

## **Impaired social cognition processes in Asperger Syndrome and Anorexia Nervosa. In search for endophenotypes of social cognition**

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### **Summary**

A growing number of publications indicates presence of significant deficits in social cognition in patients with anorexia nervosa (AN). These deficits appear to be comparable in qualitative and quantitative dimension with impairment of the same functions among people with Asperger syndrome (AS). The aim of this study is to identify subject areas in the field of impairment of social cognition processes among people with Asperger syndrome and anorexia nervosa taking into consideration the potential contribution of genetic pathways of oxytocin and vasopressin in the pathogenesis of these diseases. In the first part of the paper a systematic analysis of studies aimed at the evaluation of the processes of social cognition among patients with AN and AS has been carried out. The results of a significant number of studies confirm the presence of deficits in social cognition in AN and AS. In addition, among patients with AN and AS there exists a similar structure and distribution of the brain functions in regions responsible for social cognition. The second part of the paper describes the role of the oxytocin-vasopressin system (OT-AVP) in the processes of social cognition in AN and AS. Its genetic basis and the possible importance of single nucleotide polymorphisms within the genes: OXT, AVP, CD38, OXTR, AVPR1A and LNPEP have also been presented.

**Key words:** anorexia nervosa, Asperger syndrome, social cognition deficits

## Introduction

In the last decade there has been a significant increase in the amount of research focused on the assessment of social cognition among people suffering from Asperger syndrome (AS) and anorexia nervosa (AN). Social cognition constitutes a separate and crucial area of social communication. It fulfils a role of a mediator between the cognitive sphere and social functioning [1]. The term ‘social cognition’ is a broad concept. It covers all aspects of social functioning and mental operations that underlie social interactions and the human capacity to perceive the intentions and dispositions of other people [2]. It is also understood as the ability to create relationships between ourselves and other people as well as the ability to use these relationships in a flexible way in social behaviour [3].

Research on social cognition consists of three main areas of activity of the human mind: the perception of emotions, perception of social signals and theory of the mind [4].

The proper mechanisms of perception of emotions and social signals allow for correct social communication and proper social adaptation processes in the human population [1]. Theory of the mind defines the cognitive process as an innate ability to assign mental states to oneself and other people with the aim of anticipating and explaining their behaviour [5]. This ability is the main way in which we give sense or predict the behaviour of another person and it plays a key role in social interaction.

## Aim

The aim of this study is to identify subject areas in the field of impairment of social cognition processes among people with Asperger syndrome and anorexia nervosa taking into consideration the potential contribution of genetic pathways of oxytocin and vasopressin in the pathogenesis of these diseases.

This paper also aims at answering the question why Asperger Syndrome (AS) and anorexia nervosa (AN) can be jointly analyzed, although those disorders seem to be radically different in terms of clinical picture, origin, course and prognosis. It is known that the two disorders were placed in separate categories of classification in ICD-10 – AS in the category of comprehensive neurodevelopmental disorders, while AN in the category of behavioural syndromes associated with physiological disturbances and physical factors.

## Asperger Syndrome

Asperger Syndrome as a neurodevelopmental disorder originates in infancy or childhood. Retarded or damaged are then those functions which are associated with the biological process of maturation of the central nervous system. AS is four times more common in boys than in girls and its prevalence is above 1% [6]. According to ICD-10, AS is characterized by the same qualitative abnormalities in social relations that occur in autism. The difference is that in AS there is no overall delay of speech and cognitive functions. Most people with AS is characterized by an average level of

intelligence, but they are physically clumsy. Disorders persist into adolescence and adulthood.

The essence of AS are difficulties in communicating with other people (axial symptom) and a difficulty in understanding the social code at both verbal and non-verbal level. Particular difficulty is found in building a map of other people's mental states (Theory of the Mind – ToM) [7–11]. Healthy people create images of mental states of other people on the basis of non-verbal elements such as eye contact, body posture and the tone of voice. People with mental health disabilities are characterized by possessing deficits in the processes of empathy and theory of the mind (ToM). Those deficits interfere with the ability of non-verbal communication; deteriorate interpretation of social signals and non-verbal emotional display. Individuals with AS have difficulty in perceiving what the interlocutor conveys in a non-direct manner. AS is characterized by a continuous course with a tendency to stabilize the functioning during adulthood [12, 13].

### Anorexia nervosa

Disorders diagnosed according to DSM-IV criteria affect approximately 2.2% of the population of young women [14] and the risk of death due to complications or committing suicide in the course of the illness amounts to almost 20% [15]. Occurrence of this disorder in the population of boys and men is ten times less frequent [16].

People with the above mentioned disorder are characterized by: 1) continuous restrictions in food intake leading to a significant decrease in body weight, 2) increased fear for gaining weight or obesity and persistent behaviour aimed at weight reduction, 3) disturbance in the way of experiencing weight and body shape, its effect on self-esteem, 4) lack of insight into the illness and disregard for its serious consequences (DSM-5) as well as a specific theory of the mind [17].

According to ICD-10 anorexia nervosa is diagnosed when the body weight of a sick person reaches and remains below 15% of the weight expected for his/her age, and/or if the weight loss is induced by avoidance of foods, provoking vomiting, purging, performing exhaustive exercise, the use of appetite suppressants, laxatives or diuretics, and/or if weight control is manifested in the psychopathological image as intrusive superior thought. Hormonal disorders of the pituitary-adrenal axis and gonads are biological manifestation of AN that, in women, lead to lack of menstruation. Other hormonal changes include an increase of levels of growth hormone, cortisol, and changes in thyroid hormone metabolism and impaired insulin secretion.

### A common feature – social cognition

In 1992, Gillberg proposed a hypothesis that anorexia nervosa should be considered in the spectrum of autism [18]. The results of research aimed at verifying this hypothesis suggest that patients with AN exhibit such behaviour as people with autism, i.e., difficulties in social interaction, repetitive behaviour, weak central coherence (inability to connect information as a whole at a higher level of integration), cognitive

rigidity and difficulty in the ToM processes [19]. These results were also confirmed in the research of Lang, Oldershaw and Tchanturia [20–23] and allowed for a conclusion that neuropsychological characteristics and some behaviour patterns are common both to AN and AS, what is more, they also display a prognostic value for the treatment of AN. Therefore, from the above presented studies it can be concluded that a common symptom of both disorders is a social cognition disorder which is manifested by difficulties with understanding emotions, their correct perception (deficit in recognizing emotions of sadness, joy and repulsion) and their lower awareness as well as deficits in ToM processes and empathy [24].

Some authors have not confirmed the occurrence of social cognition deficits in AN [25–27], even though the vast majority of studies indicate their presence – albeit at a reduced intensity [22, 28, 29] – and the persistence of these deficits despite the remission of symptoms and normalisation of body weight [23]. Findings stemming from the review of the research and meta-analyses stating that the lack of intensity of cognitive rigidity among patients with AN is a result of starvation and chronic disease, are interesting [20]. However, the argument indicating that social cognition deficits are characterised as a feature is their stability during the process of the illness [30] and prevalence among families, for example, among healthy sisters of patients with AN [31].

Simon Baron-Cohen et al. [32] in a study comparing a group of 66 patients aged 12–18 with AN with a control group of 1,600 healthy participants showed that patients with AN have an above average number of characteristics typical for autism. In addition, they observed that they displayed a below average level of empathy. It is a profile similar to that observed in autism. Similar results of the research were obtained by Kate Tchanturia research team from the Institute of Psychiatry in London [23] which assessed 66 patients with AN and 66 healthy controls using a short questionnaire: Autism Spectrum Quotient (AQ-10). The group of patients differed statistically significantly from the control group in seven out of ten evaluated tasks. Moreover, in the group of patients the level of autistic traits correlated with the intensity of anxiety, depression and reduced ability to maintain close relationships with other people [23]. This may indicate that there are common features underlying both disorders and those features can be considered as endophenotype ones.

### Endophenotype

In psychiatry endophenotype is defined as a set of clinical symptoms of a particular disease, moreover, it is assumed that this disease has a biological (genetic) origin. In the case of AN and AS studying the relationship between set of symptoms and genes turned out to be very difficult. Therefore, researchers started to search for such isolated features or biochemical processes which are not a common clinical symptom, and at the same time are also directly related to the origin of the described disorder.

In addition to the above mentioned similarities, both people with AN and AS exhibit common cognitive styles characterized by the predominance of analysis over synthesis, focus on details, difficulty in seeing the whole picture as well as rigidity of thinking disclosed in limited flexibility of behaviour [33]. In addition, among patients

with anorexia and autism there is a similar structure and distribution of the brain functions in the regions responsible for social perception [34].

Due to the occurrence of a common feature in both syndromes – impaired social cognition, which is connected with the activity of the oxytocin-vasopressin hormone system, further exploration of the genetic basis of the synthesis, secretion, reception and degradation of those hormones appears to be well founded.

### Oxytocin and vasopressin – prosocial peptides

Oxytocin (OT) is a cyclic peptide hormone, a neurotransmitter produced in the paraventricular nucleus and stored in the posterior lobe of the pituitary gland. The basic functions of oxytocin include: influencing the uterus muscle contractions during labour and participation in the act of sexual intercourse and conception (causes uterus contractions during orgasms, which facilitate the transport of sperm into the fallopian tubes) as well as influencing the secretion of milk from the mammary glands and shrinking of the uterus immediately after birth. Vasopressin (AVP) is also a peptide hormone produced by the hypothalamus, stored and secreted by the posterior pituitary gland. Production of AVP may be provoked by stimuli sent from the central nervous system informing about stress or pain. Vasopressin acts on the renal tubules, thus increasing the recovery of water and sodium ions which are excreted in urine – vasopressin concentrates the urine. Additionally vasopressin constricts the blood vessels.

It was found that both hormones, OT and AVP, apart from exerting influence on many biological functions, including reproduction, also affect the regulation of social behaviour of many mammalian species. It has been proven that the social behaviour of people is subject to the same regulations. Very interesting data was provided by the studies on the effects of nasal inhalation of oxytocin. Nasal inhalation of this hormone increases level of mutual trust [35] among the subjects as well as streamlines ToM and empathy processes [36], enhances social identification with the group [37], improves communication between partners [38], and reduces the level of stress hormones among people who have experienced separation from parents in early childhood [39]. Oxytocin level in the body also affects the strength of attachment to parents [40]. The other studies have shown that oxytocin level in the saliva is positively associated with following one's supervisor with one's eyes and negatively associated with experienced stress and depressive symptoms [41]. Although there are only several studies on the nasal inhalation of vasopressin, it was possible to demonstrate that the nasal application of vasopressin has a different influence on men and women. In men, the inhaled vasopressin reduces trust for the faces of unknown men exposed in photographs, while in women it creates an opposite effect as it increases trust for the faces of foreign women presented in photographs [42, 43]. Among patients with AS oxytocin affects the perception of facial emotions. In addition, after administration of the hormone in a study using functional magnetic resonance imaging, an increase in reactivity in the amygdala and cortical areas has been observed [44].

### The studied genes

Due to the influence of oxytocin and vasopressin on social behaviour, in many research centres there is conducted a study whose aim is to investigate the polymorphic sequences of the above presented genes in conjunction with the changes in the behaviour of individuals subjected to the study. The objective is to find a correlation between occurrence of the phenotypic characteristic and the haplotype polymorphisms in the genes encoding proteins of the information flow pathway.

In the research of Yirmiya et al. [45] it has been shown that there is a correlation between symptoms of autism and haplotype of the selected microsatellite sequences of AVP receptor (*AVPR1a*). Insel et al. [46] have shown that the length of microsatellite sequences of the promoter region of the *AVPR1a* gene has an impact on the synthesis level of AVP receptor in the brain and consequently on social behaviour.

Activity of both hormones, oxytocin and vasopressin, depends mainly on: the place and time of their synthesis, their mode of release, the number and location of receptors that they reach and the speed of degradation of both hormones. For this reason, one ought to look for the differences within the gene sequences on which the above processes depend. It may facilitate the finding of the correlation between changes in social behaviour and the polymorphic nucleotide sequences of the selected genes.

In the system of regulation of oxytocin and vasopressin activity the following genes are involved:

- *OXT* gene (located in the cytogenetic band 20p13) responsible for the synthesis of the precursor protein conducive to the creation of the mature oxytocin and neurophysin I – a peptide vital for *axonal transport* of the mature hormone;
- *AVP* gene (located adjacent to the *OXT* gene, i.e., in the same band 20p13) responsible for the synthesis of the precursor protein conducive to the creation of the mature oxytocin and neurophysin II – a peptide vital for *axonal transport* of the mature hormone and glycopeptide copeptin;
- *CD38* gene (located in band 4p15) responsible for the synthesis of hydrolase of cyclic ADP conducive to the release of oxytocin in the brain;
- *OXTR* gene (located in band 3p25) responsible for the synthesis of the oxytocin receptor;
- *AVPR1A* gene (located in band 12q14-q15) responsible for the synthesis of vasopressin receptor;
- *LNPEP* gene (located in band 5q15) responsible for the synthesis of leucyl-cystinyl aminopeptidase disintegrating peptide hormones including oxytocin and vasopressin.

The activity of the above presented genes influences the amount of both above mentioned hormones secreted into the bloodstream, the time and place of their appearance and the power of the induced effect, among other things, the profile of social behaviour (social cognition). Within each gene, there are a number of single nucleotide polymorphism – SNP, however, only a few seem to correlate with the specific phenotypes and these were selected for further studies. Within the *OXT* gene the SNP – rs6133010 was selected in the promoter area [47], in the *AVP* gene – rs2740204 [48],

in the *CD38* gene – rs6449197 and rs3796863 located in the introns [49], in the *OXTR* gene – rs2254298 and rs53576 in the introns [50], in the *LNPEP* gene – rs4869317 in the intron [51].

The research on communication and regulation of social behaviour in mammals with the participation of neuropeptides OT and AVP indicated that both of these hormones may be involved to a limited extent in the flow of neurotransmitters or intrasynaptic transmission and due to that fact only partially contribute to the risk of occurrence of autism spectrum disorders including AS [52], hence, there is a need for further study of polymorphism of the genes involved in neurotransmission among people with AS and AN.

The research carried out at the present stage of knowledge comes down to the search for a haplotype or haplotypes underlying predisposition to social disorders. A direct cause of the disorders are most likely changes (or only fluctuations) within the oxytocin-vasopressin hormonal system, which, in turn, result from the level of genes expression whose products are hormones and their receptors as well as proteins determining the level of secretion and degradation of the hormones. The expression of each gene depends on the system of regulation of these genes which must be affected by environmental factors. We still have a long way to understand the dependencies between the genetic, hormonal and intellectual levels and environmental factors. However, finding the regularity which must connect the nucleotide sequence with measurable phenotypic symptoms brings us closer to understand the entire process of the disease. In a further consequence, obtaining knowledge about the neurobiological mechanisms that link genetic variation with phenotypic effects will allow for an attempt of a pharmacological treatment of people with AS and AN in the future. It might also allow us to make use of the findings in the rehabilitation of social cognition among patients with AS and AN and may prevent the occurrence of the disease among patients who are genetically predisposed to the disease development.

## Conclusions

Results of the previous studies do not give a satisfactory answer to the question whether the above-mentioned disorders are an endophenotypic feature or condition in a disease episode, although, significant number of results indicate that a constant nature of the deficits is not dependent on the disease dynamics.

Undoubtedly, the future studies investigating the genetic substrate and nature of the deficits in the perception of emotions should include a larger number of patients in different stages of the disease (study of illnesses in the early childhood) and have longitudinal and prospective character, allowing for an assessment of whether the social cognition deficits have a characteristic of a trait or illness condition. These studies should include the level of gene expression measured by the levels of particular mRNA. In addition, introducing first-degree relatives into the research would allow for a better understanding of the complex nature of endophenotypes of social cognition in AN and AS.

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