The interaction between serotonin and stress as underlying mechanism leading to neurobiological dysfunction associated with antisocial personality disorder.

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Abstract.

Antisocial personality disorder (ASPD) is a DSM-IV Axis II personality disorder with a prevalence of 3% and 1% in males and females respectively. Among the psychosocial traits associated with ASPD are anxiety, aggressive behavior, impulsivity as well as a dysfunctional planning and overall functioning within the social context. Imaging studies on subjects either with ASPD or displaying some of the main associated psychosocial traits, have shown significant abnormalities in volumetric measurements and activation, in several brain regions including the prefrontal cortex (PFC), orbitofrontal cortex (OFC), the temporal lobe and the amygdala-hippocampus complex. Abnormalities in the serotonergic pathway have often been found in subjects diagnosed with ASPD. Specific functional polymorphisms associated with reduced serotonergic activity including tryptophan (TPH) synthesis, serotonin (5-HT) reuptake into the presynaptic terminal regulated by the 5-HT transporter (5-HTT), and deamination of 5-HT by monoamine oxidase-A (MAOA), have been reported as precipitating factors, particularly in subjects with a history of exposure to stressful environments during their childhood. Exposure to adversity during childhood in and of itself, has been associated with an increased probability of developing ASPD. However, the molecular mechanisms through which chronic stress exerts its effect are largely unknown and have been studied, at best, within the context of other mental disorders like major depression disorder (MDD). Furthermore, examination of the role of stress and 5-HT interactions in the development and maintenance of ASPD as well as their potential mechanisms is for the most part absent. This review intends to give an overall image of the most consistent results that are relevant for the understanding of what the causes of ASPD may be, placing particular interest on two main modulating factors, stress and 5-HT.

Introduction.

Mental disorders can be diagnosed based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) published by the American Psychiatric association (American Psychiatric Association, 2000). This manual is comprised of five sections or axes that provide different types of information about the diagnosis of mental conditions.

The Axis II of the DSM-IV, which describes the diagnostic criteria for personality disorders and retardation, includes the clinical definition of Antisocial Personality Disorder (ASPD).

As indicated in Table 1, in order for an individual to be diagnosed with ASPD according to the DSM-IV criteria, the individual has to show unlawful behavior

as early as during adolescence, and certain traits like a lack of empathy, impulsivity, irritability and aggression, lack of remorse and difficulty planning. According to the DSM-IV-TR the prevalence of this disorder is 3% in males and 1% in females. The point of origin of this disorder is hard to track down and perhaps impossible to exactly pin-point, however, early forms of disruptive behavior categorized as oppositional defiant disorder (ODD) in infants, and conduct disorder (CD) in adolescents have been associated with the later development of ASPD (Myers et al., 1998; Van Goozen & Fairchild, 2006; Susman et al., 2010; Glenn & Raine 2011). It is known that left untreated, these two conditions increase significantly the chances of ASPD in adulthood. It is of course not a strict relationship and not every child diagnosed with ODD develops ASPD, the diagnosis of all these conditions is based on a number of behavioral symptoms who's expression varies over time modulated not only by the intrinsic physiological or genetic characteristics of every individual but also in response to their social environment and upbringing. It is for this reason that treatment of these early forms of antisocial behavior is thought to be crucial in the prevention of a further precipitation into a more serious mental disorder. This spectrum of symptoms also plays an important role during adulthood. Perhaps one of the most socially condemned mental disorders is psychopathy. This condition leads subjects to commit acts of violence without feeling any kind of guilt or remorse, reason why their behavior has such a strong impact on the general population. When looked at closely however, it seems that it can very well be a stronger manifestation of the same symptoms that cause ASPD. This shows that given a combination of a specific genetic background, social environment and potentially a lack of treatment, the same individual could progress from manifesting ODD to being a psychopath as an adult. The identification of treatments that could be implemented at different ages and stages of the disorder has the potential to stop this process reducing the severity of the symptoms to a manageable level.

ASPD is very hard to treat since diagnosed individuals very rarely seek help on their own and the most common referral is done by courts of law. There is currently no pharmacological treatment for ASPD and the most common type of therapy used is psychotherapy. There is a high co-morbidity of ASPD with other mental disorders such as anxiety and depression, in which case a parallel pharmacological treatment will be conducted to manage these symptoms.

Because ASPD is essentially a set of psychosocial signs and symptoms, research must be based on humans in order to properly target the right disorder. Some animal models have been established to investigate a specific subset of symptoms such as impulsivity, anxiety and aggression. However. not only do these not comprise the full spectrum of the disorder, they are also found in other mental disorders, implying that any potential treatment derived from these animal models, however broadly useful, would not necessarily target a specific mental disorder.

Another line of research regarding ASPD has focused on imaging studies to try and elucidate morphological or functional changes in the brain that may underlie the psychosocial symptoms.

Several studies have found differences in various brain regions of ASPD patients that have helped unravel the complexity of what causes this mental disorder. As would be expected, the results so far reported are vast, diverse, and at times controversial, highlighting that mental disorders like ASPD arise from the convergence of a number of factors (developmental or from lesions), that often have an additional contribution from the environment. In this case, up-bringing conditions seem to have a rather relevant role in ASPD development.

The aim of this manuscript is to give an outline of the common anatomical brain abnormalities that have been associated with ASPD and more specifically with some of it's more characteristic symptoms such as aggression and impulsivity. Discussing two of the factors that have been identified as high risk precipitators for ASPD, that is, exposure to stressful life conditions during childhood, and abnormalities in the serotonergic pathway. And finally examining how an interaction between these two factors may be a strong contributor to the anatomical changes reported in ASPD patients.

301.7Antisocial Personality Disorder

Diagnostic criteria for* 301.7*Antisocial Personality Disorder

A. There is a pervasive pattern of disregard for and violation of the rights of others occurring since age 15 years, as indicated by three or more of the following:

1. failure to conform to social norms with respect to lawful behaviors as indicated by repeatedly performing acts that are grounds for arrest;
2. deceitfulness, as indicated by repeatedly lying, use of aliases, or connig others for personal profit or pleasure;
3. impulsivity or failure to plan ahead;
4. irritability and aggressiveness, as indicated by repeated physical fights or assaults;
5. reckless disregard for safety of self or others;
6. consistent irresponsibility, as indicated by repeated failure to sustain consistent work behavior or honor financial obligations;
7. lack of remorse, as indicated by being indifferent to or rationalizing having hurt, mistreated, or stolen from another;

B. The individual is at least age 18 years.

C. There is evidence of conduct disorder with onset before age 15 years.

D. The occurrence of antisocial behavior is not exclusively during the course of schizophrenia or a manic episode.

Table 1. DSM-IV criteria for the diagnosis of Antisocial Personality Disorder.

Brain abnormalities associated with ASPD.

PFC dysfunction in ASPD.

Several studies have reported reduced frontal lobe activity and volumetric measurements in patients with ASPD suggesting that the underlying molecular mechanisms ultimately lead to either an underdevelopment or dysfunction in the frontal lobe. In this regard, Raine et al., (2000) reported gray matter reduction in the prefrontal cortex (PFC) of antisocial and psychopathic subjects, showing an 11% reduction in PFC gray matter volume in the absence of apparent lesions of ASPD subjects, as well as a reduced autonomic response to a social stressor, giving one of the first indications of a structural brain deficit possibly leading to the psychological traits associated with ASPD. Yang et al., (2005) showed a 22.3% reduction in PFC gray matter only in unsuccessful psychopaths, pointing out an important difference between successful (uncaught) and unsuccessful (caught) psychopaths, indicating that unsuccessful psychopaths either have a predisposition to more severe crimes, or a more strongly impaired planning capability that would make them unlikely to avoid law enforcement. The deficits in the PFC associated with ASPD may underlie some of the traits that would lead to poor decision making and bad planning, which are hallmarks of ASPD, that would potentially bring a psychopath to get caught. It is worth highlighting once again that psychopathy is not ASPD, however some consider it a more severe form of ASPD, thereby relevant to understanding the underlying causes of both the disorders.

As specified in the DSM-IV diagnostic criteria, ASPD usually has an early onset. A similar disorder diagnosed in adolescence, conduct disorder (CD), is thought to lead to ASPD (Myers et al., 1998). For this reason research focusing on young adolescents diagnosed with CD may prove valuable in establishing the possible early causes that ultimately lead to a fully developed personality disorder.

In a study with 10 young adolescents diagnosed with CD and 10 matched controls, Kruesi et al., (2004) showed reduced gray matter volume in the temporal lobe of CD patients, as well as a 16% reduction in PFC volumes, that however did not reach statistical significance. This could be due to a limited number of participants in the study, or could indicate that the changes taking place in the brain at this stage are not fully developed yet, and with time the difference between diagnosed and healthy subjects is more marked. This would support the theory that potential early treatments based on CD diagnosis could have a preventive effect and perhaps increase the chances of future therapies such as psychotherapy, of having successful results.

***OFC dysfunction in ASPD*.**

The orbitofrontal cortex (OFC) has also been identified as one of the brain regions where ASPD patients often present abnormalities (Laakso et al., 2002; Yang et al., 2008). It is known that lesions in the OFC cause problems in reversal and extinction paradigms as shown by Rolls et al., (1994). This has been shown in both humans and non-human primates. The effects of lesions in this brain region suggest that the OFC has a crucial role in updating the behavioral response to a stimulus. This could imply an inability of antisocial individuals to adapt their response to different social situations causing their inappropriate behavior. Interestingly, in Rolls' study, the subjects with OFC lesions reported that they were aware that the contingencies of the paradigm had changed, but were unable to modify their behavioral response accordingly. ASPD patients, however, often do not find anything wrong with their behavior, suggesting once again that other factors come into play to produce this mental disorder. An interesting question is whether these other factors develop in an independent way, or that the inability to act according to social rules eventually leads to a maladaptive behavior and ultimately the extinction of remorse. In a review Brower & Pierce (2001) point out that OFC lesions are also often found in individuals with aggressive and violent behavior. In their analysis, however, they suggest that OFC lesions do not necessarily increase the risk of violence, but rather are associated with a subtype of violent behavior that is often dictated by impulsivity. In light of previous findings, it is possible that the violent behavior is only part of the abnormal response to social situations. From the ASPD point of view, the inability to modify behavioral responses is a target with high value for possible treatments, while the violent behavior is a probably a consequence of the disorder's progression in time.

Additionally, abnormal activation of the OFC has been reported in impulsive individuals (Horn et al., 2003) and in subjects with ASPD (Vollm et al., 2004) during a response inhibition task.

DLPFC dysfunction in ASPD.

As established by the DSM-IV, one of the hallmarks of ASPD is the display of poor decision making and difficulty with planning. A study by Manes et al., (2002) showed that patients with lesions in the frontal cortex, particularly the dorsolateral PFC cortex (DLPFC), even when compared with subjects with OFC lesions, displayed significant deficits on working memory, planning and attentional shifting across a series of cognitive tasks. Another study by Gomez et al., (2004) also showed a significant impairment in decision making and planning in subjects with DLPFC and OFC lesions. In this case the subjects were exposed to a series of gambling tasks. As a difference from other, similar studies, the subjects also received advice on how to optimize their performance in such tasks. Interestingly, the subjects with brain lesions were unable to integrate the advice they received to modify their strategy, and even more strikingly, were overconfident about their performance when compared to controls. When translated to an ASPD condition, these findings may turn very relevant since the overconfidence could be a sign of narcissism, a trait often found in ASPD individuals. It is perhaps more likely that the inability to plan and calculate outcomes reflected in the poor performance of lesioned subjects, also translates into a misperception of their own performance.

Considering the fact that psychotherapy is currently the most common treatment for ASPD, it would be imperative to elucidate whether the inability of these subjects to integrate advice to modify their strategies is specific for gambling tasks with a certain degree of mathematical complexity, or it extends to more general areas of the daily life, which would render much less effective any counseling used as therapy.

To the best of our knowledge no studies have tackled this possibility and thus, there is no evidence nor confirming or refuting this hypothesis.

Further highlighting the dysfunctionality of the DLPFC in ASPD subjects, Völlm et al., (2004) reported irregular activation of the DLPFC during response inhibition tasks, in particular, a more bilateral and extended activation when compared to controls.

When examining the response to a differential aversive classical conditioning paradigm, using faces as conditioned stimuli and odors as unconditioned stimuli in ASPD patients, Schneider et al., (2000) reported a rather surprising finding. While controls showed decreased activation in the DLPFC and the amygdala, patients showed increased activation, suggesting that abnormalities in the DLPFC are not exclusively involved in decision making and planning but in emotional processing as well, likely not in a direct way but via co-signaling with the amygdala (as shown in this study), a brain structure largely characterized and known to be involved in emotion processing.

Temporal lobe Dysfunction in ASPD.

Additional imaging studies have provided interesting results that indicate the involvement of the temporal lobe in abnormalities associated with ASPD traits. In an fMRI study, Raine et al., (2001) provide evidence of how dysfunction of the right and left temporal lobes could determine violent behavior. This study focused on violent individuals that had suffered physical abuse during their childhood. This is often the situation reported by individuals diagnosed with ASPD, although violent behavior is not synonymous of ASPD, rather only one of the psychosocial traits associated with the disorder. It is know that environmental factors such as an adverse childhood exacerbate potentially congenital conditions greatly increasing the probability of developing a mental disorder. This study compared violent individuals that had and had not been abused during their childhood and that expressed or refrained from serious violent behavior. Analysis of the fMRI data showed that violent subjects that had been abused as children showed a reduction of activity in the right temporal cortex during a visual/verbal working task. Individuals with a history of severe abuse, independently of whether they displayed violent behavior or not, showed reduced activity in the left temporal cortex. An additional interesting finding of this study showed that abused subjects that did not display serious violent behavior, showed a relative good functioning of the right temporal cortex. This suggests that abnormalities in the right temporal cortex (congenital or acquired) underlie the predisposition towards violent behavior, and that increased activity in this region could have a protective effect against one of the highest risk factors for ASPD such as childhood adversity.

Several studies have also reported an abnormal activation of the temporal lobe in ASPD subjects via measurement of the regional cerebral blood flow (rCBF) (Kuruogly et al., 1996; Amen et al., (1996); Wong et al., 1997), providing driving evidence of the involvement of the temporal lobe in mental disorders like ASPD.

Dysfunctionality of the Amygdala and the Hippocampus in ASPD.

As is the case with the majority of studies that examine anomalies in brain functioning of ASPD subjects, abnormalities in the amygdala and hippocampus have been reported mainly via fMRI studies.

Muller et al., (2003) showed an increased activation of PFC regions and the amygdala in criminal psychopaths, showing how there is a disequilibrium in emotion-mediating brain regions in subjects that show lack of empathy or remorse. It would be expected that individuals lacking these emotional capabilities would show a reduced or impaired activation of the amygdaloid complex. However this study showed an increased activation of the amygdala. Interestingly, the activation seen was in response to pictures presented with negative content. As alluded to in the introduction, the debate whether ASPD and Psychopathy are two different disorders or the latter is a more severe case of the former, is still unresolved; however they have indisputably some common traits such as the already mentioned lack of empathy and/or remorse. From this point of view, Muller's findings are interesting but not entirely surprising. The amygdala has long been known to be involved in the processing of emotions; particularly the amygdalo-hippocampal complex is known to be

involved in the processing of aversive stimuli. Recent evidence, however, has indicated that the amygdala has a just as important role in the processing of positive stimuli and reward (Baxter et al., 2002; Murray 2007). In the case of ASPD or psychopathic subjects, the increased activation of the amygdala following negative content images could indicate that there is a rewarding component to antisocial behavior that is likely contributing to the reinforcement of such behavior. A second possibility would be that the increased activation of the amygdala responds to a compensatory mechanism in order to comply with the required function. This would seem more likely and in line with the absence of reported activation of reward areas such as the ventral tegmental area (VTA) or the Nucleus Accumbens (Nacc). This would further be confirmed by the reported absence of emotion rather than a sense of pleasure reported by ASPD patients and psychopaths following acts of violence or crimes. In another study, Schneider et al., (2000) also showed increased activation of the amygdala and the DLPFC during the acquisition phase of conditioned aversive emotional responses in subjects with ASPD. These authors hypothesized that this increased activation responds to a higher effort towards the acquisition of the affective stimuli. It would be interesting to investigate whether there is a correlation of the activity in the amygdala or other brain structures involved in positive reward processing.

Anatomical studies have provided evidence showing significant volumetric hippocampal reductions in violent offenders with ASPD (Laakso et al., 2002), subjects with ASPD and alcoholism (Laakso et al., 2001) and psychopaths (Raine et al., 2004). One important point of discussion is whether this hippocampal abnormality is a consequence of the persistent antisocial behavior or it acts as neural substrate for the development of the disorder. ASPD subjects have been reported to perform worse than controls in working memory tasks where the hippocampus is suspected of playing a role (Poch et al., 2011). Additionally, antisocial and psychopathic subjects are known to have impaired processing of aversive stimuli and punishment. The abnormalities reported in the amygdalo-hippocampal complex could be responsible for this particular trait of ASPD.

It is clear that several different approaches have been used to unravel the causes of ASPD, focusing on diverse brain regions as well as different psychological traits of the disorder. Overall, the results that have been more largely reproduced and seem to be more consistent indicate that the PFC is responsible for a large portion of the behavioral differences in subjects with ASPD.

In this regard, abnormalities in the OFC seem to be more frequently involved in some of the features of ASPD such as the poor inhibition that leads to impulsivity, the bad decision making and the aberrant reward/punishment processing mediated by the amygdala. Abnormalities in the DLPFC are likely underlying other ASPD traits such as the difficulty when planning ahead, the socially dysfunctional lifestyle or reckless behavior and the response preservation.

It is apparent that several brain regions are involved in the development of ASPD. Abnormalities in these regions cause a series of psychological symptoms that are medically categorized as ASPD. It is likely that the number of brain regions involved, and the severity of the changes in them, is correlated with the severity of the disorder and perhaps its onset.

A number of factors are responsible for the variation in severity and onset of the disorder. These factors are canonically divided in different fronts, two of the main being the genetical profile of every subject and the other the environment that surrounds him (nature vs. nurture).

From the genetical background perspective, there is evidence suggesting that in many cases there is a history of similar disorders already present during the life development of the individual, starting with oppositional defiant disorder (ODD) early in life, progressing to CD during adolescence and culminating with an ASPD diagnosis in adulthood (Myers et al., 1998; Van Goozen & Fairchild, 2006; Susman et al., 2010; Glenn & Raine 2011). This evidence stresses the crucial role of the identification of early molecular changes that lead to this behavioral phenotype during childhood.

It is well known that neurogenesis only happens in certain regions of the adult brain, and the evidence from all the imaging studies reporting a loss of volume makes a clear statement, once the disorder has developed, it can be treatable but not curable.

This means that the best approach against ASPD is to focus on finding targets for prevention therapies.

Role of the serotonergic pathway in ASPD.

Serotonin (5-hydroxytryptamine; 5-HT) is one of the most ubiquitous neurotransmitters in the brain. Irregularities in 5-HT signaling have been associated with a series of mental disorders such as anxiety, impulsivity, depression as well as ASPD. The majority of the 5-HT projections to the PFC originate in the raphe nuclei, a structures found in the brain stem, responsible for the synthesis of 5-HT throughout the whole brain.

The variety in the targeted projections of the raphe nuclei overlaps with the different brain regions and symptoms that have been associated with ASPD, making 5-HT a good candidate for an entry point into the molecular mechanisms behind the mental disorder.

Abnormalities in the 5-HT pathway have long known to be associated with antisocial behavior. Mehlman et al., (1994) reported that cerebrospinal fluid (CSF) levels of 5-HIAA (the main metabolite of 5-HT) are inversely correlated with aggressive and impulsive behavior in non human primates.

Similar results were reported in humans (Linnoila et al., 1983) with different personality disorders (Brown et al., 1979).

5-HT re-uptake in ASPD.

More detailed research into the role of 5-HT in ASPD has shown how abnormalities in 5-HT reuptake are often associated with antisocial behavior. Two alleles for the promoter region of the 5-HTT transporter, responsible for the reuptake of 5-HT into neuronal terminals, have been identified; the long one (L) being associated with higher levels of expression and thus increased activity compared to the short (S) allele. (Heils et al., 1996; Lesch et al., 1996). A single nucleotide polymorphism (SNP) of the (L) allele has also been identified and linked to reduced transcriptional efficacy (Hu et al., 2006).

These functional variations of the 5-HTTLPR gene have been widely studied as contributing factors to different mental disorders including ASPD. It has been reported that deleterious experiences suffered early in life can interact with the 5-HTT(S) causing long lasting effects that may contribute to the conformation of certain ASPD traits (Higley et al., 1991; Bennet et al., 2002). Hallikainen et al., (1999) reported an association of the (S) allele genotype with early onset alcoholism associated with ASPD. Liao et al., (2004) on the other hand, reported an association of the (S) allele with extremely violent convicted men, but did not find a correlation between the genotype and ASPD, substance abuse or alcohol abuse. Similar results were reported by Retz et al., (2004), who also reported an association between the short allele and violent behavior but not with personality disorders or increased impulsivity. Interestingly, when controlling for the severity of various psychopathologies associated with violent behavior, an association between the genotype and individuals with a history of ADHD was found. Not all the studies that have focused on the relationship between the 5-HTT genotype and antisocial behavior have been able to identify significant associations despite the clear evidence reported by others. One of the most common explanations for this is that gene-environment interactions may play a role and depending on the circumstances, these can have both a beneficial or detrimental effect. Life experiences during childhood seem to be particularly relevant. In an example of how up-bringing conditions influence the probability of developing antisocial behavior, Sadeh et al., (2010) reported an association between the (S/S) genotype and impulsivity in psychopathic individuals, as well as an interaction effect with decreasing socio-economical conditions, only in individuals with the (L/L) allele. These findings suggest that the low activity characteristic of the (S) allele may be involved in the increased susceptibility to develop ASPD whereas the increased reuptake associated with a (L/L) genotype may dictate susceptibility to environmental factors, particularly adverse childhood conditions.

Monoamine oxidase A activity in ASPD.

Another line of research investigating the role of the 5-HT system in ASPD has focused on a different step in the 5-HT cycle. Monoamine oxidase A (MAOA) is an enzyme that de-aminates 5-HT and other

neurotransmitters. An interesting study by Caspi et al., (2002) reported that a functional polymorphism of the gene encoding for MAOA has the ability to moderate the effects of childhood maltreatment. More specifically, children with a genotype associated with high levels of expression of MAOA were more resilient to maltreatment, and were less likely to develop antisocial behavior. In a similar study, Ducci et al., (2008) demonstrated the interaction between a length polymorphism in the promoter region (MAOA-LPR) and childhood abuse and how this increases the likelihood of developing alcoholism and ASPD. In this study 168 females, 39 of which were diagnosed with ASPD, were genotyped for MAOA-LPR. They found that the low activity MAOA-LPR allele was highly associated with antisocial alcoholism (a subtype of alcoholism characterized by early onset and a high prevalence of ASPD diagnosis among the subjects and their relatives) exclusively on those women that had reported sexual abuse during their childhood. In addition this study reports that women who where homozygous for the low activity allele reported higher rates of alcoholism and more ASPD traits. This study not only confirms the crucial modulatory role of MAOA regarding childhood adversity and its effects that lead to a higher chance of developing mental disorders like ASPD, but also makes a strong case for MAOA as a potential target for protective therapies, especially during childhood. It is worth highlighting that in every research field the differences between male and female subjects are considerable. The fact that these results have been replicated both in male and female human subjects clearly shows that MAOA activity is a key component of ASPD, especially taking into account that the ASPD rate in females is far lower than that in males, suggesting that females have a lower susceptibility to the disorder. Several other studies have demonstrated the role of MAOA genotype in the response to adverse life conditions (Huang et al., 2004; Foley et al., 2004). A study by Nilsson et al., (2006) showed once more that the combination of MAOA promoter region genotype and adverse psychosocial conditions during childhood is correlated with criminal activity during adolescence, giving a time frame of the protective effect of MAOA activity over ASPD development, and suggesting that potential prevention therapies should focus their action even before subjects reach adolescence. Abnormalities in MAOA activity have not only been associated with antisocial behavior but also with some psychosocial hallmarks of the disorder such as impulsivity (Huang et al., 2004) and violent behavior (Reif et al., 2007). Increased aggression has also been reported in mice lacking the MAOA gene (Casos et al., 1995).

From an anatomical point of view, Meyer-Lindenberg et al. (2005) reported an association between the low expression MAOA allele and reduced volumetric measurements in the OFC and amygdala as well as hippocampal hyper reactivity during aversive recall. A study by Williams et al., (2009) reported interesting results, forming a bridge between the association studies that have linked MAOA activity to ASPD susceptibility and the anatomical and functional studies on ASPD patients. In this case, an association was reported between the low activity MAOA genotype and scores of antisocial traits. Additionally these traits were linked with abnormal event related potentials (ERPs) elicited by negative emotion content, particularly anger, showing altered emotion processing in the medial-frontal, parietal and superior temporal-occipital regions. This suggests that the low activity MAOA may contribute to the conformation of ASPD causing altered processing and response to threat related emotions, which would be in line with the reduced responsiveness to punishment often reported in ASPD individuals.

5-HT synthesis in ASPD.

Some studies have also shown that ASPD can not only be linked to 5-HT metabolism in the brain but also to its precursor tryptophan. Tiihonen et al., (2001) showed that free L-tryptophan levels in violent offenders were dramatically higher than those in controls, reporting that a third of the violent offenders had L-tryptophan levels of more than twice the SD of the mean value of controls. Soderstrom et al., (2004) also reported increased plasma and CSF levels of L-tryptophan and its competitor amino acids as well as cortisol in violent offenders. Similar results reported by Eriksson & Lidberg (1997) showed increased plasma levels of tryptophan and competitor amino acids in subjects that had committed violent crimes when compared to controls and interestingly, to offenders that committed non violent crimes. No

difference between tryptophan and its competing amino acids was reported indicating that the link between violent behavior and the 5-HT precursor is non-specific.

In a recent comprehensive study, Cicchetti, Rogosch and Thibodeau (2012) analyzed gene-environment interactions in maltreated children. Their results essentially sum up the evidence that has been gathered so far regarding this topic. Subjects in their late childhood (N=627 mean age 11.27) were genotyped for three different gene variants, tryptophan hydroxylase 1 (TPH1), 5-HT transporter 5-HTTLPR and MAOA. The genotype data was analyzed for covariance with reported indicators of antisocial behavior gathered from self, peer, and adult counselor reports. The data indicated a gene-dependent mediating factor only on maltreated children. The polymorphisms of all three genes previously reported in other studies (TPH1, 5-HTT and MAOA) where associated with increased antisocial behavior scores, and early onset of the maltreatment corresponded to higher antisocial behavior scores in a genotype-dependent way.

This study not only confirms all the indications provided by previous literature implicating abnormalities in the 5-HT pathway in the development of antisocial behavior but also shows how quick the effects of maltreatment during childhood can have consequences over the personality development. It also provides very useful information about how genetic strategies are very valuable when trying to identify children with a higher susceptibility to develop ASPD. Without ignoring the rest of the population, in order to maximize effectiveness from a social point of view, potential therapies should focus on these highly susceptible subjects, perhaps even through genetic strategies, making the genetic characterization both a diagnostic (to a certain extent) and therapeutic tool.

Childhood stress and ASPD.

So far, clear evidence of the deleterious effects of childhood adversity and some genetic profiles associated with the 5-HT system has been given. A natural question is in which way do these two factors interact and whether childhood adversity by itself can cause an increase in the probability of developing mental disorders like ASPD. Extensive psychosocial evidence has been gathered in this regard. Luntz et al., (1994) compiled a study where information from subjects abused or neglected during childhood was gathered through an interview with the participants. The data indicated that childhood abuse or neglect is a significant predictor of antisocial behavior and ASPD diagnosis, even when controlling for demographic parameters and history of arrests. Another study by Brierer et al., (2003) also reported sexual and physical abuse during childhood as a significant predictor of ASPD. An interesting feature of this particular study is that while other types of childhood abuse where associated with cluster A and C personality disorders, from the cluster B personality disorders, only ASPD was associated with childhood abuse. A study by Hosser et al., (2007) comparing violent and non-violent incarcerated men between 14 and 24 years old, showed that child maltreatment doubles the risk of violent victimization during adolescence as well as increasing the probability of self reported violence. In addition, repeated victimization during adolescence increases the probability of violent offending later in life. Knapp (1998) brought attention to the fact that not only suffering abuse first hand during childhood can increase the chances of expressing violent or abusive behavior in adulthood, but the mere witnessing of repeated violence within the family nucleus increases the chances of subjects repeating this behavior later in life. An interesting question to be answered is whether there is also a genetic predisposition to this. In other words, research has shown that subjects with certain functional polymorphisms abused during childhood have higher chances of developing mental disorders like ASPD. The question is whether this is also true for subjects that have not been abused, yet have witnessed acts of violence during their childhood. A study by Cadoret et al., (1995) showed how there are several factors that determine the increased chances of ASPD. Analyzing the life history of adopted children from parents with documented ASPD, the authors reported that not only the biological background of having a parent with ASPD was a significant predictor of adolescent aggressive behavior, conduct disorder and adult antisocial

behavior, but having adverse environmental conditions (i.e. adoptive parents with marital problems or mental conditions) was also a significant predictor. The combination of both resulted in highly increased chances of display of antisocial behavior later in life. This study provided evidence towards the several research lines that need to be taken in order to thoroughly unravel the pathogenesis of ASPD.

Coming to evidence more closely related to ASPD, Lovallo (2012) pointed out how exposure to adversity during childhood causes a change in the autonomic response to stress, and in turn this homeostatic disruption leads to a series of physiological and cognitive changes that promote impulsive and antisocial behavior. Another study by Dodge, Bates and Pettit (1990), provided evidence along the same lines, showing with a prospective study of 309 children, that childhood abuse is a significant risk factor for the development of antisocial behavior. On a more interesting aspect of this study, the authors indicate that a possible way through which the antisocial pattern of behavior is established is through a dysfunctional processing of social information. This theory is in line with more recent evidence from fMRI studies showing abnormal activation of emotion processing centers in the brain when ASPD subjects are presented with affective content. A study by Enoch et al., (2010) provided some evidence showing how vulnerable the first years of life are to adversity. In line with similar studies showing associations between antisocial behavior, MAOA polymorphisms and childhood abuse, this study showed that exposure to adverse conditions even during early life (pre-birth to 3 years), is a predictor of behavioral traits associated with an antisocial personality at age 7, modulated by MAOA activity. This essentially shows that there is no limit as to how early the effects of abuse can set in. Similar results, although not specifically focused on such an early age, have also been reported and previously discussed (Reif et al., 2007; Douglas et al., 2011). A more specific study (McGowan et al., 2009) focusing on the stress response of subjects abused as children, and translating to humans previous evidence reported in rats, took under examination glucocorticoid expression (GR) levels in the hippocampus. It has previously been reported that maternal care modulates the hypothalamic-pituitary-adrenal (HPA) axis activity, by epigenetically modifying GR expression (Weaver 2007), as reported by McGowan, the same effect is potentially taking place in humans. Post mortem analysis of GR mRNA in suicide victims with a history of childhood abuse compared to suicide victims with no history of childhood abuse and controls, showed an epigenetically mediated reduction in GR mRNA in abused subjects. A positive aspect of these findings is that as opposed to genetic modifications, changes in personality and behavior that result from epigenetically mediated effects of stress are potentially reversible. Some studies have tackled this possibility showing that this reversibility is possible at least in rats (Weaver et al., 2005).

Studying genetically and epigenetically mediated effects of childhood sexual abuse on adult psychopathology, Beach et al., (2013) reported an association between sexual abuse during childhood and substance abuse, depression and antisocial personality later in life. In addition, it was reported that the effect of abuse on antisocial personality was partially mediated by epigenetic factors. On a more general scale, several studies have linked cortisol levels to antisocial behavioral traits in childhood and adolescence (O'Neal et al., 2010; Susman et al., 2010; Hawes et al., 2009).

All this data shows that a stressful environment during childhood can have a rather determinant role in the development of a mental disorder like ASPD. As has been shown for the 5-HT pathway, when more than one factor is present in a subject, his susceptibility will grow.

Conclusions.

So far, abundant literature has provided clear evidence of the link between the 5-HT system and ASPD. It has been shown that specific low activity genotypes of the 5-HT transporter 5-HTT, its deaminating enzyme monoamine oxidase A MAOA, and its precursor tryptophan, modulate the susceptibility to developing the mental disorder. The molecular mechanisms underlying this process are however completely unknown, and although imaging studies have pointed out various regions in the PFC that present significant changes in subjects

diagnosed with ASPD, the widespread character of the 5-HT projections, make an anatomical delineation of ASPD difficult.

In a parallel way, a stressful environment during childhood has been linked to ASPD among several mental disorders. Copious research has shown that regardless of the domain, any potentially traumatic stressors (particularly at a young age), such as physical abuse, sexual abuse, or abandonment, to cite the most common, will increase the probability of developing antisocial behavioral traits which will increase the risk of repeating the kind of abuse suffered during childhood and can go further and facilitate the descent onto depression and substance abuse (Huang et al., 2012). Some exploratory research has tried to elucidate the mode of action of these stressors probing hormonal levels, particularly testosterone and cortisol, in abused and non-abused subjects, but as is the case with 5-HT, specific mechanisms are yet to be unraveled.

Additional research has shown that interaction between these two factors can exacerbate the process of ASPD development causing a stronger consolidation of its psychosocial traits. Molecular mechanisms behind this process are however unknown, which opens the debate of whether these two factors interact with each other at a molecular level causing the exacerbation effect, or are acting perhaps on different aspects of the disorder following parallel paths.

This same question has been vastly investigated under the scope of other mental disorders, particularly major depression disorder (MDD). As is the case with ASPD, chronic stress and irregularities in the 5-HT system are indicated as two major risk factors for MDD. It is clear that all the literature in this regard was produced with an aim specific to MDD, however the results obtained can be extended to an ASPD context with some caution.

As opposed to ASPD, several animal models for MDD have been established and allow for a more specific manipulation of treatment conditions at a cellular and molecular level. When considering the details of these manipulations (with some obvious exceptions, for instance specific molecular mediators implicated exclusively in MDD), there is no reason why these results could not be applied to ASPD.

In this regard, several studies have tried different stress exposure paradigms in animal models to elucidate the effect of chronic stress on the 5-HT system. The majority of these studies have focused in upstream targets, i.e. the dorsal (DRN) and medial (MRN) raphe nuclei. The majority of the 5-HT projections throughout the brain originate from these nuclei, so any effects of stress shown on them, would potentially have downstream consequences in diverse brain structures and regions.

It has been shown that exposure to stressful conditions such as chronic social defeat (CSD) paradigms (Zhang et al., 2012; Keran et al., 2010) or social subordination paradigms (Shively et al., 2003) causes discrete changes in the 5-HT system. An up-regulation of the 5-HT transporter following CSD has been reported in rats, as well as reduced expression of the 5-HT1A receptor in the PFC of the same species. On the other hand reduced tryptophan (TPH) levels were observed in macaques following social subordination. A more specific manipulation of the stress conditions, focusing on corticosterone (CORT) effects on the 5-HT system has produced controversial evidence that the effects of stress on 5-HT are partially mediated by CORT. In a direct comparison Donner et al., (2002) reported increased tryptophan-2 (TPH2) mRNA levels measured in the DRN following chronic oral exposure to CORT. Clark et al., (2008) on the other hand, reported decreased levels of TPH2 mRNA in the DRN, and additionally reported decreased 5-HT levels in the PFC after chronic CORT treatment.

There is compelling evidence of the role of corticotrophin-releasing factor (CRF) in the modulation of the 5-HT response to stress. A study done by Lemos et al., (2012) in Wistar Kyoto (WKY) rats, known for their exaggerated behavioral responses to stressors, showed reduced excitability of 5-HT neurons as well as a decreased production of TPH2 when compared to Sprague-Dawley control rats. Additionally, Prince et al., (1998) showed how intracerebroventricular (I.C.V.) injections of CRF had an inhibitory effect on the firing rate of DRN 5-HT neurons.

It is clear that there is an interaction at a molecular level between the 5-HT system and the stress response system. Exposure to chronic stressful conditions can cause several changes in 5-HT signaling that have been shown to also cause

abnormalities in downstream targets such as the PFC. In this regard, different results have been reported that indicate both enhancing or inhibiting effects of stress on the overall 5-HT transmission. This opposite effects show that there are likely several ways in which stress is putting pressure on 5-HT signaling, and this responds to multiple factors such as different mediators (i.e. cortisol, CRF, specific corticosteroid receptors) that not only modulate 5-HT at different stages, but also have diverse effects based on the nature of the stress paradigm used in the animal models. When translating this to the human context, it is easy to imagine how complex the interaction between stress and 5-HT is when it comes to facilitating ASPD. In the human scenario, additional factors come into play. Particular susceptibilities dictated by specific functional polymorphisms acting on 5-HT synthesis, transport, reuptake or metabolism; changes in the stress response as an adaptation to a history of adverse conditions; and also abnormalities in 5-HT target regions such as the PFC due to a highly increased complexity that modulates the behavioral adaptation of every subject to different social states, are some of the aspects that need consideration. It is noteworthy that any abnormalities that eventually lead to a mental disorder in humans, will of course have a molecular substrate, but will also be a result of the subject's cognitive processes as well as the perception of self and others, likely the reason why the most diffused course of action for ASPD is psychotherapy.

The majority of evidence gathered so far seems to point to an overall suppressive effect of chronic stress on the 5-HT system, acting differently on different targets, but causing in the end an inhibition of 5-HT signaling. These findings are coherent with all the evidence that has taken under analysis specific functional polymorphisms and that has reported associations between genotypes with low transcription levels and a higher risks of developing ASPD. It is logical then, that exposure of these already reduced systems to conditions of stress that will additionally inhibit them, will exacerbate the psychosocial symptoms that trigger the mental disorder, eventually leading to the anatomical changes in brain volume that have been reported in imaging studies.

So far abundant evidence has separately implicated 5-HT and stress with ASPD. It has also been shown that an interaction between them stands as a major precipitating factor often associated with a more severe manifestation of this mental disorder. A parallel research line has given insight into the possible neuro-anatomical and functional substrates that may be underlying the plethora of psychosocial traits identified as ASPD, repeatedly reporting abnormalities mainly in the PFC. It is surprising however, that little effort has been put into understanding what role stress and 5-HT interactions may be playing in the development and maintenance of PFC deficits and all the abnormalities reported in imaging studies.

The identification of specific molecular mechanisms bridging the two lines of evidence, would provide high value therapeutic targets that would essentially allow a reduction or even a complete neutralization of the detrimental effects of stress and 5-HT over ASPD development.

The knowledge surrounding ASPD and the various abnormalities associated with it has increased dramatically in the last decade with the help of novel, complex and more specific techniques. The complete mechanisms underlying ASPD are however far from unraveled and they will likely remain so for several years due to the number of factors that come into play and that determine the set of symptoms that can, however, reach subjectivity when it comes to a diagnosis.

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