettività tra le regioni del sistema limbico, come il nucleo accumbens e l'amigdala, ed aumentata connettività nello striato dorsale, tra il nucleo accumbens e la corteccia cingolata posteriore, tra corteccia fronto-orbitale e gangli della base e tra corteccia cingolata anteriore e amigdala.

Sulla base di questi risultati ipotizziamo che l'alterata connettività in queste specifiche aree possa rappresentare la modificazione del comportamento in senso maladattativo degli individui del gruppo sperimentale, in termini di alterata risposta emotiva circa le proprie violazioni morali o di mancanza di empatia verso gli altri al fine di ottenere vantaggi personali o riguardo al controllo dell'impulsività.

Nonostante la bassa numerosità campionaria non consenta di approdare a conclusioni definitive, questo studio cerca di approfondire i correlati neurali degli individui autori di reato con ridotta responsabilità penale e socialmente pericolosi al fine di fornire un eventuale strumento di ausilio nella valutazione di questa particolare categoria di persone, con importanti risvolti giuridici ed etici oltre che nella pianificazione e nello sviluppo del trattamento di questi pazienti durante la loro permanenza nelle REMS.

BACKGROUND 1

1.1

SOCIAL DANGEROUSNESS IN MENTALLY ILL CRIMINAL OFFENDERS

The relation between mental illness and criminality is a relevant social issue that has been debated over the years. Socially dangerous actions committed by mentally ill patients often have severe consequences, which is why much public attention is directed toward the prevention of these actions by these individuals.

From a criminological perspective, the social dangerousness of a crime is measured by the consequences of the committed action in inflicting significant damage to society or by the real threat of inflicting such damage. In addition to social dangerousness, there is also the criminological concept of a socially dangerous individual, which is a much debated concept because it only refers to the possibility that the individual will commit an offense. When such individuals are mentally healthy, preventive measures involve educational efforts aimed at instilling sensitivity to ethical concerns. To label a mentally healthy person as a “socially dangerous individual” is extremely controversial and would require very specific and convincing evidence. The potential dangerousness of the mental patient when in a psychotic state, however, may be quite real and must be determined by a forensic psychiatrist on the basis of the patient’s clinical and social characteristics. It’s important to emphasize that the social dangerousness of a mental patient must be viewed over time: it’s extremely uncorrect to affirm that mental disease predetermines that a patient will be dangerous to others and to himself. However, a mental disease requires both initial treatment and follow-up observation, with the goal of reducing or eliminating the potential of the patient’s state to pose a danger to society. Shostakovic offer a general definition of the social dangerousness presented by mental patients: it is a mental state in which psychopathologic manifestations determine the patient's behavior, which is inappropriate to the patient's circumstances and may pose a danger to the society or to the patient himself [1].

The social dangerousness of mental patients remains relatively high. As compared to patients with episodic disorders, schizophrenic patients more often commit thefts and violate the public order; assassination attempts account for approximately 5 percent of their dangerous actions. The highest incidence of socially dangerous actions characteristically occurs during the first 4 years of the illness. Clinical experience and data obtained in forensic-psychiatric research give the psychiatrist clues to the understanding of the most dangerous syndromes, periods, and stages during the course of mental disorder. Although the potential social dangerousness of a mental patient may be determined by psychopathologic symptoms, the form that danger takes (even in patients with acute psychosis) is related to the personal attributes of the patient and the influence of the microsocial environment [2–4]. These influences must be taken into account in attempting to predict dangerous actions of the individual mental patient [5]. Statistics support the argument that early identification and treatment is the best way to reduce the risk for violent act in patients with mental illness. The risk that an individual in the general population will commit a homicide is approximately 1 in 25,000. Worldwide risk for homicide in first-episode patients with psychosis is one in 629 presentations, whereas the risk drops to one in 9,090 presentations if the patient receives treatment [6].

The risk of socially dangerous actions of mental patients is variable in nature and consists of the following stages: dangerous state-dangerous behavior-dangerous actions. Each stage is a result of complex interactions between psychopathologic phenomena, environmental stimuli, and personality characteristics of the patient. Certain psychiatric conditions do increase a person's risk of committing a crime. Research suggests that patients with mental illness may be more prone to violence if they do not receive adequate treatment, are actively experiencing delusions, or have long-standing paranoia. Such patients are often under the influence of their psychiatric illness such as command hallucinations. Other comorbidities include conditions such as substance use disorder, unemployment, homelessness, and secondary effects of mental illness such as cognitive impairment, compound the risk of committing a violent crime [1].

The most important and independent risk factor for criminality and violence among individuals with mental illness is a long-term substance use disorder. In patients with a major psychiatric illness, comorbid substance use disorder, there is a four-fold increase in the risk of committing a crime or violence. Studies have shown that the rise in violent crime committed by individuals with mental illness, may entirely be accounted for with a history of alcohol and/or drug use [7,8]. Individuals with a severe mental illness that are non-adherent to treatment are particularly at higher risk of committing grave acts of violence. Untreated profound mental illness is particularly significant in cases of homicide—the zenith of the criminal spectrum, and such illness is even more significant for mass murders of strangers. Still, these cases are a smaller proportion to senseless acts of violence committed by criminals who act out of sheer criminal intent [9].

1.2

ITALIAN LEGAL SYSTEM

Since the 18th century, Italian criminal law has rested on two main pillars. On one hand, imputability (criminal responsibility) is the personal responsibility for a criminal act that justifies the sentence. On the other hand, social dangerousness is the basis for the system of security measures that are imposed on criminal offenders. The sentence has a retributive purpose, whereas security measures are mainly rehabilitative. Even if an offender is not imputable due to insanity, the mentally ill offender can still be considered as socially dangerous under Article 203 of the Italian Penal Code because of the risk of future criminal acts. Consequently, security measures are applied to the socially dangerous offender. Accordingly, the dangerousness judgment is a prediction of an offender's future criminal behavior. The defendant can be evaluated to determine whether or not he is dangerous pre-trial, pre-sentencing, or post-sentencing. The determination of dangerousness justifies the use of measures that can neutralize this risk.

A security measure can be imposed only on persons who commit a crime (Article 202, Italian Penal Code). There are two different kinds of security measures: one for criminal offenders who are convicted and subject to criminal sentencing and one for psychiatric social dangerousness for offenders who are found not guilty by reason of insanity (NGRI). For over a century maximum security forensic security psychiatric hospitals (OPGs) provided the security measures that were used for NGRI offenders. After they were established in 1891 (Royal Decree Number 260), hospitalization in an OPG was the only security measure for NGRI offenders (Articles 219 and 222 of

the Penal Code).
After a long cultural and scientific transformational journey OPGs (as well as civil psychiatric hospitals) have been replaced in 2012 by special communities named REMS (Residences for Execution of Security Measures), distributed in the 20 italian regions. To the extent that these facilities approximate hospitals with appropriate mental health services, not just restraints and enforced medication, together with a well developed, full spectrum of outpatient mental health services, the Italian model may be best able to meet the individual treatment needs, promote a high level of functioning, and minimize risk to the public. Once patients are discharged from REMS, they are treated by public service psychiatrists and/or provided with other public outpatient services such as day hospitals in the community.
The closure of the OPGs created new scientific, cultural, and social opportunities for Italy. The benefits of this transformed mental health system for serving severely disordered forensic patients will accrue from exploiting the regional locations of the REMS. The decentralized, regional locations of these treatment programs should facilitate continuity of care, visits from family and friends, and reintegration back into the patients' respective communities. A concerted effort to ensure that providers are fully trained in methods of risk assessment and that such methods are put to effective use will be important. A graduated strategy of providing the security measures that correspond to the individual patient's risk level and security needs, including stepping down security measures as the

patient is transitioned from institutional to completely ambulatory care in the community, could be a challenge to implement, where each patient is treated in the regional REMS [10].

1.3

LAW AND NEUROSCIENCE

Our criminal justice system is designed to determine if a violation of society's rules occurred and whether that violation warrants a sanction. If so, the justice system assesses the level of responsibility, culpability, and punishment appropriate for individual offenders [11]. One of the central goals of the judicial authority has always been to make society safe by preventing violent behavior. As a result, although violence risk assessment has traditionally not played any role in determinations of guilt, it has played a role at nearly every other stage of the criminal law—from decisions concerning whether to grant bail to decisions concerning whether to grant parole [12].

The risk of social dangerousness in mentally ill patients depends on complex interactions between psychopathologic phenomena, environmental stimuli and personality characteristics [3,13,14].

When exploring the legal role played by violence risk assessment, we must first distinguish clinical assessment from actuarial assessment. Clinical assessment in forensic settings is performed by mental health professionals (usually psychiatrists or psychologists) who would evaluate if the offender was suffering from any mental health or other medical conditions and whether he or she was likely to be dangerous in the future. Traditional assessments used to evaluate future risk of recidivism includes self-reporting measures, interviews, and expert-administered test batteries. These tools seek to assess possible intellectual and cognitive impairment and to measure psychological and neuropsychological constructs, including personality states and traits [12,15]. The mechanical combining of information for classification purposes, and the resultant probability figure which is an empirically determined relative frequency, are the characteristics that define the actuarial or statistical type of prediction [16]. In other words, whereas clinical risk assessment employs "intuitive" and "subjective" methods, actuarial risk assessment employs "mechanistic" and "automatic" methods.

A recent and promising tools is the Classification of Violence Risk (COVR) Software that was developed by Monahan et al. as part of the MacArthur Study of Mental Disorder and Violence [17]. In analyzing the MacRisk data, Monahan and colleagues developed a model of violence risk assessment that was based on an iterative classification tree (ICT) method rather than the more commonly used method of linear regression. One of the key benefits of the ICT approach is that it enables researchers to focus more narrowly on specific sub-classes of risk.

Beside actuarial methods, that remains very controversial, other assessment procedures are useful in judicial decision making and in creating release plans that minimize risk factors (e.g. substance abuse) or accentuate protective factors (e.g. social support, stable employment). Modern neuroimaging investigations support, side by side, the joint efforts of both psychiatrists and lawyers to study the relationship between psychiatric illness and criminality [18–21].

There is a growing belief, especially in US, that neuroscience could become a mainstay of the criminal justice system. Over the past decade, in US the outcomes of hundreds of criminal cases have been influenced by neurobiological data. Over 1585 judicial opinions issued between 2005 and 2012 discuss the use of neurobiological evidence by criminal defendants to bolster their criminal defense. In 2012 alone, over 250 judicial opinions—more than double the number in 2007—cited defendants arguing in some form or another that their 'brains made them do it'. Approximately 5 per cent of all murder trials and 25 per cent of death penalty trials feature criminal defendants making a bid for lower responsibility or lighter punishment using neurobiological data. While these claims often overstate the science, used responsibly neurobiological evidence has the potential to improve the accuracy and decrease errors in the criminal justice system [22].

Some authors suggest that direct measures of brain structure and function could be more accurate and objective than proxy measures in predicting future recidivism. In this perspective two main studies of neuroimaging have focusing their attention on neuroscience and prediction.

The first one by Aharoni et al. in 2013, focused on impulsivity, or behavioral disinhibition, that is one of the strongest and most studied risk factors for recidivism [23].This study collected neuroimaging data from approximately one hundred offenders prior to their release. The experiment studied whether brain activity could predict which offenders would be rearrested after release. Brain activity was measured using fMRI technique as offenders completed a task known to engage inhibitory processes. The task is known as a "Go/No-Go task," and it requires that the participant respond to some stimuli ("Go trials") and withhold a response to other stimuli ("No-Go trials"). The brain regions and circuits involved in impulse control, also referred to as response inhibition, are well documented.The brain regions involved include the basal ganglia, dorsolateral prefrontal cortex, and anterior cingulate cortex (ACC). ACC activity predicted recidivism above and beyond traditional risk assessment measures. Within the four year follow-up period after release, inmates with low ACC activity were four times more likely to be rearrested for a nonviolent crime than inmates with high ACC activity.

The second study, by Kiehl et al. in 2018, examined the relative utility of neuroimaging measures compared to chronological age in the prediction of antisocial behavior [24]. Because age is a very strong predictor of recidivism, it was hypothesized that neural correlates of age derived from structural MRI data could be used in place of chronological age in a prediction model.

Their research question essentially asked: What is a better predictor of recidivism—chronological age, which is more traditionally used in prediction models, or brain age, which is theoretically more sensitive to the biological differences that actually influence our behavior? Brain-age measures outperformed chronological age in calculating how likely an individual was to be reincarcerated. Specifically, reduced gray matter in the anterior temporal lobes, amygdala, and orbital frontal cortex was more helpful in predicting rearrest than was chronological age. The brain areas implicated in this study are not only known to change with age, but they also are reasonable targets for assessing the relationship between antisocial behavior and neural function. The amygdala, for instance, plays an important role in detecting threatening stimuli in our environment as well as in reinforcement learning. Abnormalities in the structure and function of the amygdala have been associated with chronic antisocial behavior and psychopathic personality traits.

The frontal cortex is largely responsible for complex "executive functions" of the brain, such as decision making, planning ahead, and behavioral control. The lower (inferior) portions of the frontal cortex (e.g., the ventromedial prefrontal cortex and the orbitofrontal cortex) are especially important for the prediction of consequences and incorporating learned reinforcement contingencies into ongoing decision making.Dysfunction and abnormal structural properties in these frontal regions likewise have been prominently associated with antisocial behavior, psychopathic traits, and disorders of behavioral control.The anterior temporal cortex has complex functional properties that have been associated with social and emotional cognition, including theory of mind reasoning—i.e., taking someone else's perspective and moral judgment.

Dysfunction and abnormal structure here has been associated with unstable mood and irritability, psychopathic traits, and abnormal moral processing.

Then there is an emerging field of research that focused on behavioral genetics and neuroscience together. Scientific developments increasingly link findings from behavioral genetics to neural correlates. As a result, the emerging scientific inquiry into human behavior is trending toward a neurobiological approach over a purely genetic or neuroscientific one. This integration is reflected in the use of behavioral genetics and neuroscience in the criminal justice system. Legal practitioners take a multifaceted approach to characterizing defendants' behaviors by introducing genetic, neurological, and environmental contributions. Monamine Oxidase A (MAOA), which is in turn partly responsible for the catabolism of serotonin (5-HT) and norepinephrine (NE) is the first gene–environment interaction associated with temperament and antisocial behavior and is a well-studied example. Although MAOA was first characterized as a genetic polymorphism, which together with environmental triggers is associated with behavioral variation in antisocial personality, more recent studies link the genetic and neurological correlates of MAOA. Buckholtz et al. published a study in 2008 utilizing a combined genetic and imaging approach to the study of MAOA, which implicates a neural circuit for variation in human personality under genetic control [25]. Researchers used both VBM and fMRI to explore the relationship between MAOA-L and inhibitory control. They found significant morphological differences in the limbic system (including cingulate gyrus, amygdala, hippocampus) in MAOA-L and a decrease in 8% grey matter volume. Moreover, they found highly significant genotype-related differences in brain functioning. Already, a multifaceted criminal defense using MAOA genotyping and neuroimaging has been introduced into criminal cases. Even assuming differences in scientific methodology and results between behavioral genetics and neuroscience, the substantive legal claims raised are nearly identical when either science is used in a criminal case. As a result in this study sample, anytime behavioral genetics was raised a neuroscientific claim was also advanced.

Bibliography

[1] B.V. Shostakovich, On Social Dangerousness of Mental Patients, Schizophr. Bull. 15 (1989) 555–558. doi:10.1093/schbul/15.4.555.

[2] S.M. Silverstein, J. Del Pozzo, M. Roché, D. Boyle, T. Miskimen, Schizophrenia and violence: realities and recommendations, Crime Psychol. Rev. 1 (2015) 21–42. doi:10.1 080/23744006.2015.1033154.

[3] E.D. Gottfried, S.C. Christopher, Mental Disorders Among Criminal Offenders: A Review of the Literature, J. Correct. Health Care Off. J. Natl. Comm. Correct. Health Care. 23 (2017) 336–346. doi:10.1177/1078345817716180.

[4] B.R. Rund, A review of factors associated with severe violence in schizophrenia, Nord. J. Psychiatry. 72 (2018) 561–571. doi:10.1080/08039488.2018.1497199.

[5] M.J. Hoptman, D. Antonius, Neuroimaging correlates of aggression in schizophrenia: an update, Curr. Opin. Psychiatry. 24 (2011) 100–106. doi:10.1097/YCO.0b013e328342c8e0.

[6] O. Nielssen, M. Large, Rates of Homicide During the First Episode of Psychosis and After Treatment: A Systematic Review and Meta-analysis, Schizophr. Bull. 36 (2010) 702–712. doi:10.1093/schbul/sbn144.

[7] H. Pickard, S. Fazel, Substance abuse as a risk factor for violence in mental illness: some implications for forensic psychiatric practice and clinical ethics, Curr. Opin. Psychiatry. 26 (2013) 349–354. doi:10.1097/YCO.0b013e328361e798.

[8] H.G. Claro, M.A.F. de Oliveira, J.T. Bourdreaux, I.F. de A.L. Fernandes, P.H. Pinho, R.R. Tarifa, Drug use, mental health and problems related to crime and violence: cross-sectional study, Rev. Lat. Am. Enfermagem. 23 (2015) 1173–1180. doi:10.1590/0104-1169.0478.2663.

[9] N. Ghiasi, J. Singh, Psychiatric Illness And Criminality, in: StatPearls, StatPearls Publishing, Treasure Island (FL), 2019. http://www.ncbi.nlm.nih.gov/books/NBK537064/ (accessed August 22, 2019).

[10] F. Carabellese, A.R. Felthous, Closing Italian Forensic Psychiatry Hospitals in Favor of Treating Insanity Acquittees in the Community, Behav. Sci. Law. 34 (2016) 444–459. doi:10.1002/bsl.2234.

[11] L.M. Gaudet, J. Kerkmans, N. Anderson, K. Kiehl, Can Neuroscience Help Predict Future Antisocial Behavior?, Social Science Research Network, Rochester, NY, 2016. https://papers.ssrn.com/abstract=2862083 (accessed April 2, 2019).

[12] T. Nadelhoffer, S. Bibas, S. Grafton, K.A. Kiehl, A. Mansfield, W. Sinnott-Armstrong, M. Gazzaniga, Neuroprediction, Violence, and the Law: Setting the Stage, Neuroethics. 5 (2012) 67–99. doi:10.1007/s12152-010-9095-z.

[13] B.V. Shostakovich, On Social Dangerousness of Mental Patients, Schizophr. Bull. 15 (1989) 555–558. doi:10.1093/schbul/15.4.555.

[14] H. Pickard, Choice, deliberation, violence: Mental capacity and criminal responsibility in personality disorder, Int. J. Law Psychiatry. 40 (2015) 15–24. doi:10.1016/j.ijlp.2015.04.008.

[15] S. Ferracuti, D. Pucci, F. Trobia, M.C. Alessi, C. Rapinesi, G.D. Kotzalidis, A. Del Casale, Evolution of forensic psychiatry in Italy over the past 40 years (1978-2018), Int. J. Law Psychiatry. 62 (2019) 45–49. doi:10.1016/j.ijlp.2018.10.003.

[16] S. Sreenivasan, P. Kirkish, T. Garrick, L.E. Weinberger, A. Phenix, Actuarial risk assessment models: a review of critical issues related to violence and sex-offender recidivism assessments, J. Am. Acad. Psychiatry Law. 28 (2000) 438–448.

[17] J. Monahan, H.J. Steadman, P.C. Robbins, P. Appelbaum, S. Banks, T. Grisso, K. Heilbrun, E.P. Mulvey, L. Roth, E. Silver, An Actuarial Model of Violence Risk Assessment for Persons With Mental Disorders, Psychiatr. Serv. 56 (2005) 810–815. doi:10.1176/appi.ps.56.7.810.

[18] M.A. MD, R.E. MD, S.F. MD, P.F. MD, K.G.-L. MD, S.M.D. PhD, Brain Abnormalities and Violent Behavior, J. Psychol. Hum. Sex. 11 (2000) 57–64. doi:10.1300/J056v11n03_06.

[19] P. Sterzer, C. Stadler, F. Poustka, A. Kleinschmidt, A structural neural deficit in adolescents with conduct disorder and its association with lack of empathy, NeuroImage. 37 (2007) 335–342. doi:10.1016/j.neuroimage.2007.04.043.

[20] C.L. Philippi, M.S. Pujara, J.C. Motzkin, J. Newman, K.A. Kiehl, M. Koenigs, Altered resting-state functional connectivity in cortical networks in psychopathy, J. Neurosci. Off. J. Soc. Neurosci. 35 (2015) 6068–6078. doi:10.1523/JNEUROSCI.5010-14.2015.

[21] T.B. Poeppl, M.R. Donges, A. Mokros, R. Rupprecht, P.T. Fox, A.R. Laird, D. Bzdok, B. Langguth, S.B. Eickhoff, A view behind the mask of sanity: meta-analysis of aberrant brain activity in psychopaths, Mol. Psychiatry. (2018). doi:10.1038/s41380-018-0122-5.

[22] N.A. Farahany, Neuroscience and behavioral genetics in US criminal law: an empirical analysis, J. Law Biosci. 2 (2015) 485–509. doi:10.1093/jlb/lsv059.

[23] E. Aharoni, G.M. Vincent, C.L. Harenski, V.D. Calhoun, W. Sinnott-Armstrong, M.S. Gazzaniga, K.A. Kiehl, Neuroprediction of future rearrest, Proc. Natl. Acad. Sci. U. S. A. 110 (2013) 6223–6228. doi:10.1073/pnas.1219302110.

[24] K.A. Kiehl, N.E. Anderson, E. Aharoni, J.M. Maurer, K.A. Harenski, V. Rao, E.D. Claus, C. Harenski, M. Koenigs, J. Decety, D. Kosson, T.D. Wager, V.D. Calhoun, V.R. Steele, Age of gray matters: Neuroprediction of recidivism, NeuroImage Clin. 19 (2018) 813–823. doi:10.1016/j.nicl.2018.05.036.

[25] J.W. Buckholtz, J.H. Callicott, B. Kolachana, A.R. Hariri, T.E. Goldberg, M. Genderson, M.F. Egan, V.S. Mattay, D.R. Weinberger, A. Meyer-Lindenberg, Genetic variation in MAOA modulates ventromedial prefrontal circuitry mediating individual differences in human personality, Mol. Psychiatry. 13 (2008) 313–324. doi:10.1038/sj.mp.4002020.

METHODS 2

2.1 RESTING-STATE FUNCTIONAL MRI

Throughout the last two decades, fMRI has developed into the most prominent method used for functional brain imaging and it is increasingly used to probe the functional integrity of brain networks. fMRI is a non-invasive technique for examining brain function through the use of blood oxygen level-dependent (BOLD) contrast. This contrast relies on two basic principles:
i) hemoglobin has different properties according to its level of oxygenation (oxyhemoglobin is diamagnetic, while deoxyhemoglobin is paramagnetic);
ii) regional blood oxygenation varies according to the levels of neural activity [1].
These properties can be used to indirectly assess brain activity: the activation of a cortical area causes an increase of oxygenated blood inflow, higher than the strict metabolic consumption. This is indirectly sensed, since the arterial blood accelerates the hemodynamic mean transit time in the district, thus pushing away a portion of de-oxygenated blood in the venous capillaries. As deoxyhemoglobin is paramagnetic, it increases the local microscopic magnetic field inhomogeneity Δ B thus shortening the T2* relaxation time thus accelerating signal fading. In this way, changes in BOLD signal can be used to identify areas of increased or decreased neuronal activity [2] while subjects perform motor, sensory, cognitive or emotion-provoking tasks [3].
FMRI studies can be divided in two approaches: task-induced and task-independent protocols. The initial fMRI studies in humans focused on task-induced responses in the BOLD signal [4]. In

standard task-induced fMRI, an experimental task of interest is presented alternately with a control condition (control task or rest) and the BOLD signal during the experimental task is compared to the BOLD signal during the control condition.

As the difference between baseline and task-related activation accounts for about 1–5% of the total BOLD signal, statistics over repeated activations (either with a block design or event-related design) is necessary in order to provide response images as statistical parametric maps. In doing this, a parametric model linking the BOLD signal of each voxel to the experimental task is required [5]. The mainly adopted model is the general linear model [6]. Regressors are the model inputs (design of the experimental task), which include the expected hemodynamic response (or a set of possible responses, with more sophisticated approaches), and possible confounding factors (registered movements, slow drifts, average signal). A modified version, named event-related, considers events either randomly presented or a-posteriori registered, again compared to baseline.

One of the new trends in functional neuroimaging is studying human brain ongoing activity expressed by structured BOLD fluctuations when subjects are not performing any particular task. This practice is task-independent and is also known as resting state fMRI (rs-fMRI). In rs-fMRI studies, subjects are asked to rest quietly for several minutes while brain images are acquired. Since no external time reference is available as in task induced protocols, detection of significant activity relies only on the mutual dependence of the ongoing activity in different areas. Yet, a strong link with task related activity is recognized and has had a primary role in the discovery and classification of rs networks. In fact, the brain regions similarly modulated (i.e., either activated or inhibited) by stimuli or tasks, rather than being idle during rest, display instead vigorous and persistent functional activity detected as spontaneous low-frequency (<0.1 Hz) BOLD signal fluctuations [7]. Interregional correlations of these fluctuations can be estimated, and these quantitative estimates provide measures of functional connectivity. Functional connectivity is traditionally defined as the temporal dependency between spatially remote neurophysiological events [8]. In the context of functional neuroimaging, functional connectivity is suggested to describe the relationship between the neuronal activation patterns of anatomically separated brain regions, reflecting the level of functional communication between regions [9]. The coherent activity of functionally related brain areas can be captured in BOLD signal during rs-fMRI acquisitions. The first rs-fMRI study was conducted by Biswal and colleagues in 1995 [10], who, correlating the time course of a seed region of interest (ROI) in the motor area with the time course of all other brain voxels, saw that during rest the left and right hemispheric regions of the primary motor network are not silent, but show a high correlation between their fMRI BOLD time series, suggesting ongoing information processing and ongoing functional connectivity between these regions during rest.

Several studies replicated these pioneering results, showing a high level of functional connectivity in other regions. In fact, when fMRI studies started to examine the possibility of measuring functional connectivity between brain regions as the level of co-activation of spontaneous fMRI time series recorded during rest, it was observed that, at rest, the brain is organized into networks, called Resting State Networks (RSNs), consistent across subjects and highly similar to networks of task-induced activations and deactivations [11–13]. They are believed to belong to distinct networks serving different functions such as vision, language, etc. Today the most studied RSNs are: the default mode network (DMN), the sensory motor network (SMN), the right and the left lateral networks, the salience network (SN), the ventral stream network, the task positive network, the primary, the medial and the lateral visual networks and the auditory network.

The FC analysis of the RSNs is currently used to study a wide range of neurological and psychiatric disorders, like Alzheimer's disease, dementia with Lewy bodies, frontotemporal dementia, epilepsy, Parkinson's disease, stroke, depression and schizophrenia among others. It is therefore of crucial importance the development of sensitive and accurate methods for the detection of functional connectivity alterations, to be used as non-invasive biomarkers.

Functional connectivity analysis methods

The lack of an a priori hypothesis about the brain activation (no specific task during acquisition) makes the rs-fMRI data analysis more challenging than the task-based fMRI. Various methods exist for analysing RS-fMRI functional connectivity, among which, the most widely used are: seed-based, model-free methods and network analysis methods.

Seed-based functional connectivity analysis

The first method used for RS-fMRI functional connectivity analyses is called seed-based or voxel-based (seed-based hereafter) technique. Firstly described by Biswal and colleagues (1995), it was subsequently applied in several studies. In seed-based approaches one or more regions of interest (ROIs) are a priori selected to evaluate the similarity (e.g., temporal correlation) of their average time course with each other area or single voxel in the brain. The result is a map of brain voxels significantly correlated with the chosen seed ROI or a quantitative assessment of the strength of correlation within the target ROI. Seed-based correlation has proven to be a powerful, easily interpretable, and effective tool in identifying and characterising the brain areas that show activity during the resting state. However, the networks obtained from seed-based method depend on the way the seed regions are defined. Typically, seeds are chosen based on the location of activity during a task, using anatomical images as a guide, or based on standardized coordinates. However, the anatomical volume of known regions may vary between subjects, in the presence of neurological disease, or with aging, and functional boundaries of brain regions may not be well defined. Hence, using this approach undesired voxels may be included, or functionally relevant voxels may be excluded. Moreover, the seed-based method only evaluates the relationship between the brain and the seed and considers one seed at a time, while, in absence of an a priori hypothesis, it might be more informative to simultaneously detect and characterise various different resting state networks from a single RS-fMRI acquisition.

Independent Component Analysis (ICA)

Data-driven methods, like principal component analysis (PCA) and independent component analysis (ICA) were introduced as functional connectivity analysis methods to look for general connectivity patterns across brain regions. They aim to discover the underlying structure of the data rather than impose an a-priori knowledge on the model, with a blind separation of meaningful sources. In this case, instead of pointing a specific RSN by setting a seed, data analysis proceeds on indirect measurements, which are a mixture of true underlying source signals orthogonal (PCA) or maximally independent (ICA) one to each other. Usually neither the original signals nor the mixing transformation is known and undoing this mixing process is a challenging problem known in the field of signal processing as the blind source separation (BSS) problem. In this framework, ICA has therefore developed over the course of decades as an extension of PCA for investigating solutions to the BSS problem. ICA was introduced as an fMRI analysis method able to use decomposition into spatially independent components in order to distinguish between non-task-related signal components, movements and other artefacts, as well as task-related activations. From clinical experience it was noted that psychomotor functions are performed in localized brain areas that can be inferred from specific deficits in patients. This led to the assumption that brain areas that respond to a psychomotor task are independently distributed from brain areas affected by other sources of variability. This does not require these areas to be completely non-overlapping, but only that other sources of signal change are not distributed in the same way as the task-related areas, i.e. that knowledge about the spatial distribution of one does not provide any information on the spatial distribution of the other.

Network analysis

An alternative to seed-based and model-free analyses is provided by network analyses. In fact, one area of rapidly increasing interest is the mapping of functional networks. Such mapping typically starts by identifying a set of functional "nodes", and then attempts to estimate the set of connections or "edges" between these nodes, based on an analysis of the fMRI time series associated with the nodes. There are many ways to define network nodes from fMRI; nodes are often defined as spatial regions of interest, for example, as obtained from task-fMRI activation or from brain atlases.

2.2

VOXEL-BASED MORPHOMETRY

Morphometry is the study of the size and shape of the brain and its structures. The brain changes as it grows into adulthood, decays with age, and undergoes disease processes. The shape of the brain is highly dependent on genetic factors as well. All these properties have made brain morphometry one of the most studied modalities in brain imaging. In recent years, a whole-brain unbiased objective technique, known as voxel-based morphometry (VBM), has been developed to characterise brain differences in vivo using structural high resolution MRI. The aim of VBM is to identify differences in the local composition of brain tissue, while discounting large scale differences in gross anatomy and position. This is achieved by spatially normalising all the structural images to the same stereotactic space, segmenting the normalised images into gray and white matter, smoothing the gray and white matter images and finally performing a statistical analysis to localize significant differences between two or more experimental groups. The output is a statistical parametric map (SPM) showing regions where gray or white matter differs significantly among the groups [14].

Spatial Normalisation

Spatial normalisation involves registering the individual MRI images to the same template image. An ideal template consists of the average of a large number of MR images that have been registered in the same stereotactic space. In the SPM2 software, spatial normalisation is achieved in two steps. The first step involves estimating the optimum 12- parameter affine transformation that maps the individual MRI images to the template. Here, a Bayesian framework is used to compute the maximum a posteriori estimate of the spatial transformation based on the a priori knowledge of the normal brain size variability. The second step accounts for global nonlinear shape differences, which are modeled by a linear combination of smooth spatial basis functions. This step involves estimating the coefficients of the basis functions that minimize the residual squared difference between the image and the template, while simultaneously maximizing the smoothness of the deformations. The ensuing spatially-normalised images should have a relatively high-resolution (1mm or 1.5mm isotropic voxels), so that the segmentation of gray and white matter (described in the next section) is not excessively confounded by partial volume effects, that arise when voxels contain a mixture of different tissue types. It should be noted that spatial normalisation does not attempt to match every cortical feature exactly, but merely corrects for global brain shape differences. This is because VBM tries to detect differences in the local concentration or volume of gray and white matter having discounted global shape differences. Indeed, if the spatial normalisation was perfectly exact, all the segmented images would appear identical and no significant differences would be detected at a local scale.

Segmentation

The spatially normalised images are then segmented into gray matter, white matter, cerebrospinal fluid and three non- brain partitions. This is generally achieved by combining a priori probability maps or "Bayesian priors", which encode the knowledge of the spatial distribution of different tissues in normal subjects, with a mixture model cluster analysis which identifies voxel intensity distributions of particular tissue types.

The segmentation step also incorporates an image intensity non-uniformity correction to account for smooth intensity variations caused by different positions of cranial structures within the MRI coil. A further possible step after segmentation would be the binarization of the resulting tissue class images. Tissue classification methods typically produce images where each voxel has an a posteriori probability that that voxel should be assigned to a particular tissue type according to the model. These probabilities are values between zero and one. Binarization would involve assigning each voxel to its most probable tissue class.

Smoothing

The segmented gray and white matter images are now smoothed by convolving with an isotropic Gaussian kernel. The size of the smoothing kernel should be comparable to the size of the expected regional differences between the groups of brains, but most studies have employed a 12-mm FWHM kernel.

The motivation for smoothing the images before the statistical analysis is three-fold.

First, smoothing ensures that each voxel in the images contains the average amount of gray or white matter from around the voxel (where the region around the voxel is defined by the smoothing kernel).

Second, the smoothing step has the effect of rendering the data more normally distributed by the central limit theorem, thus increasing the validity of parametric statistical tests.
Third, smoothing helps compensate for the inexact nature of the spatial normalisation. Smoothing also has the effect of reducing the effective number of statistical comparisons, thus making the correction for multiple comparisons less severe.
However it may also reduce the accuracy of localization, as discussed in the last section of this paper.

Statistical Analysis

Following the pre-processing, the final step of a VBM analysis involves a voxel-wise statistical analysis. This employs the general linear model (GLM), a flexible framework that allows a variety of different statistical tests such as group comparisons and correlations with covariates of interest. The standard parametric procedures (t tests and F tests) used are valid providing that the residuals, after fitting the model, are normally distributed. If the statistical model is appropriate, the residuals are most likely to be normally distributed once the segmented images have been smoothed.
The results of these standard parametric procedures are statistical parametric maps [6]. Since a statistical parametric map comprises the results of many voxel-wise statistical tests, it is necessary to correct for multiple comparisons when assessing the significance of an effect in any given voxel. A standard Bonferroni correction for multiple independent comparisons would be inappropriate here, given the smoothing and the fact that gray or white matter

in contiguous voxels is highly correlated. Thus, corrections for multiple dependent comparisons are made using the Theory of Random Fields. It should be noted that the Random Field correction should be based on the local maxima of the t statistic rather than the extent statistic which relates to the size of the clusters. This is because, for a correction based on the extent statistic to be valid, the smoothness of the residuals needs to be spatially invariant throughout the brain. However, this is unlikely to be the case in VBM studies by virtue of the highly non-stationary nature of the underlying neuroanatomy. For example, by chance alone, large size clusters will occur in regions where the images are very smooth and small size clusters will occur in regions where the images are very rough.

Bibliography

[1] S.-G. Kim, S. Ogawa, Biophysical and physiological origins of blood oxygenation level-dependent fMRI signals, J. Cereb. Blood Flow Metab. Off. J. Int. Soc. Cereb. Blood Flow Metab. 32 (2012) 1188–1206. doi:10.1038/jcbfm.2012.23.

[2] N.K. Logothetis, J. Pfeuffer, On the nature of the BOLD fMRI contrast mechanism, Magn. Reson. Imaging. 22 (2004) 1517–1531. doi:10.1016/j.mri.2004.10.018.

[3] A. Drobyshevsky, S.B. Baumann, W. Schneider, A rapid fMRI task battery for mapping of visual, motor, cognitive, and emotional function, NeuroImage. 31 (2006) 732–744. doi:10.1016/j.neuroimage.2005.12.016.

[4] P.A. Bandettini, Twenty years of functional MRI: the science and the stories, NeuroImage. 62 (2012) 575–588. doi:10.1016/j.neuroimage.2012.04.026.

[5] K.E. Stephan, J. Mattout, O. David, K.J. Friston, Models of functional neuroimaging data, Curr. Med. Imaging Rev. 2 (2006) 15–34.

[6] K.J. Friston, A.P. Holmes, K.J. Worsley, J. -p Poline, C.D. Frith, R.S.J. Frackowiak, + Human Brain Mapping 2:189-ZlO(1995) + Statistical Parametric Maps in Functional Imaging: A General Linear Approach, n.d.

[7] R.L. Buckner, J.R. Andrews-Hanna, D.L. Schacter, The brain's default network: anatomy, function, and relevance to disease, Ann. N. Y. Acad. Sci. 1124 (2008) 1–38. doi:10.1196/annals.1440.011.

[8] K.J. Friston, Functional and effective connectivity: a review, Brain Connect. 1 (2011) 13–36. doi:10.1089/brain.2011.0008.

[9] M.P. van den Heuvel, H.E. Hulshoff Pol, Exploring the brain network: a review on resting-state fMRI functional connectivity, Eur. Neuropsychopharmacol. J. Eur. Coll. Neuropsychopharmacol. 20 (2010) 519–534. doi:10.1016/j.euroneuro.2010.03.008.

[10] B. Biswal, F.Z. Yetkin, V.M. Haughton, J.S. Hyde, Functional connectivity in the motor cortex of resting human brain using echo-planar MRI, Magn. Reson. Med. 34 (1995) 537–541. doi:10.1002/mrm.1910340409.

[11] C.F. Beckmann, M. DeLuca, J.T. Devlin, S.M. Smith, Investigations into resting-state connectivity using independent component analysis, Philos. Trans. R. Soc. Lond. B. Biol. Sci. 360 (2005) 1001–1013. doi:10.1098/rstb.2005.1634.

[12] J.S. Damoiseaux, S. a. R.B. Rombouts, F. Barkhof, P. Scheltens, C.J. Stam, S.M. Smith, C.F. Beckmann, Consistent resting-state networks across healthy subjects, Proc. Natl. Acad. Sci. U. S. A. 103 (2006) 13848–13853. doi:10.1073/pnas.0601417103.

[13] M. De Luca, C.F. Beckmann, N. De Stefano, P.M. Matthews, S.M. Smith, fMRI resting state networks define distinct modes of long-distance interactions in the human brain, NeuroImage. 29 (2006) 1359–1367. doi:10.1016/j.neuroimage.2005.08.035.

[14] A. Mechelli, C. Price, K. Friston, J. Ashburner, Voxel-Based Morphometry of the Human Brain: Methods and Applications, Curr. Med. Imaging Rev. 1 (2005) 105–113. doi:10.2174/1573405054038726.

AIM AND HYPOTESIS 3

- *The aim of study I was to investigate differences in GM volumes in a population of mentally ill persons detained in REMS (Experimental Group : EG), compared to a control group of healthy non-offender participants, using a VBM analysis of structural MRI. We also aimed to assess the effects of clinical characteristics on brain morphometry performing a correlation analysis between psychiatric severity of EG and regions with reduced GM volume.*
- *The aim of study II was to investigate brain networks underpinning moral behaviour, salience attribution and reward processes performing a functional MRI at resting-state in the same experimental group of mentally ill persons detained in REMS mentioned above, compared to a control group of healthy non-offender participants.*

We hypothesised, as descripted in the two studies that:

I. GM volume of EG will differ from healthy control, particulary in brain regions subserving emotions, empathy and self-regulation (study I).

II. The severity of psychiatric symptoms could be correlated to the reduced GM volume (study I).

III. Aberrant connectivity of EG in brain network subserving moral behaviour, salience attribution and reward processing will reflects the maladaptive behavior of socially dangerous subjects in terms of an altered emotional response to their own moral violations and a lack of empathy for others when making personal desire-oriented decisions (study II).

STUDY I 4

Abnormal brain structure in mentally ill persons with diminished penal responsibility considered socially dangerous

Introduction

The relation between mental illness and criminality is a relevant social issue that has been debated over the years. In Italy, when an offender is judged to be insane, he/she may be sanctioned by two different articles of the Italian Penal Code: 1) Art. 88 (total infirmity of mind, implying total mitigation of criminal responsibility) or 2) Art. 89 (partial infirmity of mind, i.e. partial mitigation of criminal responsibility, with judging ability "greatly diminished"). The judge, based on expert opinion, may declare a person to be socially dangerous if there is a high probability of crime recidivism. More specifically, a person is socially dangerous, irrespective of criminal responsibility, when he/she has committed a crime (Art. 49 and 115 of the Italian Penal Code [IPC]) and it is probable that he/she will commit new acts that the law classifies as crimes (IPC Art. 203, Italy, 2017a, 2017b). If the estimated degree of social dangerousness is high, an internment in special residences for the execution of security measures (REMS) can be established by the judicial authority, according to Italian law 81/2014 (GU n.125, 31 March 2014) [1,2].

The risk of social dangerousness in mentally ill patients depends on complex interactions between psychopathologic phenomena, environmental stimuli, and personality characteristics[3–5]. Modern neuroimaging investigations support the joint efforts of psychiatrists and lawyers to study the relationship between psychiatric illness and criminality. Interestingly, previous morphometric studies have shown a reduction in grey matter (GM) volume in persistent violent offenders in the brain regions subserving emotional regulation, reactive aggression, and empathy, namely the frontopolar cortex, orbitofrontal cortex, insular cortex, and amygdala [6–10]. Other research has identified structural abnormalities in the hippocampus and posterior insula [11] and orbitofrontal cortex and striatus [12] in individuals accused of homicide.

The aim of our study was to investigate differences in cortical GM volume between a population of mentally ill persons detained in a REMS psychiatric unit who had performed a violent act, been judged not criminally responsible because of their mental illness, and been declared socially dangerous, and a control group of healthy non-offender participants using voxel-based morphometry (VBM) analysis of structural magnetic resonance imaging (MRI). Our secondary aim was to assess the relation between psychiatric symptom severity and regions with reduced GM volume.

Methods and Materials

Participants

The experimental group (EG) included 13 right-handed individuals (mean age: 44 ± 7 yrs) who committed violent crimes (homicides, attempted homicides, aggressions, and domestic violence), had a diagnosis included in the psychotic spectrum (schizophrenia, bipolar disorder with psychotic features, schizoaffective disorder, delusional disorders) and were declared socially dangerous by the judicial authority due to a high risk of criminal recidivism.

All subjects of the EG were institutionalized in the REMS psychiatric unit of ASL RM5 (Rome, Italy) for no longer than two years.

Thirteen healthy right-handed men, who had never received a psychiatric diagnosis, undergone any psychiatric treatment, or been convicted of any crime were included in the control group (CG) (mean age: 38 ± 11yrs). None of the participants had contraindications to performing an MRI scan. All participants gave written informed consent after receiving a complete description of the study, which was approved by the ethics committee of Sapienza University of Rome (727/18, CE n.5155). Participants in the EG underwent a neurocognitive and psychiatric evaluation. All performed within the normal range on the Mini-Mental State Examination (MMSE), confirming the absence of global cognitive functioning deficits (mean 28; SD 1.4). Psychiatric symptoms were assessed with the Brief Psychiatric Rating Scale (BPRS), where patient values ranged between 35 and 75 (mean 61; SD 9.9). A psychiatrist also assessed psychopathy severity using the Psychopathy Checklist-Revised (PCL-R) and values ranged between 8 and 32 (mean 17.1; SD 15.9).

Imaging acquisition and analysis

A Siemens Magnetom Verio 3-Tesla scanner was used to acquire all images. Structural scans of the brain were acquired for each participant using a T1-weighted three dimensional sagittal magnetization-prepared rapid gradient echo sequence with the following parameters: 176 slices, repetition time: 1900 ms, echo time: 2.93 ms, slice thickness: 1 mm, and an in-plane resolution of 0.508 × 0.508 mm. We performed voxel-based morphometry (VBM) analyses on participant T1-weighted structural images using Computational Anatomy Toolbox (CAT12), which runs within SPM12 (www.fil.ion.ucl.ac.uk). The T1 anatomical images were manually checked for scanner artefacts and gross anatomical abnormalities. The images were then normalized using high-dimensional Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL) normalization and segmented into grey matter (GM), white matter (WM), and cerebrospinal fluid (CSF).

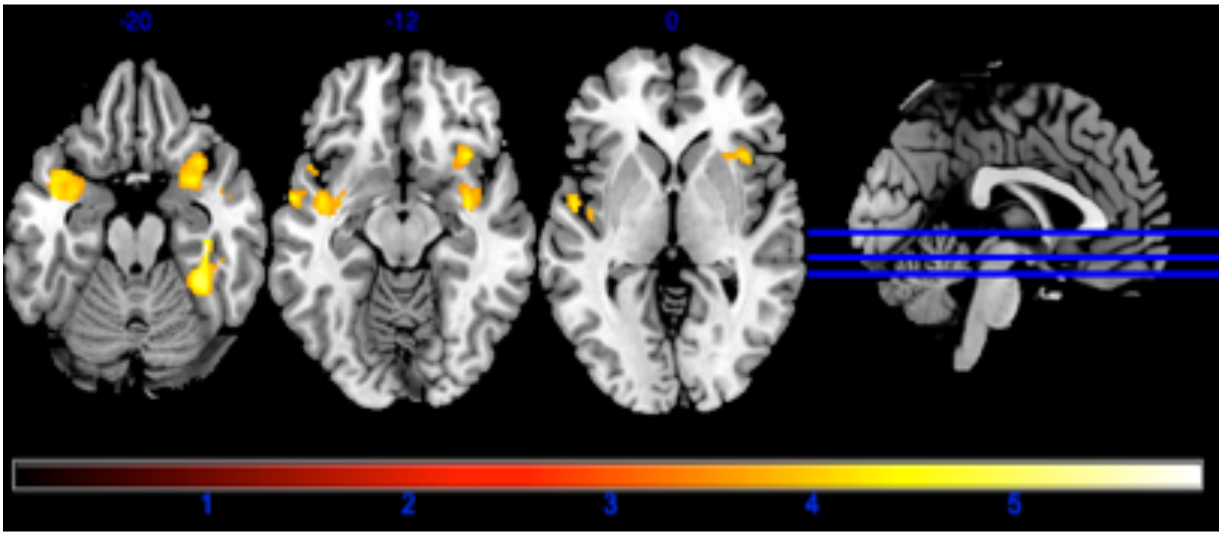
Segmented GM images were checked for quality and smoothed using an 8-mm full-width half-maximum (FWHM) kernel.

Total intracranial volume (TIV) was estimated for each participant and used as a covariate in the second-level statistical test.

The statistical parametrical maps resulting from group comparisons were thresholded at $p < 0.05$ and corrected for multiple comparisons at the cluster level using family-wise error (FWE) after forming clusters of adjacent voxels surviving a threshold of $p < 0.001$ uncorrected. The association between clinical data and average regional volume in brain areas showing a significant decrease in volume in the EG was assessed by calculating Pearson correlation coefficients.

Results

All participants completed the study. Regarding structural differences between the two groups, the total cerebral GM volume was significantly reduced in the EG in specific regions, as compared with controls (**Fig. 1**).



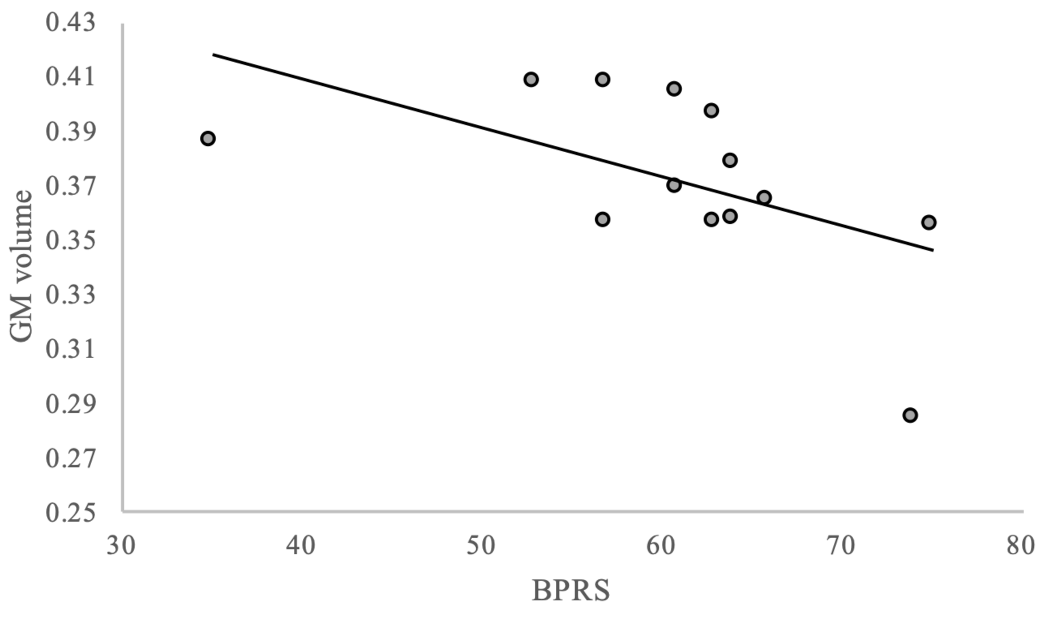
[Fig.1] The red-to-yellow patches show, on axial slices, the t statistics of the comparisons between grey matter volume of EG and CG for $p < 0.05$, corrected for multiple comparisons at the cluster level using false discovery rate and uncorrected peak $p < 0.001$.

In particular, we found distinct clusters of reduced GM volume within the bilateral insular cortex in the EG. We also found reduced GM volume in the superior temporal gyrus (STG) of the left hemisphere and in the fusiform gyrus of the right hemisphere (**Table 1**).

REGION	HEMISPHERE	CLUSTER P (fdr-corr)	VOLUME (K)	T	PEAK P (unc)	x	y	z
Fusiform Gyrus	R	0.018	1164	5.9	0	38	-26	-21
				5.11	0	34	-40	-18
				4.91	0	48	-26	-24
Insula	R	0.018	1203	4.94	0	34	20	-6
				4.48	0	32	6	-20
				4.47	0	36	-4	-12
STG	L	0.01	1609	4.63	0	-51	-6	3
				4.53	0	-58	-2	-12
				4.47	0	-42	8	-18

[Tab. 1] The table lists the regions showing brain regions with reduced GM volume in EG, the hemisphere, the T-score (p FDR-corrected < 0.05), the region volume (voxels), the peak p value and the MNI coordinates.

To further assess the effects of EG clinical characteristics on brain morphometry, we also performed a correlation analysis between psychiatric symptoms and regions with reduced GM volume.
The clusters in the STG and insula of the left hemisphere significantly correlated with symptom severity as measured by the BPRS ($r = -0.542$; $p = 0.028$) (**Fig. 2**). No other significant associations were detected.



[Fig. 2] Scatter plot depicting the correlation between BPRS score and GM volume in the EG.

Discussion

Using high resolution structural MRI and VBM analyses, we identified regional GM volume differences between a population of mentally ill persons considered socially dangerous and detained in a REMS psychiatric unit who had performed a violent act and had been judged not criminally responsible because of their mental illness, and a control group of healthy non-offender participants. In these regions we also detected a variation of GM volume as a function of psychiatric symptom severity.

The most interesting result of our study was the widespread volumetric reduction in brain areas of the EG implicated in empathy, emotional awareness, and regulation, namely the bilateral insula. The insular cortex is a critical site where bodily sensations, autonomic control, and afferents from brain regions implicated in emotional processing converge [13,14]. The insula represents the brain hub where incoming external sensory information is integrated with the internal physiological response related to emotional state [15,16]. Early theories of emotions emphasized the link between interoception and emotions by arguing that emotions are evoked by the perceptions of physical responses of the body and cannot exist without the experience of bodily feelings [13].

A striking example of a deficit in sensory-emotional integration is that of pain asymbolia, in which patients suffering from an insular lesion can recognize pain, but lack an appropriate emotional response and do not attribute a negative valence to this usually adverse experience [17]. Recent findings have demonstrated that the right insula contributes to emotional feeling states originating in representations of visceral arousal [18]. Differential roles of the right and left insula in representing sympathetic and parasympathetic nervous system activity have been proposed by Craig et al. in a homeostatic neuroanatomical model of emotional asymmetry [19]. The bilateral insular finding in our study may thus reflect the involvement of both sympathetic and parasympathetic representations in the experience of empathy and emotional regulation in the EG.

As mentioned previously, the insular cortex is a key node of the salience network (SN), together with the dorsal anterior cingulate cortex, and plays an integrative role in coordinating awareness of bodily feelings, contextual social clues, and emotional salient stimuli [13,20,21]. Saliency detection can be conceptualized into two general mechanisms. The first is a fast, automatic, bottom-up 'primitive' mechanism for filtering stimuli based on their perceptual features; the second is a higher-order system for focusing the 'spotlight of attention' and enhancing access to resources needed for goal-directed behavior [22]. The misattribution of salience to external and internal stimuli in individuals with mental illness is a core feature of the disorder and may explain the genesis of psychotic symptoms [23]. Indeed, salience dysfunction has been linked to violence, aggression, psychopathy, criminal behavior, and recidivism [24,25].

The insular cortex has also been associated with the integration of sensory phenomena and mediates temporally defined auditory/ visual interaction at an early stage of cortical processing [26,27].

The reduced GM volume in auditory areas like the STG or the fusiform gyrus (implicated in facial recognition and the identification of facial expressions [28]) supports the notion that multiple brain regions other than the insula may contribute to a disrupted empathic response in the EG. Volumetric alterations in the insula, fusiform gyrus, and STG may be related to a profound lack of empathy and to a propensity for aggressive and violent behavior.

The STG is a site of multisensory integration[29]. It is implicated in spoken word recognition and in visual analysis of social information conveyed by gaze and body movement [30,31].

A progressive GM reduction in the STG has been found to precede the first expression of florid psychosis [32]. Here we found a significant correlation between GM volume reduction in clusters spanning from the STG to the insula in the left hemisphere and psychotic symptom severity, as scored by the BPRS.

These findings are in line with previous VBM studies that have demonstrated that high-risk subjects who later developed psychosis exhibited progressive GM reduction in left temporal lobe regions, particularly the STG. Volume reduction in these regions has been found to correlate with auditory hallucinations or thought disorders [33,34]. Changes in insular and STG morphometry and the consistent correlation between GM volume and psychotic symptom severity in the EG suggest that the left insula and the STG contributed to psychotic symptom manifestation in this group through their significant interaction. However, it remains to be determined whether these morphometric changes are a cause or consequence of social dangerousness.

Conclusion

The relation between psychiatric illness and criminality represents a relevant social issue and a topic of intense debate involving psychiatrists, lawyers, and neuroscientists. Improved technology has made high-quality neuroimaging data more accessible and exploitable for scientific research and in clinical practice and it is widely accepted that neuroscience variables can be used to improve existing behavioral prediction methods in the evaluation of recidivism. Our findings should serve as a starting point for future research exploring the neural correlations of pathological social behavior in mentally ill persons who committed violent crimes and should add predictive information for the purposes of understanding and assessing the risk of recidivism in these individuals.

Bibliography

[1] S. Ferracuti, D. Pucci, F. Trobia, M.C. Alessi, C. Rapinesi, G.D. Kotzalidis, A. Del Casale, Evolution of forensic psychiatry in Italy over the past 40 years (1978-2018), Int. J. Law Psychiatry. 62 (2019) 45–49. doi:10.1016/j.ijlp.2018.10.003.

[2] F. Carabellese, A.R. Felthous, Closing Italian Forensic Psychiatry Hospitals in Favor of Treating Insanity Acquittees in the Community, Behav. Sci. Law. 34 (2016) 444–459. doi:10.1002/bsl.2234

[3] E.D. Gottfried, S.C. Christopher, Mental Disorders Among Criminal Offenders: A Review of the Literature, J. Correct. Health Care Off. J. Natl. Comm. Correct. Health Care. 23 (2017) 336–346. doi:10.1177/1078345817716180.

[4] B.V. Shostakovich, On Social Dangerousness of Mental Patients, Schizophr. Bull. 15 (1989) 555–558. doi:10.1093/schbul/15.4.555.

[5] H. Pickard, Choice, deliberation, violence: Mental capacity and criminal responsibility in personality disorder, Int. J. Law Psychiatry. 40 (2015) 15–24. doi:10.1016/j.ijlp.2015.04.008.

[6] J. Tiihonen, R. Rossi, M.P. Laakso, S. Hodgins, C. Testa, J. Perez, E. Repo-Tiihonen, O. Vaurio, H. Soininen, H.J. Aronen, M. Könönen, P.M. Thompson, G.B. Frisoni, Brain anatomy of persistent violent offenders: more rather than less, Psychiatry Res. 163 (2008) 201–212. doi:10.1016/j.pscychresns.2007.08.012.

[7] S. Gregory, D. ffytche, A. Simmons, V. Kumari, M. Howard, S. Hodgins, N. Blackwood, The antisocial brain: psychopathy matters, Arch. Gen. Psychiatry. 69 (2012) 962–972. doi:10.1001/archgenpsychiatry.2012.222.

[8] M.D. Cohn, L.E. Pape, L. Schmaal, W. van den Brink, G. van Wingen, R.R.J.M. Vermeiren, T.A.H. Doreleijers, D.J. Veltman, A. Popma, Differential relations between juvenile psychopathic traits and resting state network connectivity, Hum. Brain Mapp. 36 (2015) 2396–2405. doi:10.1002/hbm.22779.

[9] P. Sterzer, C. Stadler, F. Poustka, A. Kleinschmidt, A structural neural deficit in adolescents with conduct disorder and its association with lack of empathy, NeuroImage. 37 (2007) 335–342. doi:10.1016/j.neuroimage.2007.04.043.

[10] K. Bertsch, M. Grothe, K. Prehn, K. Vohs, C. Berger, K. Hauenstein, P. Keiper, G. Domes, S. Teipel, S.C. Herpertz, Brain volumes differ between diagnostic groups of violent criminal offenders, Eur. Arch. Psychiatry Clin. Neurosci. 263 (2013) 593–606. doi:10.1007/s00406-013-0391-6.

[11] L.M. Cope, E. Ermer, L.M. Gaudet, V.R. Steele, A.L. Eckhardt, M.R. Arbabshirani, M.F. Caldwell, V.D. Calhoun, K.A. Kiehl, Abnormal brain structure in youth who commit homicide, NeuroImage Clin. 4 (2014) 800–807. doi:10.1016/j.nicl.2014.05.002.

[12] B.Y.H. Lam, Y. Yang, R.A. Schug, C. Han, J. Liu, T.M.C. Lee, Psychopathy Moderates the Relationship between Orbitofrontal and Striatal Alterations and Violence: The Investigation of Individuals Accused of Homicide, Front. Hum. Neurosci. 11 (2017). doi:10.3389/fnhum.2017.00579.

[13] N. Gogolla, The insular cortex, Curr. Biol. 27 (2017) R580–R586. doi:10.1016/j.cub.2017.05.010.

[14] A.D.B. Craig, How do you feel--now? The anterior insula and human awareness, Nat. Rev. Neurosci. 10 (2009) 59–70. doi:10.1038/nrn2555.

[15] C. Chiarello, D. Vazquez, A. Felton, C.M. Leonard, Structural Asymmetry of Anterior Insula: Behavioral Correlates and Individual Differences, Brain Lang. 126 (2013) 109–122. doi:10.1016/j.bandl.2013.03.005.

[16] T. Singer, B. Seymour, J. O'Doherty, H. Kaube, R.J. Dolan, C.D. Frith, Empathy for pain involves the affective but not sensory components of pain, Science. 303 (2004) 1157–1162. doi:10.1126/science.1093535.

[17] M. Berthier, S. Starkstein, R. Leiguarda, Asymbolia for pain: a sensory-limbic disconnection syndrome, Ann. Neurol. 24 (1988) 41–49. doi:10.1002/ana.410240109.

[18] H.D. Critchley, S. Wiens, P. Rotshtein, A. Ohman, R.J. Dolan, Neural systems supporting interoceptive awareness, Nat. Neurosci. 7 (2004) 189–195. doi:10.1038/nn1176.

[19] A.D. (Bud) Craig, Forebrain emotional asymmetry: a neuroanatomical basis?, Trends Cogn. Sci. 9 (2005) 566–571. doi:10.1016/j.tics.2005.10.005.

[20] R. Limongi, A. Tomio, A. Ibanez, Dynamical predictions of insular hubs for social cognition and their application to stroke, Front. Behav. Neurosci. 8 (2014). doi:10.3389/fnbeh.2014.00380.

[21] V. Menon, L.Q. Uddin, Saliency, switching, attention and control: a network model of insula function, Brain Struct. Funct. 214 (2010) 655–667. doi:10.1007/s00429-010-0262-0.

[22] E.I. Knudsen, Fundamental Components of Attention, Annu. Rev. Neurosci. 30 (2007) 57–78. doi:10.1146/annurev.neuro.30.051606.094256.

[23] R.H. Morley, P.B. Jantz, R. Graham, The Salience Network structures as a mediator of violence and perceptions of hostility, Neuropsychol. Trends. (2019) 7–20. doi:10.7358/neur-2019-025-morl.

[24] E. Aharoni, G.M. Vincent, C.L. Harenski, V.D. Calhoun, W. Sinnott-Armstrong, M.S. Gazzaniga, K.A. Kiehl, Neuroprediction of future rearrest, Proc. Natl. Acad. Sci. U. S. A. 110 (2013) 6223–6228. doi:10.1073/pnas.1219302110.

[25] C.L. Philippi, M.S. Pujara, J.C. Motzkin, J. Newman, K.A. Kiehl, M. Koenigs, Altered resting-state functional connectivity in cortical networks in psychopathy, J. Neurosci. Off. J. Soc. Neurosci. 35 (2015) 6068–6078. doi:10.1523/JNEUROSCI.5010-14.2015.

[26] K.O. Bushara, J. Grafman, M. Hallett, Neural correlates of auditory-visual stimulus onset asynchrony detection, J. Neurosci. Off. J. Soc. Neurosci. 21 (2001) 300–304.

[27] G.A. Calvert, P.C. Hansen, S.D. Iversen, M.J. Brammer, Detection of audio-visual integration sites in humans by application of electrophysiological criteria to the BOLD effect, NeuroImage. 14 (2001) 427–438. doi:10.1006/nimg.2001.0812.

[28] J.V. Haxby, M.I. Gobbini, M.L. Furey, A. Ishai, J.L. Schouten, P. Pietrini, Distributed and overlapping representations of faces and objects in ventral temporal cortex, Science. 293 (2001) 2425–2430. doi:10.1126/science.1063736.

[29] H.-O. Karnath, New insights into the functions of the superior temporal cortex, Nat. Rev. Neurosci. 2 (2001) 568–576. doi:10.1038/35086057.

[30] T. Allison, A. Puce, G. McCarthy, Social perception from visual cues: role of the STS region, Trends Cogn. Sci. 4 (2000) 267–278. doi:10.1016/S1364-6613(00)01501-1.

[31] K.A. Pelphrey, J.P. Morris, G. McCarthy, Neural basis of eye gaze processing deficits in autism, Brain J. Neurol. 128 (2005) 1038–1048. doi:10.1093/brain/awh404.

[32] T. Takahashi, S.J. Wood, A.R. Yung, B. Soulsby, P.D. McGorry, M. Suzuki, Y. Kawasaki, L.J. Phillips, D. Velakoulis, C. Pantelis, Progressive Gray Matter Reduction of the Superior Temporal Gyrus During Transition to Psychosis,

Arch. Gen. Psychiatry. 66 (2009) 366–376. doi:10.1001 archgenpsychiatry.2009.12.

[33] C. Pantelis, D. Velakoulis, P.D. McGorry, S.J. Wood, J. Suckling, L.J. Phillips, A.R. Yung, E.T. Bullmore, W. Brewer, B. Soulsby, P. Desmond, P.K. McGuire, Neuroanatomical abnormalities before and after onset of psychosis: a cross-sectional and longitudinal MRI comparison, Lancet Lond. Engl. 361 (2003) 281–288. doi:10.1016/S0140-6736(03)12323-9.

[34] D.E. Job, H.C. Whalley, E.C. Johnstone, S.M. Lawrie, Grey matter changes over time in high risk subjects developing schizophrenia, NeuroImage. 25 (2005) 1023–1030. doi:10.1016/j.neuroimage.2005.01.006.

STUDY II 5

Resting state fMRI study in mentally ill persons with diminished penal responsibility considered socially dangerous

Introduction

Criminal responsibility is the personal responsibility for a criminal act that justifies the sentence. Most legal systems have some provisions for mentally ill persons who commit crimes. In Italy, if a person is considered not guilty by reason of insanity and forensic evaluation reveals a high risk of recidivism, and thus social dangerousness, a security measure is enacted by the judicial authority that may involve an internment in special residences for the execution of security measures (REMS), in accordance with Italian law 81/2014 (GU n.125, 31 March 2014). Although laws for an insanity defense vary across countries, it is widely accepted that a serious mental impairment may eliminate or diminish criminal responsibility [1–5]. In these situations, the crime is considered an expression of the mental illness.

There is a growing interest in understanding the cerebral organization of severely mentally ill persons who commit crimes [6]. Abnormal behavior is the product of a complex process primed by genes and environmental factors, which is ultimately controlled by specific brain mechanisms [7]. In general, this population seems to have significant difficulties in terms of social behavior, which often guides them to maladaptive decision making [8–12]. Social behavior is inevitably associated with salience attribution and reward processing [13], which are elaborated in the anterior insular and anterior cingulate cortices, the amygdala, and the ventral striatum. Social behavior is also intimately connected with morality, which is defined as the customs and values that guide social conduct. Morality involves a highly complex neural circuitry that includes a large functional network comprised of several brain structures that control different behavioral processes [14]. In normal functioning, moral behavior is associated with a well-defined brain network that includes the ventromedial prefrontal cortex, anterior and posterior cingulate cortices, precuneus, orbitofrontal cortex, insula, amygdala, supramarginal gyrus, inferior parietal lobule, and superior and middle temporal gyri [15].

Interestingly, previous functional neuroimaging studies have shown a dysfunctional connectivity in these networks in violent offenders [9,16–21]. As regards neuropsychiatric disorders, studies using resting state functional magnetic resonance imaging (MRI) have documented changes in cerebral functional connectivity or activity in a variety of mental illnesses [20,22]. Although preliminary results have been fairly consistent in some disorders (i.e. Alzheimer's disease), they were less reproducible in others, like schizophrenia [21].

To the best of our knowledge no study has assessed functional connectivity in the brain network involved in morality and related processes in criminal offenders with a serious mental impairment, diminished penal responsibility, and a social dangerousness measure. In our exploratory/pilot study we decided to investigate the brain networks underpinning moral behavior, salience attribution, and reward processing by analyzing resting state functional MRI (rs-fMRI) results from a population of mentally ill subjects who had performed a violent act, been judged not criminally responsible due to their mental illness, and been declared socially dangerous. All were institutionalized in a REMS psychiatric unit. The rs-fMRI results of these subjects were compared with healthy age and gender-matched participants who did not have a criminal history or a history of neurological/psychiatric disorders.

Based on previous studies we predicted that criminal offenders would show aberrant connectivity patterns in the brain network devoted to moral behavior, salience attribution, and reward processing, which would in turn sustain maladaptive behavior in these individuals.

Methods and Materials

Participants

The experimental group (EG) of this exploratory observational study included 13 right-handed individuals (mean age: 44 ± 7 yrs) who committed violent crimes (homicides, attempted homicides, aggressions, and domestic violence), had a diagnosis included in the psychotic spectrum (schizophrenia, bipolar disorder with psychotic features, schizoaffective disorder, delusional disorders), and were declared socially dangerous by the judicial authority due to a high risk of criminal recidivism. All subjects of the EG were institutionalized in the REMS psychiatric unit of ASL RM5 (Rome, Italy) for no longer than two years. Thirteen healthy right-handed men who had never received a psychiatric diagnosis, undergone any psychiatric treatment, or been convicted of a crime were included in the control group (CG) (mean age: 38 ± 11 yrs). None of the participants had contraindications to performing the MRI scan. All participants gave written informed consent after receiving a complete description of the study, which was approved by the ethics committee of Sapienza University of Rome (727/18, CE n.5155). Participants in the EG underwent a neurocognitive and psychiatric evaluation.

All patients performed within the normal range on the Mini-Mental State Examination (MMSE), confirming the absence of global cognitive functioning deficits (mean 28; SD 1.4). Psychiatric symptoms were assessed with the Brief Psychiatric Rating Scale (BPRS) (range 35-75; mean 61; SD 9.9). A psychiatrist also assessed psychopathy severity using the Psychopathy Checklist-Revised (PCL-R) and values ranged between 8 and 32 (mean 17.1; SD 15.9).

Functional imaging: acquisition and analysis

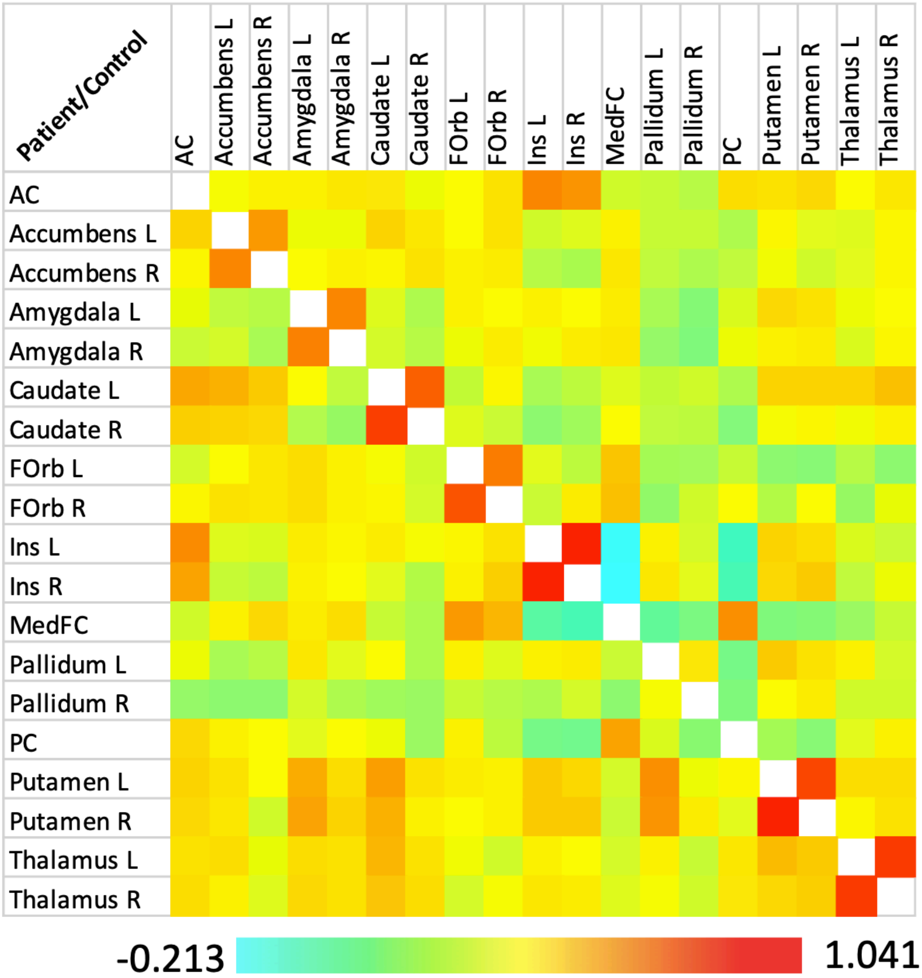
MRI data were acquired using a 3 Tesla Siemens imaging system (Siemens, Verio, Erlangen, Germany) equipped with a 12-channel head coil. The rs-fMRI data were collected while participants lay still and awake with their eyes closed. T2*-weighted gradient-echo echo-planar functional images (EPIs) were acquired with the following parameters: TR = 3000 ms, TE = 31 ms, flip angle = 80°, FOV = 260x260 mm, FOV phase 100 matrix = 86 × 86, slice thickness

= 1 mm, no gap, voxel size = 3.0 mm × 3.0 mm × 3.0 mm. The resting state sequence lasted 10.11 min (200 volumes). A high-resolution T1-weighted structural image was acquired with the following parameters: TR = 1900, TE = 2.93 ms, flip angle = 9°, FOV = 260 × 260 mm, matrix = 251 × 256, slice thickness = 1.00 mm, no gap, voxel size = 1.0 mm × 1.0 mm × 1.0 mm.

The rs-fMRI data were preprocessed using CONN v. 18a, running in Matlab. The first four volumes of each scan were discarded to allow for T1 equilibration. Data were then preprocessed using the standard pipeline: T1-weighted anatomical volumes for each subject were segmented into grey matter (GM), white matter (WM), and cerebrospinal fluid (CSF) and normalized to Montreal Neurological Institute (MNI) space. The time courses of WM and CSF blood oxygen level-dependent (BOLD) signals were then removed from the fMRI data through linear regression, along with a linear trend and the six motion parameters (i.e. rotations and shifts along the three orthogonal main axes, as derived from the previous rigid body coregistration procedure). In addition, a band-pass filter (0.008–0.09 Hz) was applied. Resulting fMRI volumes were realigned, slice timing corrected, coregistered to the high-resolution T1-weighted image, normalized to the MNI EPI template, and spatially smoothed with an 8 mm full-width at half-maximum (FWHM) Gaussian kernel. Temporal correlations of the resting state BOLD signal time series were examined between the nineteen theoretically motivated seed regions, namely those involved in moral behavior, reward processing, and salience attribution. Specifically, we included the insular cortex (IC), frontal medial cortex (medFC), posterior division of the cingulate gyrus (PCC), anterior division of the cingulate gyrus (ACC), frontal orbital cortex (FOrb), thalamus, caudate, putamen, amygdala (Amy), and nucleus accumbens (NAcc) bilaterally. Seed regions were derived from the Automated Anatomical Labeling (AAL) toolbox implemented in CONN. Differences between the EG and CG were tested for each relevant seed-to-seed combination using two sample t-tests on Fisher transformed correlation coefficients.

Results

As compared to the CG, the EG showed a significantly greater functional connectivity between the left FOrb and left putamen (t_{24}= 3.272; p=0.003), left FOrb and left pallidum (t_{24}=3.000; p=0.006), left pallidum and left Amy (t_{24}= 3.481; p=0.001), PCC and left NAcc (t_{24}=2.558; p=0.017), left caudate and left putamen (t_{24}= 2.471; p=0.020), and right putamen and left pallidum (t_{24}=3.009; p=0.019). In the EG we also found increased functional connectivity between the left and right putamen (t_{24}=2.314; p=0.029) as compared with the CG. Furthermore, we also found higher functional connectivity between the ACC and caudate of both hemispheres in the EG (right: t_{24}=2.161, p=0.040; left: t_{24}=2.432, p=0.022). In the right hemisphere of the CG, we observed augmented connectivity between the NAcc and Amy (t_{24}= 2.278; p=0.031) as compared to the EG. Results are summarized in Fig. 1.



[Fig. 1] Correlation matrix. Fisher transformed correlation coefficients are plotted in light blue-to-red patches for each seed-to-seed combination. Matrix elements below the main diagonal represent EG subjects; elements above the main diagonal represent CG subjects.

Discussion

The present research uses rs-fMRI to investigate differences in the brain networks underpinning moral behavior, salience attribution, and reward processing between a population of severely mentally ill persons with a history of violent crime who were declared socially dangerous and institutionalised in a REMS psychiatric unit and healthy age and gender-matched controls.

The EG displayed aberrant connectivity of the NAcc with brain regions linked to reward processing and emotionality. In particular, the EG showed reduced connectivity between the NAcc and Amy in the right hemisphere, but increased connectivity between the NAcc and PCC in the left hemisphere. The NAcc is the major component of the ventral striatum and represents a key structure in the reward system, which identifies the purpose of actions and reinforces motivation for reward-seeking behavior [23]. It is also the functional interface between the limbic and motor systems where it plays a fundamental role in controlling the biological drives necessary for survival and reproduction due to its limbic afferents in brain regions like the amygdala and output to the mesencephalon and basal ganglia [24]. Our findings are consistent with previous findings in psychiatric and personality disorders that suggest that reduced connectivity between the Amy and NAcc is associated with aberrant behavior [25,26]. More specifically, our results support the idea that the downregulation of limbic inputs in the Amy/NAcc connection reflects the maladaptive behavior of socially dangerous subjects in terms of an altered emotional response to their own moral violations [27] and a lack of empathy for others when making personal desire-oriented decisions [16].

Conversely, the increased connectivity between the NAcc and PCC that we found in the EG may represent an interesting interconnection between the reward system and the default mode network (DMN). The PCC plays a pivotal role in retrieving autobiographical memories and planning for the future [22,23]. The PCC has also been hypothesized to play a direct role in regulating the focus of attention, potentially controlling the balance between internal and external control [30–32]. Previous neuroimaging studies have demonstrated that PCC hyperactivity may contribute to thought disturbances in schizophrenia and can predict the risk for illness [27,28]. It known that PCC activity varies with arousal state, and its interactions with other brain networks like the reward system may influence conscious awareness and behavior.

Another interesting finding of our research implicates the role of the dorsal striatum (caudate and putamen), which we found to be hyperconnected in the left hemisphere of EG subjects, as compared with those in the CG. It has long been recognized that the dorsal striatum is involved in programming behavior on the basis of interoceptive or internally generated input, particularly when the available actions are bound to rewarding outcomes [35]. A previous study on monkeys [36] showed that enhanced activation in the caudate nucleus influenced the internal control of ongoing behavior, rather than that triggered by their partners (external control). The dorsal and ventral striatum play opposite roles in the organization of social behavior.

The dorsal striatum is involved in the cognitive control system, which controls the set of brain processes necessary for goal-directed thought and action, whereas the ventral striatum is part of the emotional system that also includes structures like the FOrb and Amy [37]. The emotional system is involved in the immediate response to potential rewards, impulsivity, and emotional control. When the balance between the dorsal and ventral striatum tends towards the former, the locus of control becomes more internal, leading individuals to self-focusing. Thus, these individuals are less prone to respond to inputs from other people or from society (social obliviousness). Social obliviousness may express itself in different ways, including an inability to understand communication and social meaning (autistic-like) or a high tendency to socially manipulate or act at the expense of social partners (psychopathy-like). The latter case is consistent with the description of proactive aggression, a label used in aggression-related psychiatric research that denotes aggression characterized by planning and premeditation and a lack of anger that is motivated by the desire to achieve a specific goal, or acquired instrumental behavior that is controlled by an anticipated reward [37].

In the EG we also observed a significantly augmented connectivity of the FOrb cortex with the putamen and pallidum in the left hemisphere. The FOrb cortex is a key node in sensory integration, modulation of autonomic reactions, and participation in learning, prediction, and decision making for emotional and reward-related behaviors [38]. The FOrb and ACC cortices have been implicated in decision making since 1848, when the classic case of Phineas Gage [33,34] was described. The recent convergence of neuroimaging, neuropsychology, and neurophysiology findings indicates that the human FOrb cortex is an important node for emotional processing and hedonic experience [38]. It has been associated with the representation of reward and punishment and subserves aspects of moral behavior [17] such as guilt, regret, and empathy [41–43]. Here, we found that the FOrb was more connected with basal ganglia in the EG, suggesting that this node is crucial for signalling information when it has to be integrated to predict future outcomes or anticipate reward through instrumental and self-focused behavior [44].

Finally, we found increased connectivity within the basal ganglia, between the left pallidum/left Amy, and between the ACC/caudate bilaterally in the EG. All of these areas are pivotal for moral behavior and impulse control. In particular, the ACC is thought to play a central role in the error-monitoring circuit, where it receives error-related information from the basal ganglia and frontal cortex to motor areas [41]. The ACC is normally also closely connected with the Amy, which displayed a higher connectivity in the EG in relation to the pallidum. These findings relate emotional processing with the reward system and salience attribution through a complex network that may be hyperactivated in psychiatric criminals [47]. Consistent with this interpretation, a task-based study conducted by da Cunha-

Bang et al. revealed high neural reactivity to provocations within the Amy and striatum in violent offenders [19].

ACC activity may also be an important marker to predict recidivism beyond traditional clinical measures of risk assessment, as demonstrated by Aharoni et al. with a go/no-go (GNG) impulse control task that helped predict future recidivism in criminal offenders [46].

Conclusions

In this study we found that mentally ill persons who were considered socially dangerous and institutionalized in a REMS psychiatric unit displayed greater functional connectivity in subcortical networks, especially in brain areas related to morality, reward processing, and impulse control. We suggest that dysregulation in these areas drives maladaptive decision making, antisocial behaviors, and possible criminal recidivism in offenders with a documented history of mental illness. While the small sample size does not allow definitive conclusions to be reached, the present study sheds some light on the neural correlates of this specific population, which deserve further attention due to their theoretical and clinical implications.

A further understanding of the neural basis of risk evaluation in mentally ill persons with a history of violence who are judged not criminally responsible could aid in forensic assessment and treatment development.

Bibliography

[1] F. Carabellese, A.R. Felthous, Closing Italian Forensic Psychiatry Hospitals in Favor of Treating Insanity Acquittees in the Community, Behav. Sci. Law. 34 (2016) 444–459. doi:10.1002/bsl.2234.

[2] H. Pickard, Choice, deliberation, violence: Mental capacity and criminal responsibility in personality disorder, Int. J. Law Psychiatry. 40 (2015) 15–24. doi:10.1016/j.ijlp.2015.04.008.

[3] B.V. Shostakovich, On Social Dangerousness of Mental Patients, Schizophr. Bull. 15 (1989) 555–558. doi:10.1093/schbul/15.4.555.

[4] S.J. Morse, Diminished Rationality, Diminished Responsibility, Ohio State J. Crim. Law. 1 (2003) 289.

[5] H. Häfner, W. Boker, H. Immich, C. Kohler, Crimes of Violence by Mentally Abnormal Offenders: A Psychiatric and Epidemiological Study in the Federal German Republic, Cambridge University Press, 2011.

[6] S. Ferracuti, D. Pucci, F. Trobia, M.C. Alessi, C. Rapinesi, G.D. Kotzalidis, A. Del Casale, Evolution of forensic psychiatry in Italy over the past 40 years (1978-2018), Int. J. Law Psychiatry. 62 (2019) 45–49. doi:10.1016/j.ijlp.2018.10.003.

[7] M. Fumagalli, A. Priori, Functional and clinical neuroanatomy of morality, Brain J. Neurol. 135 (2012) 2006–2021. doi:10.1093/brain/awr334.

[8] J.W. Buckholtz, Social norms, self-control, and the value of antisocial behavior, Curr. Opin. Behav. Sci. 3 (2015) 122–129. doi:10.1016/j.cobeha.2015.03.004.

[9] J. Meijers, J.M. Harte, F.A. Jonker, G. Meynen, Prison brain? Executive dysfunction in prisoners, Front. Psychol. 6 (2015). doi:10.3389/fpsyg.2015.00043.

[10] C. Kisa, S.G. Yildirim, E. Göka, [Impulsivity and mental disorders], Turk Psikiyatri Derg. Turk. J. Psychiatry. 16 (2005) 46–54.

[11] E. Hollander, J. Rosen, Impulsivity, J. Psychopharmacol. Oxf. Engl. 14 (2000) S39-44. doi:10.1177/02698811000142S106.

[12] J. Rojahn, L.J. Meier, Epidemiology of Mental Illness and Maladaptive Behavior in Intellectual Disabilities, in: Int. Rev. Res. Ment. Retard., Elsevier, 2009: pp. 239–287. doi:10.1016/S0074-7750(08)38009-4.

[13] S.N.L. Schmidt, S.C. Fenske, P. Kirsch, D. Mier, Nucleus accumbens activation is linked to salience in social decision making, Eur. Arch. Psychiatry Clin. Neurosci. (2018). doi:10.1007/s00406-018-0947-6.

[14] J. Pujol, I. Batalla, O. Contreras-Rodríguez, B.J. Harrison, V. Pera, R. Hernández-Ribas, E. Real, L. Bosa, C. Soriano-Mas, J. Deus, M. López-Solà, J. Pifarré, J.M. Menchón, N. Cardoner, Breakdown in the brain network subserving moral judgment in criminal psychopathy, Soc. Cogn. Affect. Neurosci. 7 (2012) 917–923. doi:10.1093/scan/nsr075.

[15] M. Boccia, C. Dacquino, L. Piccardi, P. Cordellieri, C. Guariglia, F. Ferlazzo, S. Ferracuti, A.M. Giannini, Neural foundation of human moral reasoning: an ALE meta-analysis about the role of personal perspective, Brain Imaging Behav. 11 (2017) 278–292. doi:10.1007/s11682-016-9505-x.

[16] J.D. Greene, R.B. Sommerville, L.E. Nystrom, J.M. Darley, J.D. Cohen, An fMRI investigation of emotional engagement in moral judgment, Science. 293 (2001) 2105–2108. doi:10.1126/science.1062872.

[17] J. Greene, J. Haidt, How (and where) does moral judgment work?, Trends Cogn. Sci. 6 (2002) 517–523.

[18] N. Birbaumer, R. Veit, M. Lotze, M. Erb, C. Hermann, W. Grodd, H. Flor, Deficient fear conditioning in psychopathy: a functional magnetic resonance imaging study, Arch. Gen. Psychiatry. 62 (2005) 799–805. doi:10.1001/archpsyc.62.7.799.

[19] S. da Cunha-Bang, P.M. Fisher, L.V. Hjordt, E. Perfalk, A. Persson Skibsted, C. Bock, A. Ohlhues Baandrup, M. Deen, C. Thomsen, D.M. Sestoft, G.M. Knudsen, Violent offenders respond to provocations with high amygdala and striatal reactivity, Soc. Cogn. Affect. Neurosci. 12 (2017) 802–810. doi:10.1093/scan/nsx006.

[20] C.L. Harenski, V.D. Calhoun, J.R. Bustillo, B.W. Haas, J. Decety, K.A. Harenski, M.F. Caldwell, G.J. Van Rybroek, M. Koenigs, D.M. Thornton, K.A. Kiehl, Functional connectivity during affective mentalizing in criminal offenders with psychotic disorders: Associations with clinical symptoms, Psychiatry Res. Neuroimaging. 271 (2018) 91–99. doi:10.1016/j.pscychresns.2017.11.003.

[21] M. Greicius, Resting-state functional connectivity in neuropsychiatric disorders, Curr. Opin. Neurol. 21 (2008) 424–430. doi:10.1097/WCO.0b013e328306f2c5.

[22] G.D. Pearlson, Applications of Resting State Functional MR Imaging to Neuropsychiatric Diseases, Neuroimaging Clin. N. Am. 27 (2017) 709–723. doi:10.1016/j.nic.2017.06.005.

[23] S. Salgado, M.G. Kaplitt, The Nucleus Accumbens: A Comprehensive Review, Stereotact. Funct. Neurosurg. 93 (2015) 75–93. doi:10.1159/000368279.

[24] T.W. Robbins, J.W. Dalley, Dissecting Impulsivity: Brain Mechanisms and Neuropsychiatric Implications, in: J.R. Stevens (Ed.), Impuls. Time Risk Influ. Decis. Mak., Springer International Publishing, Cham, 2017: pp. 201–226. doi:10.1007/978-3-319-51721-6_7.

[25] Grace AA (2000) Gating of information flow within the limbic system and the pathophysiology of schizophrenia. Brain Res Brain Res Rev 31: 330 –341 [26]

[26] R. Ito, M. Canseliet, Amphetamine Exposure Selectively Enhances Hippocampus-Dependent Spatial Learning and Attenuates Amygdala-Dependent Cue Learning, Neuropsychopharmacology. 35 (2010) 1440. doi:10.1038/npp.2010.14.

[27] S. Berthoz, J. Grèzes, J.L. Armony, R.E. Passingham, R.J. Dolan, Affective response to one's own moral violations, NeuroImage. 31 (2006) 945–950. doi:10.1016/j.neuroimage.2005.12.039.

[28] D.R. Addis, A.T. Wong, D.L. Schacter, Remembering the past and imagining the future: common and distinct neural substrates during event construction and elaboration, Neuropsychologia. 45 (2007) 1363–1377. doi:10.1016/j.neuropsychologia.2006.10.016.

[29] M.F. Mason, M.I. Norton, J.D. Van Horn, D.M. Wegner, S.T. Grafton, C.N. Macrae, Wandering minds: the default network and stimulus-independent thought, Science. 315 (2007) 393–395. doi:10.1126/science.1131295.

[30] R. Leech, D.J. Sharp, The role of the posterior cingulate cortex in cognition and disease, Brain. 137 (2014) 12–32. doi:10.1093/brain/awt162.

[31] J.M. Pearson, B.Y. Hayden, S. Raghavachari, M.L. Platt, Neurons in posterior cingulate cortex signal exploratory decisions in a dynamic multioption choice task, Curr. Biol. CB. 19 (2009) 1532–1537. doi:10.1016/j.cub.2009.07.048.

[32] J.M. Pearson, S.R. Heilbronner, D.L. Barack, B.Y. Hayden, M.L. Platt, Posterior cingulate cortex: adapting behavior to a changing world, Trends Cogn. Sci. 15 (2011) 143–151. doi:10.1016/j.tics.2011.02.002.

[33] S. Whitfield-Gabrieli, J.M. Ford, Default mode network activity and connectivity in psychopathology, Annu. Rev. Clin. Psychol. 8 (2012) 49–76. doi:10.1146/annurev-clinpsy-032511-143049.

[34] S. Whitfield-Gabrieli, H.W. Thermenos, S. Milanovic, M.T. Tsuang, S.V. Faraone, R.W. McCarley, M.E. Shenton, A.I. Green, A. Nieto-Castanon, P. LaViolette, J. Wojcik, J.D.E. Gabrieli, L.J. Seidman, Hyperactivity and hyperconnectivity of the default network in schizophrenia and in first-degree relatives of persons with schizophrenia, Proc. Natl. Acad. Sci. U. S. A. 106 (2009) 1279–1284. doi:10.1073/pnas.0809141106.

[35] B. Kim, H.-I. Im, The role of the dorsal striatum in choice impulsivity, Ann. N. Y. Acad. Sci. (2018). doi:10.1111/nyas.13961.

[36] J.H. Van den Bercken, A.R. Cools, Evidence for a role of the caudate nucleus in the sequential organization of behavior, Behav. Brain Res. 4 (1982) 319–327.

[37] R. van den Bos, The dorsal striatum and ventral striatum play different roles in the programming of social behaviour: a tribute to Lex Cools, Behav. Pharmacol. 26 (2015) 6–17. doi:10.1097/FBP.0000000000000110.

[38] M.L. Kringelbach, The human orbitofrontal cortex: linking reward to hedonic experience, Nat. Rev. Neurosci. 6 (2005) 691–702. doi:10.1038/nrn1747.

[39] Damasio AR., Descartes' error: emotion, rationality and the human brain., n.d.

[40] J.D. Van Horn, A. Irimia, C.M. Torgerson, M.C. Chambers, R. Kikinis, A.W. Toga, Mapping Connectivity Damage in the Case of Phineas Gage, PLoS ONE. 7 (2012). doi:10.1371/journal.pone.0037454.

[41] N. Camille, G. Coricelli, J. Sallet, P. Pradat-Diehl, J.-R. Duhamel, A. Sirigu, The involvement of the orbitofrontal cortex in the experience of regret, Science. 304 (2004) 1167–1170. doi:10.1126/science.1094550.

[42] B.A. Völlm, A.N.W. Taylor, P. Richardson, R. Corcoran, J. Stirling, S. McKie, J.F.W. Deakin, R. Elliott, Neuronal correlates of theory of mind and empathy: a functional magnetic resonance imaging study in a nonverbal task, NeuroImage. 29 (2006) 90–98. doi:10.1016/j.neuroimage.2005.07.022.

[43] L. Pascual, P. Rodrigues, D. Gallardo-Pujol, How does morality work in the brain? A functional and structural perspective of moral behavior, Front. Integr. Neurosci. 7 (2013) 65. doi:10.3389/fnint.2013.00065.

[44] G. Schoenbaum, G.R. Esber, How do you (estimate you will) like them apples? Integration as a defining trait of orbitofrontal function, Curr. Opin. Neurobiol. 20 (2010) 205–211. doi:10.1016/j.conb.2010.01.009.

[45] C. Orr, R. Hester, Error-related anterior cingulate cortex activity and the prediction of conscious error awareness, Front. Hum. Neurosci. 6 (2012). doi:10.3389/fnhum.2012.00177.

[46] E. Aharoni, G.M. Vincent, C.L. Harenski, V.D. Calhoun, W. Sinnott-Armstrong, M.S. Gazzaniga, K.A. Kiehl, Neuroprediction of future rearrest, Proc. Natl. Acad. Sci. U. S. A. 110 (2013) 6223–6228. doi:10.1073/pnas.1219302110.

[47] J.G. Hosking, E.K. Kastman, H.M. Dorfman, G.R. Samanez-Larkin, A. Baskin-Sommers, K.A. Kiehl, J.P. Newman, J.W. Buckholtz, Disrupted Prefrontal Regulation of Striatal Subjective Value Signals in Psychopathy, Neuron. 95 (2017) 221-231.e4. doi:10.1016/j.neuron.2017.06.030.

DISCUSSION AND CONCLUSION 6

Discussion

The relationship between mental illness and criminality is a topic of public attention that has been debated over the years and is still of current interest. Our criminal justice system is designed to determine if a violation of society's rules occurred and whether that violation warrants a sanction. If so, the justice system assesses the level of responsibility, culpability, and punishment appropriate for individual offenders [1].

In Italy, when an offender is judged to be insane, he/she may be sanctioned by two different articles of the Italian Penal Code: 1) Art. 88 (total infirmity of mind, implying total mitigation of criminal responsibility) or 2) Art. 89 (partial infirmity of mind, i.e., partial mitigation of criminal responsibility, with judging ability "greatly diminished"). If the judge, based on the expert's opinion, ensures a current condition of social dangerousness, defined as a probability of crime recidivism, the person is declared "socially dangerous." More specifically, a person is socially dangerous – even if not responsible or not punishable for criminal acts – when he/she has committed a crime (Articles 49 and 115 of the Italian Penal Code [IPC]) and it is probable that he/she can commit new acts that the law classifies as crimes (IPC Article 203, Italy, 2017a, 2017b). If the estimated degree of social dangerousness is high, an internment in special communities named REMS can be established by the judicial authority, according to the Italian law 81/2014 (GU n.125, 31 March 2014)[2].

Clinical assessment in forensic settings is performed by mental health professionals (usually psychiatrists or psychologists) who would evaluate if the offender was suffering from any mental health or other medical conditions and whether he or she was likely to be dangerous in the future. Traditional assessments used to evaluate future risk of recidivism includes self-reporting measures, interviews, and expert-administered test batteries. These tools seek to assess possible intellectual and cognitive impairment and to measure psychological and neuropsychological constructs, including personality states and traits [3,4].

There is a growing belief, especially in US, that neuroscience could become a mainstay of the criminal justice system. Some authors suggest that direct measures of brain structure and function using MRI techniques could be more accurate and objective than proxy measures in predicting future recidivism [5–7]. A common critique of neuroimaging-based predictions is that they are designed to predict membership in a group rather than predict the outcome associated with a single individual, but this is true of any type of prediction instrument that is based on group statistics. The ability to compare individual neuroimaging datasets to large normative databases (of healthy control subjects) allow for statistically based statements about one individual's data being within or outside of normal limits. However, it is reasonable to recognize the utility in continuing to collect neuroimaging data in forensic populations to fully explore how measures of brain structure and function relate to complex behaviors and to improve tools we use to both measure behavior and evaluate risk. This is all done in pursuit of the goal of making better decisions—not perfect decisions, simply the most informed decisions possible—using attainable information [1].

In light of these observations, we decided to get more informations from neuroimaging techniques investigating a criminal population of mentally ill patients detained in the psychiatric unit of a REMS in Italy, who had performed a violent act, had been evaluated non responsible because of their mental illness and were considered socially dangerous.

The overall aim of this PhD project was to investigate differences in cortical GM volumes of this population, compared to a control group of healthy non-offender participants, using a VBM analysis of structural MRI. We also decided to investigate brain networks underpinning moral behaviour, salience attribution and reward processes performing a functional MRI at resting-state.

In line with previous structural studies we observed the widespread volumetric reduction in brain areas of EG implicated in empathy, emotions awareness and regulation, namely the bilateral insula. The insular cortex is a critical site where bodily sensations, autonomic control and afferents from brain regions implicated in emotion processing, converge [8,9]. The insula represents, indeed, the brain hub where incoming external sensory information are integrated with the internal physiological response related to emotional state [10,11]. Early theories of emotions emphasize the link between interoception and emotions by arguing that emotions are evoked by the perceptions of physical responses of the body and cannot exist without the experience of bodily feelings [8]. A striking example of deficits in sensory-emotion integration is that of 'pain asymbolia', in which patients suffering from an insular lesion can recognize pain, but lack an appropriate emotional response and do not attribute a negative valence to this usually adverse experience [12]. Recent findings pointed out that the right insula contributes to emotional feeling states originating in representations of visceral arousal [13]. The differential roles of right and left insula in representing, respectively, sympathetic and parasympathetic nervous system activity has been proposed by Craig et al. in a homeostatic neuroanatomical model of "emotional asymmetry" [14]. The bilateral insular finding in our study may thus reflect an involvement of both sympathetic and parasympathetic representations in the experience of empathy and emotions regulation in EG.

As mentioned, insular cortex plays an integrative role in coordinating awareness of body feelings, contextual social clues and emotional salient stimuli, being a key node of the salience network (SN) together with the dorsal anterior cingulate cortex [8,15,16]. Saliency detection can be conceptualized into two general mechanisms. The first is a fast, automatic, bottom-up 'primitive' mechanism for filtering stimuli based on their perceptual features; the second is a higher-order system for focusing the 'spotlight of attention' and enhancing access to resources needed for goal-directed behavior [17]. The misattribution of salience to external and internal stimuli in individual with mental illness is a core feature of the disorder and may explain the genesis of psychotic symptoms [18]. Indeed, salience dysfunction has been linked to violence, aggression, psychopathy, criminal behavior and recidivism [5,19].

Insular cortex has been also associated with the integration of sensory phenomena and mediates temporally defined auditory/visual interaction at an early stage of cortical processing [20,21]. The reduced GM volume in auditory areas like STG or in the fusiform gyrus (implicate in face recognition and identification of facial expressions [22] support the notion that multiple brain regions besides the insula contribute to a disrupted empathic response in EG. Volumetric alterations in insula, fusiform gyrus and STG might be related to a profound lack of empathy and to the propensity for aggressive and violent behavior.

STG is a site of multisensory integration [23]. It is implicated in spoken word recognition and in visual analysis of social information conveyed by gaze and body movement [24,25]. A progressive GM reduction in STG has been found to precede the first expression of florid psychosis [26]. Here we found significant correlation between GM volume reduction in clusters spanning from the STG to the insula in the left hemisphere and psychotic symptom severity, as scored by the BPRS. These findings are in line with previous VBM studies that demonstrated that high-risk subjects who later developed psychosis exhibited progressive GM reduction in left temporal lobe regions, particularly STG. Volume reduction of these regions have been found to correlate with auditory hallucinations or thought disorder [27,28]. Changes in the insular and the STG morphometry and the consistent correlation between GM volume and psychotic symptom severity across mentally ill persons socially dangerous suggest that the left insula and the STG significantly interact to contribute to psychotic symptom manifestation in EG. However, whether these morphometric changes are a cause or a consequence of social dangerousness is still unknown.

The rs-fMRI study demonstrated aberrant connectivity in brain network subserving morality, salience and reward. EG showed reduced connectivity between NAcc and Amy in the right hemisphere, but increased connectivity between NAcc and PCC in the left hemisphere. NAcc is the major component of the ventral striatum and represents a key structure of reward system, which identifies purpose of actions and reinforce motivation for reward-seeking behaviour. It's the functional interface between limbic and motor systems, playing a fundamental role in controlling the biological drives necessary for survival and reproduction, thanks to its limbic afferents in brain regions like the amygdala as well as output to the mesencephalon and basal ganglia [30].

Our findings are consistent with previous findings in psychiatric and personality disorders suggesting that reduced connectivity between Amy and NAcc is associated with aberrant behaviours [31,32]. More specifically, our results support the idea that down-regulation of limbic inputs in Amy/NAcc connection reflects the maladaptive behaviour of socially dangerous subjects in term of altered emotional response to one's own moral violations [33] as well as lack of empathy with other people during personal desire-oriented decisions [34]. Instead, the increased connectivity between NAcc and PCC that we find in EG can represent an interesting inter-connection between the reward system and the default mode network (DMN). PCC plays a pivotal role in retrieving autobiographical memories or planning for the future [22, 23]. Also PCC has been hypothesized to play a direct role in regulating the focus of attention, perhaps controlling the balance between internal and external control [37–39]. Previous neuroimaging studies have demonstrated that hyperactivity of PCC may contribute to disturbances of thought in schizophrenia and can predict the risk for illness [27, 28]. Definitely, PCC activity varies with arousal state and its interactions with other brain networks, like the reward system, may influence conscious awareness and behaviour.

Another considerable content of our research implicates the role of dorsal striatum (caudate and putamen) that results to be hyperconnected in left hemisphere of EG, as compared with CG. It has long been recognized that the dorsal striatum is involved in programming behaviour on the basis of interoceptive or internally generated input, particularly when the available actions are bound to rewarding outcomes [42].

Previous studies by Cools on monkeys [43], showed that enhanced activation in the caudate nucleus influenced the internal control of ongoing behaviour rather than that triggered by its partners (external control). Dorsal and ventral striatum play opposite roles in the organization of social behaviour: the dorsal striatum is involved in cognitive control system, which control the set of brain processes necessary for goal-directed thought and action; the ventral striatum, instead, is part of the emotional system, which included also structures like the FOrb and the Amy [44]. The emotional system is involved in immediate responding to potential rewards, impulsivity and emotional control, as we discussed above. When the balance between dorsal and ventral striatum tend to the first one, the locus of control becomes more internal, leading individuals to self-focusing. Thus, individuals result less prone to respond to inputs from other people or from the society, namely "socially oblivious". 'Social obliviousness' may express on different ways: a lack of understanding communication and social meaning (autistic-like) or a high tendency to socially manipulate or act at the expenses of the well-being of social partners (psychopathy-like). The latter case matches the description of proactive aggression, a label used in aggression-related psychiatric research, that means aggression involving planning and premeditation, lack of anger and that is motivated by the desire to reach a specific goal or acquired instrumental behaviour that is controlled by an anticipated reward [44].

We also observed a significant augmented connectivity of FOrb cortex with putamen and pallidum on the left hemisphere of EG. FOrb cortex is a key node of sensory integration, the modulation of autonomic reactions and participation in learning, prediction and decision making for emotional and reward-related behaviours [45]. FOrb and ACC cortices were known to be implicated in decision making since 1848, when the classic case of Phineas Gage [33, 34] was described. The recent convergence of findings from neuroimaging, neuropsychology and neurophysiology indicates that the human FOrb cortex is an important node for emotional processing and hedonic experience [45]. It has been associated with the representation of reward and punishment and subserves aspects of moral behaviour [48] such as guilt, regret and empathy [49–51]. Here, we found that Forb is more connected with basal ganglia in EG suggesting that in this sample this node is crucial for signalling information when it has to be integrated to create an estimate of future outcomes or anticipate reward through instrumental and self-focused behaviour [52].

Finally, we find an increased connectivity within the basal ganglia, between left pallidum/left Amy and ACC/caudate bilateral in the EG. All of these areas are pivotal for moral behaviour and impulse control. Particularly, the ACC is thought to play a central role in the error-monitoring circuit, where it receives error-related information from the basal ganglia and frontal cortex to motor areas [41]. The ACC is normally also closely connected with Amy, which presents higher connectivity in EG, in relation with pallidum. These findings relate emotional processing with reward system and salience attribution, in a complex network that results hyperactivated in psychiatric criminals [54].

Consistently with this interpretation, a task-based study conducted by da Cuhna-Bang et al. revealed high neural reactivity to provocations within the amygdala and striatum in violent offenders [55]. ACC activity could be also an important marker to predict recidivism beyond traditional clinical measures of risk assessment, as demonstrated by Aharoni et al. with a go/no-go (GNG) impulse control task that will contribute to the prediction of future rearrest of criminal offenders [5].

Conclusion

The goal of any type of predictive tool is to help the legal system make better decisions than could be made without such tools. Since improved technology has made high-quality neuroimaging data more accessible and easily applicable to scientific research, it is now appropriate to start thinking about how neuroscience variables can be used to improve existing behavioral prediction methods. An understanding of brain structure and function in mentally ill individuals that have committed crimes can help identify offenders at the highest and lowest risks of recidivism. The identification of these possible offenders based on their level of risk would allow for a more efficient allocation of resources. In high risk individuals, identification of the neural mechanisms at work could help isolate targets for specific interventions, thus potentially allowing the remediation of these risks through treatment. A graduated strategy providing security measures that correspond to an individual's risk level and security needs, including stepping down security measures as the patient is transitioned from institutional to ambulatory care in the community, could be an objective to implement for patients treated in the regional REMS.

In this study we fund that mentally ill persons, considered socially dangerous and institutionalized in REMS, show a disregulated functional connectivity in brain areas subserving morality, reward-processing and impulse control and a significant volumetric reduction of GM in region concerning empathy and salience.

Despite the small sample size, which prevents definite conclusions, the present study sheds some light upon the neural correlates of this specific population, which deserves further attention for both theoretical and clinical implications. Further understanding of the neural bases of risk evaluation in mentally ill persons with an history of violence considered non responsible could be challenging for forensic assessment and treatment development.

Bibliography

[1] L.M. Gaudet, J. Kerkmans, N. Anderson, K. Kiehl, Can Neuroscience Help Predict Future Antisocial Behavior?, Social Science Research Network, Rochester, NY, 2016. https://papers.ssrn.com/abstract=2862083 (accessed April 2, 2019).

[2] F. Carabellese, A.R. Felthous, Closing Italian Forensic Psychiatry Hospitals in Favor of Treating Insanity Acquittees in the Community, Behav Sci Law. 34 (2016) 444–459. doi:10.1002/bsl.2234.

[3] T. Nadelhoffer, S. Bibas, S. Grafton, K.A. Kiehl, A. Mansfield, W. Sinnott-Armstrong, M. Gazzaniga, Neuroprediction, Violence, and the Law: Setting the Stage, Neuroethics. 5 (2012) 67–99. doi:10.1007/s12152-010-9095-z.

[4] S. Ferracuti, D. Pucci, F. Trobia, M.C. Alessi, C. Rapinesi, G.D. Kotzalidis, A. Del Casale, Evolution of forensic psychiatry in Italy over the past 40 years (1978-2018), Int J Law Psychiatry. 62 (2019) 45–49. doi:10.1016/j.ijlp.2018.10.003.

[5] E. Aharoni, G.M. Vincent, C.L. Harenski, V.D. Calhoun, W. Sinnott-Armstrong, M.S. Gazzaniga, K.A. Kiehl, Neuroprediction of future rearrest, Proc Natl Acad Sci U S A. 110 (2013) 6223–6228. doi:10.1073/pnas.1219302110.

[6] K.A. Kiehl, N.E. Anderson, E. Aharoni, J.M. Maurer, K.A. Harenski, V. Rao, E.D. Claus, C. Harenski, M. Koenigs, J. Decety, D. Kosson, T.D. Wager, V.D. Calhoun, V.R. Steele, Age of gray matters: Neuroprediction of recidivism, Neuroimage Clin. 19 (2018) 813–823. doi:10.1016/j.nicl.2018.05.036.

[7] N.A. Farahany, Neuroscience and behavioral genetics in US criminal law: an empirical analysis, J Law Biosci. 2 (2015) 485–509. doi:10.1093/jlb/lsv059.

[8] N. Gogolla, The insular cortex, Current Biology. 27 (2017) R580–R586. doi:10.1016/j.cub.2017.05.010.

[9] A.D.B. Craig, How do you feel--now? The anterior insula and human awareness, Nat. Rev. Neurosci. 10 (2009) 59–70. doi:10.1038/nrn2555.

[10] C. Chiarello, D. Vazquez, A. Felton, C.M. Leonard, Structural Asymmetry of Anterior Insula: Behavioral Correlates and Individual Differences, Brain Lang. 126 (2013) 109–122. doi:10.1016/j.bandl.2013.03.005.

[11] T. Singer, B. Seymour, J. O'Doherty, H. Kaube, R.J. Dolan, C.D. Frith, Empathy for pain involves the affective but not sensory components of pain, Science. 303 (2004) 1157–1162. doi:10.1126/science.1093535.

[12] M. Berthier, S. Starkstein, R. Leiguarda, Asymbolia for pain: a sensory-limbic disconnection syndrome, Ann. Neurol. 24 (1988) 41–49. doi:10.1002/ana.410240109.

[13] H.D. Critchley, S. Wiens, P. Rotshtein, A. Ohman, R.J. Dolan, Neural systems supporting interoceptive awareness, Nat. Neurosci. 7 (2004) 189–195. doi:10.1038/nn1176.

[14] A.D. (Bud) Craig, Forebrain emotional asymmetry: a neuroanatomical basis?, Trends in Cognitive Sciences. 9 (2005) 566–571. doi:10.1016/j.tics.2005.10.005.

[15] R. Limongi, A. Tomio, A. Ibanez, Dynamical predictions of insular hubs for social cognition and their application to stroke, Front Behav Neurosci. 8 (2014). doi:10.3389/fnbeh.2014.00380.

[16] V. Menon, L.Q. Uddin, Saliency, switching, attention and control: a network model of insula function, Brain Struct Funct. 214 (2010) 655–667. doi:10.1007/s00429-010-0262-0.

[17] E.I. Knudsen, Fundamental Components of Attention, Annu. Rev. Neurosci. 30 (2007) 57–78. doi:10.1146/annurev.neuro.30.051606.094256.

[18] R.H. Morley, P.B. Jantz, R. Graham, The Salience Network structures as a mediator of violence and perceptions of hostility, Neuropsychological Trends. (2019) 7–20. doi:10.7358/neur-2019-025-morl.

[19] C.L. Philippi, M.S. Pujara, J.C. Motzkin, J. Newman, K.A. Kiehl, M. Koenigs, Altered resting-state functional connectivity in cortical networks in psychopathy, J. Neurosci. 35 (2015) 6068–6078. doi:10.1523/JNEUROSCI.5010-14.2015.

[20] K.O. Bushara, J. Grafman, M. Hallett, Neural correlates of auditory-visual stimulus onset asynchrony detection, J. Neurosci. 21 (2001) 300–304.

[21] G.A. Calvert, P.C. Hansen, S.D. Iversen, M.J. Brammer, Detection of audio-visual integration sites in humans by application of electrophysiological criteria to the BOLD effect, Neuroimage. 14 (2001) 427–438. doi:10.1006/nimg.2001.0812.

[22] J.V. Haxby, M.I. Gobbini, M.L. Furey, A. Ishai, J.L. Schouten, P. Pietrini, Distributed and overlapping representations of faces and objects in ventral temporal cortex, Science. 293 (2001) 2425–2430. doi:10.1126/science.1063736.

[23] H.-O. Karnath, New insights into the functions of the superior temporal cortex, Nat Rev Neurosci. 2 (2001) 568–576. doi:10.1038/35086057.

[24] T. Allison, A. Puce, G. McCarthy, Social perception from visual cues: role of the STS region, Trends in Cognitive Sciences. 4 (2000) 267–278. doi:10.1016/S1364-6613(00)01501-1.

[25] K.A. Pelphrey, J.P. Morris, G. McCarthy, Neural basis of eye gaze processing deficits in autism, Brain. 128 (2005) 1038–1048. doi:10.1093/brain/awh404.

[26] T. Takahashi, S.J. Wood, A.R. Yung, B. Soulsby, P.D. McGorry, M. Suzuki, Y. Kawasaki, L.J. Phillips, D. Velakoulis, C. Pantelis, Progressive Gray Matter Reduction of the Superior Temporal Gyrus During Transition to Psychosis, Arch Gen Psychiatry. 66 (2009) 366–376. doi:10.1001/archgenpsychiatry.2009.12.

[27] C. Pantelis, D. Velakoulis, P.D. McGorry, S.J. Wood, J. Suckling, L.J. Phillips, A.R. Yung, E.T. Bullmore, W. Brewer, B. Soulsby, P. Desmond, P.K. McGuire, Neuroanatomical abnormalities before and after onset of psychosis: a cross-sectional and longitudinal MRI comparison, Lancet. 361 (2003) 281–288. doi:10.1016/S0140-6736(03)12323-9.

[28] D.E. Job, H.C. Whalley, E.C. Johnstone, S.M. Lawrie, Grey matter changes over time in high risk subjects developing schizophrenia, Neuroimage. 25 (2005) 1023–1030. doi:10.1016/j.neuroimage.2005.01.006.

[29] S. Salgado, M.G. Kaplitt, The Nucleus Accumbens: A Comprehensive Review, Stereotact Funct Neurosurg. 93 (2015) 75–93. doi:10.1159/000368279.

[30] T.W. Robbins, J.W. Dalley, Dissecting Impulsivity: Brain Mechanisms and Neuropsychiatric Implications, in: J.R. Stevens (Ed.), Impulsivity: How Time and Risk Influence Decision Making, Springer International Publishing, Cham, 2017: pp. 201–226. doi:10.1007/978-3-319-51721-6_7.

[31] Grace AA (2000) Gating of information flow within the limbic system and the pathophysiology of schizophrenia. Brain Res Brain Res Rev 31: 330 –341

[32] R. Ito, M. Canseliet, Amphetamine Exposure Selectively Enhances Hippocampus-Dependent Spatial Learning and Attenuates Amygdala-Dependent Cue Learning, Neuropsychopharmacology. 35 (2010) 1440. doi:10.1038/npp.2010.14.

[33] S. Berthoz, J. Grèzes, J.L. Armony, R.E. Passingham, R.J. Dolan, Affective response to one's own moral violations, Neuroimage. 31 (2006) 945–950. doi:10.1016/j.neuroimage.2005.12.039.

[34] J.D. Greene, R.B. Sommerville, L.E. Nystrom, J.M. Darley, J.D. Cohen, An fMRI investigation of emotional engagement in moral judgment, Science. 293 (2001) 2105–2108. doi:10.1126/science.1062872.

[35] D.R. Addis, A.T. Wong, D.L. Schacter, Remembering the past and imagining the future: common and distinct neural substrates during event construction and elaboration, Neuropsychologia. 45 (2007) 1363–1377. doi:10.1016/j.neuropsychologia.2006.10.016.

[36] M.F. Mason, M.I. Norton, J.D. Van Horn, D.M. Wegner, S.T. Grafton, C.N. Macrae, Wandering minds: the default network and stimulus-independent thought, Science. 315 (2007) 393–395. doi:10.1126/science.1131295.

[37] R. Leech, D.J. Sharp, The role of the posterior cingulate cortex in cognition and disease, Brain. 137 (2014) 12–32. doi:10.1093/brain/awt162.

[38] J.M. Pearson, B.Y. Hayden, S. Raghavachari, M.L. Platt, Neurons in posterior cingulate cortex signal exploratory decisions in a dynamic multioption choice task, Curr. Biol. 19 (2009) 1532–1537. doi:10.1016/j.cub.2009.07.048.

[39] J.M. Pearson, S.R. Heilbronner, D.L. Barack, B.Y. Hayden, M.L. Platt, Posterior cingulate cortex: adapting behavior to a changing world, Trends Cogn. Sci. (Regul. Ed.). 15 (2011) 143–151. doi:10.1016/j.tics.2011.02.002.

[40] S. Whitfield-Gabrieli, J.M. Ford, Default mode network activity and connectivity in psychopathology, Annu Rev Clin Psychol. 8 (2012) 49–76. doi:10.1146/annurev-clinpsy-032511-143049.

[41] S. Whitfield-Gabrieli, H.W. Thermenos, S. Milanovic, M.T. Tsuang, S.V. Faraone, R.W. McCarley, M.E. Shenton, A.I. Green, A. Nieto-Castanon, P. LaViolette, J. Wojcik, J.D.E. Gabrieli, L.J. Seidman, Hyperactivity and hyperconnectivity of the default network in schizophrenia and in first-degree relatives of persons with schizophrenia, Proc. Natl. Acad. Sci. U.S.A. 106 (2009) 1279–1284. doi:10.1073/pnas.0809141106.

[42] B. Kim, H.-I. Im, The role of the dorsal striatum in choice impulsivity, Ann. N. Y. Acad. Sci. (2018). doi:10.1111/nyas.13961.

[43] J.H. Van den Bercken, A.R. Cools, Evidence for a role of the caudate nucleus in the sequential organization of behavior, Behav. Brain Res. 4 (1982) 319–327.

[44] R. van den Bos, The dorsal striatum and ventral striatum play different roles in the programming of social behaviour: a tribute to Lex Cools, Behavioural Pharmacology. 26 (2015) 6–17. doi:10.1097/FBP.0000000000000110.

[45] M.L. Kringelbach, The human orbitofrontal cortex: linking reward to hedonic experience, Nat. Rev. Neurosci. 6 (2005) 691–702. doi:10.1038/nrn1747.

[46] Damasio AR., Descartes' error: emotion, rationality and the human brain., n.d.

[47] J.D. Van Horn, A. Irimia, C.M. Torgerson, M.C. Chambers, R. Kikinis, A.W. Toga, Mapping Connectivity Damage in the Case of Phineas Gage, PLoS One. 7 (2012). doi:10.1371/journal.pone.0037454.

[48] J. Greene, J. Haidt, How (and where) does moral judgment work?, Trends Cogn. Sci. (Regul. Ed.). 6 (2002) 517–523.

[49] N. Camille, G. Coricelli, J. Sallet, P. Pradat-Diehl, J.-R. Duhamel, A. Sirigu, The involvement of the orbitofrontal cortex in the experience of regret, Science. 304 (2004) 1167–1170. doi:10.1126/science.1094550.

[50] B.A. Völlm, A.N.W. Taylor, P. Richardson, R. Corcoran, J. Stirling, S. McKie, J.F.W. Deakin, R. Elliott, Neuronal correlates of theory of mind and empathy: a functional magnetic resonance imaging study in a nonverbal task, Neuroimage. 29 (2006) 90–98. doi:10.1016/j.neuroimage.2005.07.022.

[51] L. Pascual, P. Rodrigues, D. Gallardo-Pujol, How does morality work in the brain? A functional and structural perspective of moral behavior, Front Integr Neurosci. 7 (2013) 65. doi:10.3389/fnint.2013.00065.

[52] G. Schoenbaum, G.R. Esber, How do you (estimate you will) like them apples? Integration as a defining trait of orbitofrontal function, Curr. Opin. Neurobiol. 20 (2010) 205–211. doi:10.1016/j.conb.2010.01.009.

[53] C. Orr, R. Hester, Error-related anterior cingulate cortex activity and the prediction of conscious error awareness, Front Hum Neurosci. 6 (2012). doi:10.3389/fnhum.2012.00177.

[54] J.G. Hosking, E.K. Kastman, H.M. Dorfman, G.R. Samanez-Larkin, A. Baskin-Sommers, K.A. Kiehl, J.P. Newman, J.W. Buckholtz, Disrupted Prefrontal Regulation of Striatal Subjective Value Signals in Psychopathy, Neuron. 95 (2017) 221-231.e4. doi:10.1016/j.neuron.2017.06.030.

[55] S. da Cunha-Bang, P.M. Fisher, L.V. Hjordt, E. Perfalk, A. Persson Skibsted, C. Bock, A. Ohlhues Baandrup, M. Deen, C. Thomsen, D.M. Sestoft, G.M. Knudsen, Violent offenders respond to provocations with high amygdala and striatal reactivity, Soc Cogn Affect Neurosci. 12 (2017) 802–810. doi:10.1093/scan/nsx006.