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The Serotonin-Dopamine Relationship on the Aggression-Suicidal Risk Axis in Patients with Major Depression Disorder: Describing Some Social Implications

Raluca PREPELITA[1], Ana-Caterina CRISTOFOR[2], Romeo DOBRIN[3], Constantin TRUS[4], Alin CIOBICA[5], Roxana CHIRITA[6]

Abstract

In the present report we want it to see if there is a connection between serotonin and/or dopamine and the aggression-suicidal risk axis in patients with major depression disorders. 113 patients were selected and we used the following specific scales: Hamilton Depression Rating Scale, the Colombia Suicide Risk Scale, and the Buss & Perry Aggression Questionnaire. Serotonin and dopamine were determined by high pressure liquid chromatography. The results of this study are clear in terms of the relationship between neurotransmitters serotonin and dopamine on one hand and aggression and suicide risk on the other. Our analysis of the data reveals significant Pearson correlations with both aggressive serotonin and dopamine and suicide risk. Moreover, following linear regression, both serotonin levels and dopamine levels resulted in significant predictors of aggression and suicide risk. In addition, the social implications of our results are presented and discussed.

Keywords: serotonin, dopamine, aggression, suicide, major depression disorder, social implications, social dominance.

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Introduction

Today, suicide is a major concern of the global public health, with almost one million people annually dying from suicide world-wide (World Health Organization, 2017). The World Health Organization (WHO) has already stated that reducing suicide-related mortality is a major objective in the following years. This idea is in a contrast to the traditional taboo that has surrounded suicide and suicidal behaviours. The importance of studying suicidal behaviours comes from the statistics which show that approximately 45% of individuals who die by suicide consult a primary care physician within one month of death; thereby an important percentage of suicidal events may be preventable (Ahmedani, Simon & Stewart, 2014).

Therefore, identifying individuals at imminent risk of suicidal behaviour is of major importance for physicians. The major issue with identifying individuals with suicide risk comes from the fact that suicide is hard to predict because the prevalence of risk factors is high among the population, while suicide is rare. Indeed, only a minority of those with risk factors will commit the act themselves. In addition, some of the risk factors for suicidal behaviour are not specific and some of those who die by suicide are not in any risk group. However, statistics show that 90% of people who commit suicide or who attempt to commit suicide suffer from a psychiatric disorder (affective disorders, drug / alcohol abuse disorders, and psychosis or personality disorders) (Pompili *et al.*, 2009; Soloff & Fabio, 2008). Furthermore, in psychiatric populations, suicidal behaviour varies between 15-50% (Mann *et al.*, 2008).

Among the main psychiatric risk factors of suicide are two of the variables used in this paper: depressive disorder and aggression. The statistics show that, more than half of people with clinical depression have suicidal ideation. Furthermore, major depressive disorder and bipolar disorder are the psychiatric disorders most commonly associated with suicide (Oquendo, Currier & Mann, 2006). Studies show that certain symptoms of depression have been identified as leading to a high risk of suicidal behaviour. These symptoms include loss of hope, feelings of guilt, loss of general interest, insomnia and low self-esteem (Lonnqvist, 2009). Therefore, physicians should focus especially on these symptoms when trying to identify possible suicidal behaviour or ideation in their patients (Oquendo *et al.*, 2006). Beside depressive disorder, the other important psychopathological variable in predicting suicidal behaviour is the aggressive behaviour. Studies show that even when controlling the major depressive disorder as a possible cofounding variable, the results available indicate that suicide completers had higher levels of impulsivity and a lifetime history of aggressive behaviours (Turecki, 2005).

In addition to the above mentioned psychopathological predictors, some biomarkers may be also of great value when trying to predict the suicidal behaviour. The first biomarker used and measured in our research is serotonin. The serotonin

neurotransmitter has been showed in the available literature to have an inhibitory role in the activity of the brain (Daw, Kakade & Dayan, 2002; Yan, 2002). Furthermore, it has been demonstrated that serotonin is involved in regulating emotions and behaviours, including inhibiting aggressive behaviours (Davidson, Putnam & Larson, 2000; Volavka, 1999). Additionally, a serotonergic dysfunction has been associated with an increase in observed aggressive behaviors in both animals and humans (Coccaro *et al.*, 1989; Miczek, DeBold, Van Erp, *et al.*, 1994; Raleigh *et al.,* 1991). In the animal models, an inhibited serotoninergic function is associated with murdering behaviours in rats (Gibbons *et al.,* 1979). In addition, in primates models, observed aggressive behaviours were associated with low levels of serotonin (Fairbanks *et al.,* 2001).

These associations found in animal models are extrapolated in humans. In the available literature a low serotonin concentration is associated with aggression for life (Brown *et al.,* 1979), aggression in patients with mental disorders (Virkkunen & Linnoila, 1993), violent suicide attempts (Traskman-Bendz, Asberg & Schalling, 1986), impulsive killing (Lidberg *et al.,* 1985) and criminals' recidivism (Virkkunen *et al.,* 1989). Furthermore, a meta-analysis study (Moore, Scarpa & Raine, 2002) which examined the data from 20 distinct studies, found that low levels of serotonin correlated to an increase in aggressive behaviours, regardless of mental health pathologies. Therefore, a consistent relationship between a low level of serotonin and aggression is found in the available literature (Coccaro, Bergeman & McClearn, 1993).

The other neurotransmitter used in our research is dopamine. Dopamine has a far more complex relationship with aggressive and suicidal behaviour. The dopaminergic system was found to be involved in behavioural activation, behavioural motivation and reward processing (Everitt & Robbins, 2000; Ikemoto & Panksepp, 1999). In addition dopamine has an active role in modulating aggressive behaviours. In animal models, hyperactivity in the dopamine system has been associated with an increase in the observed aggressive behaviour (Harrison, Everitt & Robbins, 1997; Netter & Rammsayer, 1991). Studies on rodents, have shown that a high level of dopamine have been observed continuously before, during and after aggressive confrontations between rats (Hadfield, 1983; Tidey & Miczek, 1996). On the other hand, in humans, the dopamine levels have been associated with the recognition of aggressive behaviours. For example, one study found that after administration of a dopamine receptor antagonist, sulpiride, the subjects showed a low ability to recognize furious facial expressions (Lawrence *et al.,* 2002). However, there is also evidence that aggressive behaviour can be amplified by an increase of dopamine level (Bergh *et al.,* 1993). In addition, a study on patients with borderline personality disorder has found that a dopaminergic hyper function positively correlated with impulsivity and emotional disturbance (Chotai, Kullgren & Asberg, 1998).

We formulated four hypotheses at the beginning of this study: (1) The first hypothesis of this paper refers to a possible correlation between the level of

aggression (measured by the Buss & Perry aggression questionnaire) and the intensity of depression (as measured by the Hamilton depression scale); (2) The second hypothesis of the study that we wanted to verify in is the link between a low serotonin level in the plasma and a high aggression score on the Buss & Perry aggression questionnaire; (3) The third hypothesis investigates whether a link exists between the level of dopamine in the patient's blood and the level of suicidal ideation. The assumed relationship is that patients with a lower level of dopamine will be at increased risk of suicide; (4) The fourth initial hypothesis refers to the relationship between dopamine levels in the blood and the level of aggression of the participants. Our assumption is that a high level of dopamine will correlate with a high level of aggression.

Methodology

The sample consisted of 113 patients from the Socola University Hospital, Iaşi, Romania. 53 of the patients were male and 60 women. The average age of the sample was 41.85 ± 3.3 years old.

The following inclusion criteria were used: patients diagnosed with major depression disorder (using DSM V criteria and a using a structured clinical interview) and with age between 18 and 65 years old. Exclusion criteria were represented by: mental retardation, patients with affective disorders of organic nature, patients with dementia, patients with psychotic disorders, patients with endocrine disorders, patients with Parkinson's disease, patients with other somatic disorders that are not medically stabilized and patients who were being treated with medications that can influence serotonin or dopamine levels. Serotonin and dopamine neurotransmitters levels were determined by high pressure liquid chromatography (HPLC). The following specific scales were used: the Hamilton Depression Rating Scale, the Colombia Suicide Risk Scale, and the Buss & Perry Aggression Questionnaire. In accordance with current national and international ethics and deontology regulations and rules, the patients included in the study explained the purpose of the study, the procedures to be followed, the possible associated risks, the measures taken to respect confidentiality, the potential benefits and the fact that they could withdraw at any moment from the study. The study was approved by the Research Ethics Commission of the University of Medicine and Pharmacy "Gr. T. Popa Iasi".

Results

Correlation between the level of depression and the level of aggression

The first hypothesis of this paper relates to a possible correlation between the level of aggression (measured by the Buss & Perry aggressiveness questionnaire) and the intensity of depression (as measured by the Hamilton depression scale).

A Pearson correlation was calculated to evaluate the relationship between the level of aggression and the level of depression. The results of our study show a statistically significant positive correlation ($r = 0.255$, $n = 113$, $p = 0.006$) between aggression scores and depression levels.

Next we wanted to calculate if the level of depression can predict the level of aggression in our sample. To find out, a simple linear regression was calculated to predict the level of aggression based on the depression level $b = 0.255$, $t(111) = 13.42$ $p < 0.001$. The P value for the independent variable indicates whether the independent variable has a statistically significant predictive capacity. So, in our case, depression is a statistically significant predictor of aggression. A significant regression equation was found to be $F(1.111) = 7.732$, $p = 0.006$ with an R2 of 0.065. The p value of the variance analysis (ANOVA) is another statistical approach, in addition to the Pearson correlation p, which tells us whether the correlation obtained is statistically significant. The value of square R indicates how much of the variation in aggressiveness is explained by the variation of depression, in our case 6.5%.

Furthermore, a one way between subjects ANOVA was conducted to compare depression scores in patients with high aggression level with patients with a low aggression level.

There was not a significant difference regarding depression scores in the high aggression scores group ($M=20.13$) compared to low aggression scores group ($M=19.96$); $F(1,111) = 0.022$, $p = 0.883$.

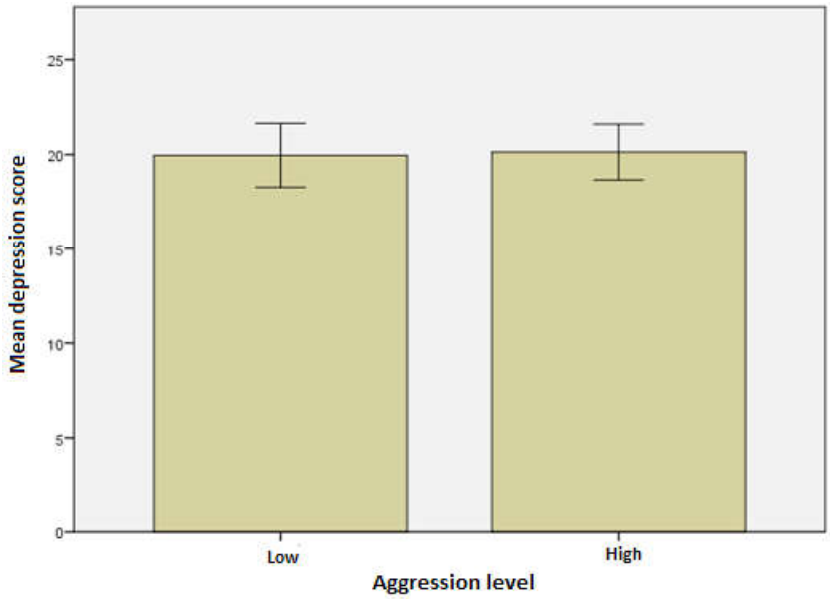

Figure 1. Mean depression score of patients with a low aggression level compared to patients with a high aggression level 3

The correlation between serotonin levels and aggression levels

The second hypothesis of the study that we wanted to verify in our study is the link between a low serotonin level and a high aggressive score. To see if this inverse correlation exists in our sample, a Pearson correlation has been calculated. The results showed a statistically significant negative correlation ($r = -0.283$, $n = 113$, $p = 0.002$) between the blood serotonin level and the aggression levels.

To determine if serotonin levels in the blood can predict the level of aggression in our sample., a simple linear regression was calculated again to predict the aggression level based on the serotonin level measured in nmol / L, $b = -0.283$, $t(111) = 36.47$, $p < 0.001$. A significant regression equation was found $F(1.111) = 9.697$, $p = 0.002$ with an $R2$ of 0.08. Therefore, blood serotonin levels are a statistically significant predictor of aggression, explaining 8% of the aggression variation in our sample. Correlation is also significant after it has been tested by variance analysis (ANOVA).

Furthermore, a one way between subjects ANOVA was conducted to compare serotonin levels (nmol/L) in patients with high aggression level with patients with a low aggression level. There was a significant difference regarding the serotonin blood levels (nmol/L) regarding in the high aggression scores group ($M=6.25$) compared to low aggression scores group ($M=8.57$); $F(1,111) = 4.243$, $p = 0.042$.

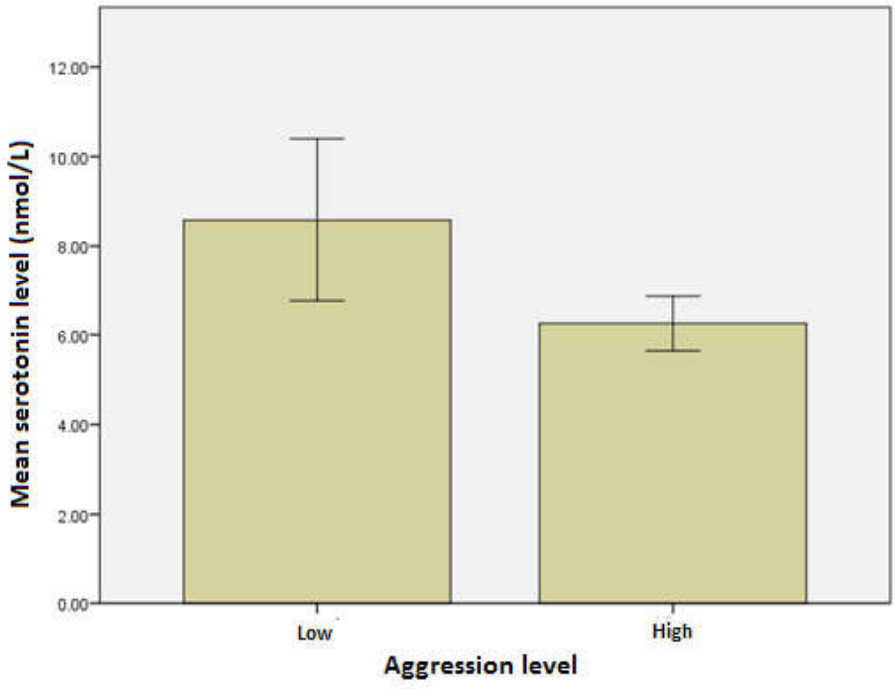

Figure 2. Mean serotonin level of patients with a low aggression level compared to patients with a high aggression level

The correlation between the dopamine level and the suicide risk

The third hypothesis investigates whether a link exists between the level of dopamine in the patient's blood and the level of suicidal ideation. To test this hypothesis a Pearson correlation was calculated. The results show a statistically significant negative correlation ($r = -0.804$, $n = 113$, $p < 0.001$) between the level of dopamine in the blood and the level of suicidal ideation.

To find out if the level of dopamine in the blood can predict the level of suicide risk in our sample a simple linear regression was calculated, $b = -0.804$, $t(111) = 25.95$, $p < 0.001$. A significant regression equation was found to be $F(1.111) = 202.689$, $p < 0.001$ with an $R2$ of 0.646. Therefore, the correlation is statistically significant; the value of p in the ANOVA analysis is less than 0.001. Also, the level of dopamine is a significant predictor of suicide risk, explaining 64% of the variation of this variable.

In addition, a one way between subjects ANOVA was conducted to compare dopamine levels (ng/L) in patients with suicide risk with patients without suicide risk. There was a significant difference regarding the dopamine blood levels (ng/L)

in the suicide risk group (M=9.4 ng/L) compared to the no suicide risk group (M=36.56 ng/L); F (1,111) =173.76, p < 0.001.

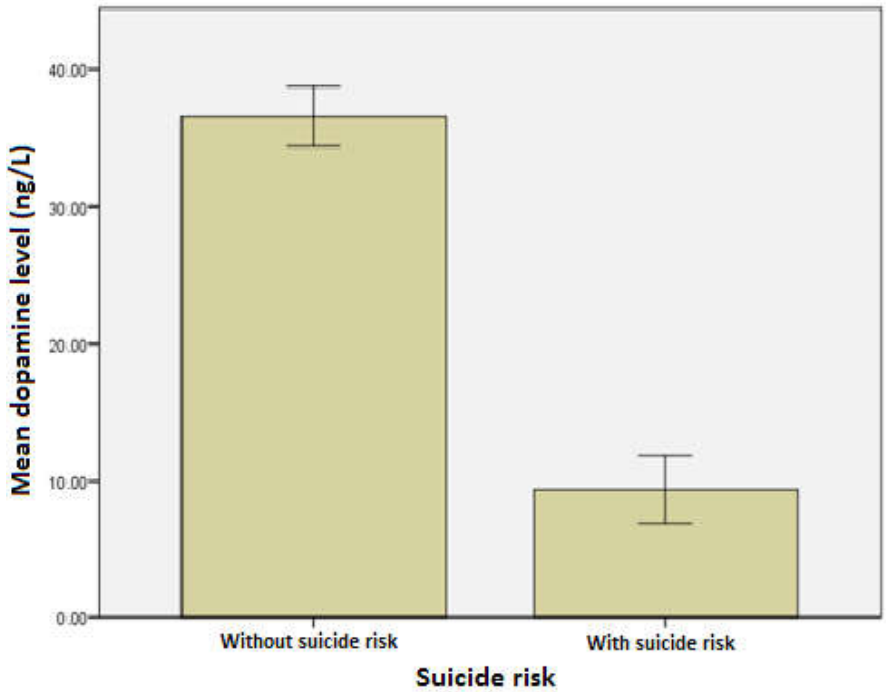

Figure 3. Mean dopamine levels of patients with suicide risk compared to patients without suicide risk

The correlation between the dopamine level and aggression

The fourth initial hypothesis refers to the relationship between dopamine levels in the blood and the level of aggression of the participants. To discover if this reverse link exists, a Pearson correlation has been calculated. The results show a statistically significant negative correlation (r = -0.277, n = 113, p = 0.003) between the level of dopamine in the blood and the level of aggression.

To discover if the level of dopamine in the blood can predict the level of aggression in our sample, a simple linear regression was calculated, b = -0.277, t (111) = 39.49, p <0.001. A significant regression equation was found F (1.111) = 9.212, p = 0.003 with an R2 of 0.077. By analyzing the variance, we found out that this correlation model is significant (p = 0.003). Moreover, the level of dopamine in the blood is a significant predictor of aggression. The level of dopamine in the blood explains 7% of the variance of the variable aggression level.

Furthermore, a one way between subjects ANOVA was conducted to compare dopamine levels (ng/L) in patients with high aggression level with patients with

a low aggression level. There was a significant difference regarding the dopamine blood levels (ng/L) in the high aggression level group (M=12.12 ng/L) compared to low aggression level group (M=20.50 ng/L); F (1,111) =8.218, p = 0.005.

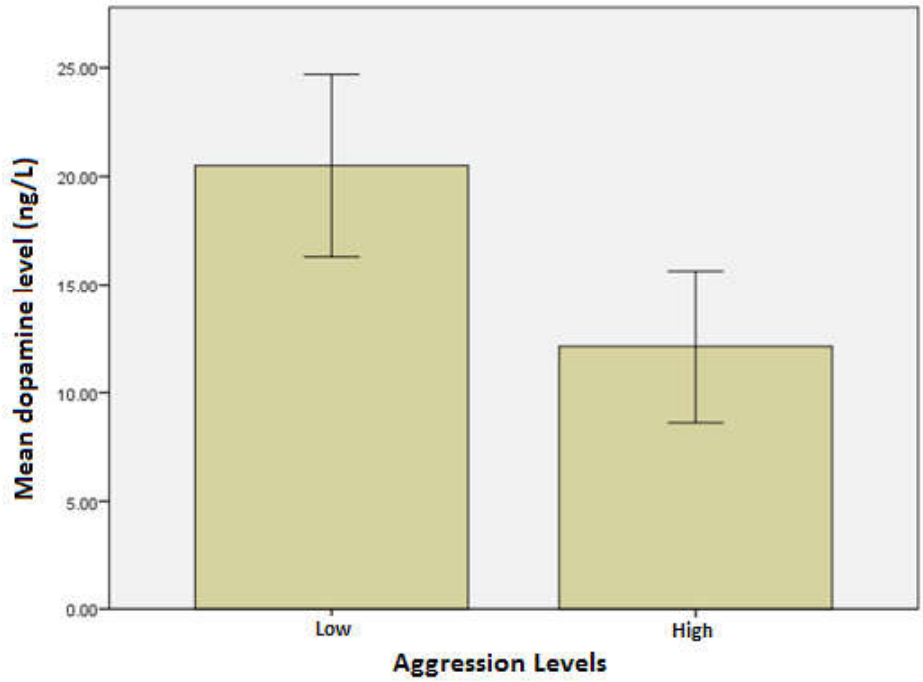

Figure 4. Mean dopamine level of patients with a low aggression level compared to patients with a high aggression level

Discussion

The results obtained confirmed our first hypothesis. Within our sample the intensity of depression correlated with the level of aggression. Moreover, we wanted to find out if the level of depression can predict the level of aggression in our sample. The linear regression calculated showed that 6.5% of the variation in the level of aggression can be explained by the variance in the intensity of depression. These results may seem surprising at first glance. Depressive symptoms usually include feelings of sadness, lack of hope and chronic fatigue. Also, depression is more commonly characterized by notions of withdrawal, isolation and chronic fatigue (American Psychiatric Association, 2013). However, psychoanalytic theory has always considered aggression and depression to be closely related. Freud argued that depression is the result of aggressive, unconscious impulses that go against the self instead of becoming conscious and turning against others (Newman

& Hirt, 1983). Although there are few empirical studies examining a direct link between depression and aggression, the results of these studies have established that this link exists (Shaffer & Piacentini, 1994).

As mentioned above, a moderate relationship between aggression and depression is reported in literature (Shaffer & Piacentini, 1994). The important question is whether depression is simply a correlation of aggression or whether depression contributes to aggressive behaviour itself. Therefore, in our statistical analysis, we included a simple linear regression. As mentioned before, in our sample the scores at the depression scale significantly predicted the scores at the aggression scale. Even so, the question remains on which way depression may predict an aggressive behaviour. It is well known that the main symptoms of depression include self-blaming easily, chronic fatigue and exhaustion (Harrington, 1994; Seligman, 1975; Shamoo & Patros, 1990). These central components of depression seem to be in contrast to aggression because aggressive individuals tend to blame others and aggressive behaviour obviously requires some energy (Apter *et al.*, 1990). A possible explanation of this unexpected connection may lie in the fact that the feelings of unhappiness and sadness accompanied by pessimism about the future, which are frequently present in depressed patients, may make an individual irritable and therefore contribute to aggressive behaviour towards others.

Thus, over the life of an individual, the internalization of symptoms, such as depression and anxiety, and the externalization of symptoms such as aggression, coexist at higher rates than pure chance, creating substantial damage to individuals' mental health. According to available literature studies, correlations between internalization disorders (depression) and externalization disorders (delinquent and aggressive behaviour) in adults are high (r = 0.48) (Kessler *et al.*, 2005). This available data is in concordance cu the results obtained in our sample of patients. A statistically significant correlation was observed in our study between the depression scores and aggression scores. Although significant, the correlation value is lower r = 0.255 in our sample compared to those found in the literature. For example, even higher values of the Pearson correlation have been reported. In one study with a sample of children aged 5 to 15 years old, the authors reported that the correlations between the symptoms of internalization and externalization was r = 0.58 (Gjone & Stevenson, 1997).

Many researches that investigated the internalization and externalization of separate symptoms have shown that, among the symptoms of internalization, depression and anxiety are the symptoms most frequent encountered throughout life (Kessler *et al.*, 2005). When it comes to the externalization of symptoms most frequent symptoms include hyperactivity and aggression (Mann *et al.*, 1992). Given the inherent complexity of studying such heterogeneous constructions, the current study focused on the relationships between the symptoms of internalization, in the case of depression and aggression, on the side of externalization. We also concentrated on the neurochemical basis of these mental health disorders.

Therefore, next we focused on the connection between the blood serotonin level and the level of the aggression measured in our sample of patients. We tested the hypothesis that a low serotonin level would correlate with a high level of aggression. The results from the statistical analysis confirmed this hypothesis as well. In our sample serotonin levels correlate negatively with the level of aggression ($r = -0.283$). Moreover, we still wanted to calculate if serotonin levels in the blood can predict the level of aggression in our sample. To find out, a simple linear regression was calculated to predict aggression level based on serotonin. Therefore, the level of serotonin in the blood of the participants is a statistically significant predictor of the level of aggression explaining 8% of the aggression variation.

The results of our study are consistent with those found in the literature. Considerable research has been devoted to the elucidation of the neurochemical base of human aggression. One of the first study on this matter found that the serotonin levels explained 80% the variance of aggression scores among a group of military men diagnosed with personality disorders (Brown, *et al.*, 1979). These results suggested that a serotonin deficiency was largely responsible for the aggressive behaviour of men in this sample. Although statistically significant as a predictor in our model, serotonin level explained only 8% of the aggression variance, and it seems like a small percentage compared to 80% found in the study before mentioned (Brown, *et al.*, 1979). This hypothesis of serotonin deficiency in human aggression has been tested hundreds of times over the last few decades and remains the most common hypothesis of the role of serotonin in pathological aggression (Montoya *et al.,* 2012; Passamonti *et al.*, 2012; Raine, 2008; Yanowitch & Coccaro, 2011). A widely cited author called the reverse relationship between serotonin activity and human aggression "perhaps the most solid finding in the history of psychiatry" (Fishbein, 2001). Looking through several recently published psychology and psychiatry textbooks, there is a lack of contradictory results the majority of available studies have found the serotonin level to be a significant predictor for aggressive behaviour (Bushman & Bartholow, 2010; Carlson, 2010; Higley & Barr, 2007).

As before mentioned, serotonin is a neurotransmitter known to be involved in regulating emotions and behaviours, including regulating aggressive impulses (Kerman *et al.*, 2011; Murphy *et al.*, 2006; Tuinier, Verhoeven & van Praag, 1996). It has been demonstrated in numerous studies that serotonin levels were lower in the cerebrospinal fluid of individuals with a high level of aggressive behaviour suggesting an inverse relationship between cerebral serotonin and impulsive aggression (Brown *et al.*, 1979; Ferguson & Savage, 2012; Linnoila *et al.*, 1983). This was later supported by numerous studies conducted in a number of methodologies, which led to a hypothesis suggesting that a serotonin deficiency could explain aggression (Duke *et al.*, 2013). However, in a recent meta-analysis, the combined weighted correlation between serotonin, aggression, anger and hostility proved to be low, with only about 1.2% of the trait being explained by

serotonin (Duke *et al.*, 2013). It is important to note that this meta-analysis does not include neuroimaging studies to evaluate serotonin function, and the size of the small effect may reflect methodological limitations. The serotonin deficiency hypothesis remains to be tested using improved methodologies such as positron emission tomography (PET) for indexing the characteristics of the serotonin system. It also remains to elucidate which specific parts of the serotonin transducer system are involved in aggression, and whether gender differences in aggression can be explained by serotonin function.

After testing the hypothesis that the serotonin neurotransmitter can influence the level of aggression, in the next hypothesis we went to another neurotransmitter, dopamine and its possible role in explaining the variation of suicidal risk in our sample. So we tested the hypothesis that a low dopamine level would correlate with a high suicide risk level. The results obtained from the statistical analysis confirmed this hypothesis as well. Within our sample, dopamine levels correlate negatively with suicide risk ($r = -0.804$). Furthermore, we still wanted to calculate if the level of dopamine in the blood can predict the level of suicide risk in our sample. To find out, a simple linear regression was calculated to predict the level of suicide risk based on dopamine Thus, no less than 64% of the variation in suicide risk can be explained by variation in blood dopamine levels.

This negative powerful correlation followed by the large percentage of the variation of the suicide risk which is explained by the dopamine blood levels may be explained by the fact that the dopaminergic system is involved in activating behaviours, the motivation to choose a particular behaviour to the detriment of another, and the processing of possible post-behavioural rewards (Ikemoto & Panksepp, 1999; Everitt & Robbins, 2000). These results should be extrapolated with caution even for psychiatric populations. The results present in the literature show that low dopamine concentrations exist in depressed patients with a suicide risk, but not in patients with suicide risk with other psychiatric diagnosis. In fact, most studies reporting an association between a low dopamine level and suicidal risk are performed in depressed patients or in different samples of psychiatric patients (Traskman-Bendz *et al.,* 1981). This is the reason why some author have speculated that dopaminergic hypoactivity in suicide attempters could be in relationship with some psychosocial risk factors related to suicidal behaviour rather than predicting it (Pitchot *et al.*, 2001).

The fourth initial hypothesis referred to the relationship between dopamine levels in the blood and the level of aggression of the participants. The expected relationship was that a high level of dopamine will correlate with a high level of aggression. To find out if this link exists, a Pearson correlation has been calculated. The results show a statistically significant but negative correlation ($r = -0.277$) between the level of dopamine in the blood and the level of aggression. And for the last hypothesis, we decided to discover if the level of dopamine in the blood can predict the level of aggression in our sample.

Therefore a simple linear regression was calculated again to predict aggression level based on dopamine level measured in ng/L. A significant regression equation was found. Moreover, the level of dopamine in the blood was found to be a significant predictor of aggression. The level of dopamine in the blood explained 7% of the variance of the aggressive level variable. Furthermore, a one way between subjects ANOVA was conducted to compare dopamine levels (ng/L) in patients with high aggression level with patients with a low aggression level. There was a significant difference regarding the dopamine blood levels (ng/L) between these two groups. However the difference was not the one expected. Patients with a low level of aggression had a significantly higher level of dopamine in their blood and patients with a high level of aggression had a significantly lower level of dopamine in the plasma.

It has been demonstrated that the dopaminergic system plays an important role in modulating aggressive behaviours (Miczek, DeBold & Van Erp, 1994). In contrast to our results, an increase in the dopamine level is associated with a higher aggressive behaviour. For example, in animal models of aggression, hyperactivity in the dopaminergic system is associated with an increase in the observed aggressive behaviour (Harrison *et al.*, 1997). Moreover, studies on rodent and their aggressive behaviours have shown that high levels of dopamine are observed continuously before, during and after aggressive confrontations between animals (Hadfield, 1983; Tidey & Miczek, 1996; Lawrence *et al.*, 2002). It is interesting to note that in humans, the dopamine system is linked, in the studies available, in particular to the recognition of aggression and previous experience of aggressive behaviours. For example, in a study on the recognition of human emotions after administration of a dopamine receptor antagonist, subjects had a low ability to recognize the facial expressions of anger compared to the control group receiving a placebo (Bergh *et al.*, 1993). Moreover, there is also concrete evidence that aggression can be enhanced by an increased dopaminergic function (Sostek, Buchsbaum & Rapoport, 1980). Furthermore, we can add that these stimulants increase aggression in humans without the presence of an ADHD disorder (Pitchot, Hansenne & Ansseau, 2001). Concerning the relationship between dopamine and other psychiatric disorders, and the influence of this neurotransmitter on aggression, dopaminergic hyperfunction has also been found to be associated with emotional impulsivity in patients with personality disorders (Chotai *et al.*, 1998).

As in our study, the available biochemical findings in the literature on suicidal, depressive and aggressive behaviour mainly involve serotonin and dopamine (Traskman-Bendz *et al.* 1986; Pitchot *et al.*, 2003; Pitchot *et al.*, 2001; Soderstrom *et al.*, 2001; Buchsbaum, Coursey & Murphy, 1976). Specifically, a correlation between serotonin dysfunction and violent, impulsive, aggressive and suicidal behaviour has been demonstrated (Coccaro *et al.*, 1989; Mann *et al.*, 1992). Furthermore, some studies have found a positive correlation with dopamine, which is shown by homovanilic metabolic acid in the cerebrospinal fluid (Verkes *et al.*, 1998). Moreover, early studies have identified a correlation between low

activity of monoamine oxidase in blood platelets and an increased risk of suicide. Interestingly, these findings were made in both healthy and depressed subjects (Skondras *et al.*, 2004). The following studies of the gene encoding monoamine oxidase limited these associations with suicidal behaviour to the monoamine oxidase-A subtype (Shih, Chen & Ridd, 1999; Du *et al.*, 2002). For example, according to the results of a study, physically or mentally abused children with a high level of monoamine oxidase-A were less likely to develop antisocial violent behaviour than those with low levels of monoamine oxidase-A (Caspi *et al.*, 2002).

Of course, all these results are opening the discussion also for the social implications of suicide and aggression in the current society. As our group also previously described, one of the most important forms of aggressive behavior which have a social and community impact are particularly delinquency and crime, and can be manifested in relation to damage, injuries, prejudice and physical harm to objects, people or one's own self (as related to suicide, as we will describe immediately) (Padurariu *et al.*, 2016). Social comparison can be also a trigger for aggressive behavior, as for example (as our group previously described) in adolescents, the frustrations may be hidden under a rather masked form as breaking rules, stealing, lying, cheating or the need for social dominance (Padurariu *et al.*, 2016). Thus the data we presented here could also have an important social component, since intervention on serotonin or dopamine neurotransmitters could have relevance on the social aspects described above.

Same goes with the suicide aspect, which are implicating a lot of social and ethical aspects to be discussed. In fact, according to some authors, the social aspects are a part of the suicidal definition, since Scripcariu *et al.* are describing this process as a tempted or actual behavior expressing a psycho-emotional tension between the individual and the social group, triggered or precipitated by circumstantial factors with a consciously designed self-destruction idea (Scripcaru, Astarastoae, & Boisteanu, 2002; Padurariu *et al.*, 2017). Again, as described by our group in the past (Padurariu *et al.*, 2017), Biberi considers the suicide as a bio-psycho-social dimensional phenomenon representing an act requiring the deviation for one of the most deeply rooted instincts of the biological structure (Beauchamps & Childress, 1994).

Thus, we do believe that the relation between these two neurotransmitters (e.g. serotonin and dopamine) and aggression/suicide versus the social aspects of life could represent an important aspect in studying the neurobiological underpinnings of these complex neurological processes and their pathophysiological manifestations, complications and associations (Balmus *et al.*, 2017; Iorga, Muraru & Soponaru, 2016; Iorga, Dondas & Ioan, 2017; Massaoudi, Ciobica, Dobrin & El Hassouni, 2019), since they are influenced by many biological variables that modify the specific neurotransmissions, including the psychosocial stress (Padurariu *et al.*, 2017).

Conclusion

The results of this study are clear in terms of the relationship between neurotransmitters serotonin and dopamine on one hand and aggression and suicide risk on the other. Our analysis of the data reveals significant Pearson correlations with both aggressive serotonin and dopamine and suicide risk. Moreover, following linear regression, both serotonin levels and dopamine levels resulted in significant predictors of aggression and suicide risk.

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