On the origin of autism

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1 Summary of the research on autism conducted so far

I shall start from the published papers by three groups lead by Courchesne, Rodier and Gillberg: the reason for this choice is due to the fact that the fundamental assumpions of my paper are based on their works.

E. Courchesne [1] by means of an fMRI examined the brain of autistic children from the age of three years up to sexual maturity. He got the following results[2]:

A) 90% of autistic children aged 3-4 have a volume of the brain greater than that of normal children of the same age (see fig.1 pag. S22)[3]

B) The almost totality of cases examined postmortem showed a reduction of Purkinje cells. This result has been confirm by fMRI measurements[4].

This means that the cerebral capacity is reduced and this fact was confirmed in the paper of G.Allen et al.[5]

C) The autistic people in the range of 2-3 years have a surplus of 12% of grey matter and of 18% of white matter in the cerebellum and 39% of white matter in the brain compared with normal children of the same age. On the other hand the older and adolescent autistics do not have such surplus of grey and white matter (see fig 1 pag. S22)

D)This means that the autistic brain follows different patterns in its de-

[1]Center for Research on Autism, 8110 La Jolla Shores Drive, La Jolla, CA 92037 (USA)-E-mail: ecourchesne@ucsd.ed

[2]See for instance

E. Courchesne: Abnormal early brain development in autism - Molecular Psychiatry **7**, S21-S23 (2002)

[3]Lemons J. et al. Human Biology **53**, 351-354 (1981)

Courchesne E. et al. Neurology **57**, 245-254 (2001)

[4]Greg Allen, Eric Courchesne: Differential effects of developmental cerebellar abnormality on cognitive and motor functions in the cerebellum: an fMRI study of autism. Am.J.Psychiatry **160**, 262-273 (2003)

[5]G.Allen, R. Mueller, E. Courchesne: Cerebellar function in autism: fMRI activation during a simple motor task. Biol.Psychiatry **56**, 269-278 (2004)

velopment: with age the surplus of grey and white matters tend to level on normal values.

C. Gillberg [6] realized that autism is also present in individuals affected by malformations concerning the brain stem which points to a presence of an embryonic damage. Gillberg' s group was particularly interested in the thalidomide epidemic happened of the 60s which had affected 10.000 people among which 6000 survived[7]. The Swedish scholars noted that alongside thalidomide there were cases of autism, of Möbius syndrome and of Goldenhar syndrome.

Statistic involvement of the cranial nerve, in the cases more studied, were approximately in the proportion:

thalidomide:

involvement of the abducens nerve (VI)(44%)

involvement of the facial nerve (VII) (20%)

involvement of the hypoglossal nerve (XII) (19%)

Möbius:

involvement of the abducens nerve (VI)(totality)

involvement of the facial nerve (VII)(totality)

involvement of the hypoglossal nerve (XII) (64%)

In all syndromes studied the presence of ocular disorders is particularly evident.

All the investigates cases bear witness to the link between autism and XII cranial nerve disorders. The problem is then to find an association (if there is one!) between them: the purpose of this paper therefore is to find a connection among these facts.

PM. Rodier [8] starts from a similar approach to that investigated by Gillberg with the difference that Rodier takes care of teratology i.e. the study of the congenital anomalies and their genetic and environmental causes[9]

Rodier's position, as is in general the American trend, considers autism depending on environmental causes and in her papers she brings forward the experiments in favour of this theory . These tests consist in exposing experimental animals to the action of valproic acid (which is a powerful

[6]Department of child and adolescent psychiatry, Göteborg University, Sweden and St. George's Hospital Medical School, University of London, UK; E-mail: christopher.gillberg@pediat.gu.se

[7]C. Gillberg et al.: Autism associated with conditions characterized by developmental errors in early embryogenesis: a mini review - Int. J.Devl. Neurol. **23**, 201-219 (2005)

[8]Department of Obstetrics and Gynecology, University of Rochester School of Medicine, New York 14642, USA; E-mail: Patricia_Rodier@urmc.rochester.edu

[9]See

TL. Arndt, CJ. Stodgell and PM. Rodier:

The teratology of autism - Int. J. Devl.Neuroscience **23**, 189-199 (2005)

teratologic factor on the mammal embryos) and then compare these results with autistic post mortem exhibits. The most interesting thing in Rodier's papers is that there are lesions in the 12 cranial nerves along the lines of Gillberg's papers. So, for instance, there is a post mortem finding in which the facial nucleus and the superior olive are lacking.

Continuing along this line Rodier noted that the exposition to valproic acid caused a reduction in the number of motor neurons in the nuclei of nerves V, XII, VI, III and VII[10].

Besides Rodier's group has noticed that when a female rat is exposed to valproic acid at the time of the closure of the neural tube the nuclei are destroyed.

2 Assumptions of this paper

In the preceding section we have seen that the experimental research was concerned with two areas in the cerebral axis: on one side the cerebellum with the involvements in the front brain (Courchesne) and on the other side the more caudal part with its 12 nerves which are created near the cerebellum (Gillberg, Rodier). These parts (front brain and 12 nerves) are anatomically linked between them and cerebellum plays a fundamental rôle. In fact the anomalies of the frontal part of the brain are linked directly with cerebellum by means of various pathways. Just to give an example of what we mean, recalling the cerebello - rubro - thalamo - cortical pathway which originates in the cerebellum, makes synapses in the red nucleus, goes to the thalamus and finally finishes in the cerebral cortex[11]. Starting from similar considerations Gillberg says in his paper: " The anomalies of the cerebral axis don't exclude dysfunctions of the front part of the brain".

Starting from this position it' s possible to unite the results by Courchesne, Gillberg e Rodier and it is possible to get a global view of autism. To this end it is sufficient to consider the XII cranial nerves as "spies" of the pathological status of the matter of the brain plus cerebellum system. In fact the XII cranial nerves originate from cerebral axis and not from the spine, according to the classical division of any book of anatomy.

According to this view the 12 cranial nerves must be considered as an integral part of the autistic disease together with the frontal part of the brain.

[10]Rodier PM et al.: Embryological origin for autism: developmental anomalies of cranial nerve motor nuclei - J.Comp. Neurol. **370** (2), 247-61 (1996)

[11]See: http://en.wikipedia.org/wiki/Neural_pathway

The latter is affected, through the motor part of the cortex, indirectly by the cerebellum. Today we are accustomed to consider autism a mental disease. In this way we put the lid on other very serious disorders (for example ocular, intestinal disorders, the lack of speech etc.) which have the same importance as mental retardation. In our view we must put all disorders of autism on the same footing because they are all neurological and linked by pathways among them[12].

According to this opinion if one wants to understand the autism syndrome one must consider the system (brain, cerebellum, XII cranial nerves) as a whole entity. In fact all three parts are linked by the motor part of the nervous system. We can therefore reasonably think of this "overgrowth" of brain mass as having produced a kind of chronic inflammation; in the following we shall indifferently speak of autism or "chronic inflammation". This situation is responsible for all the troubles both of nervous (lack of speech, intestinal trouble etc.) and psychological origin (lack of social interaction, recognition of faces linked to the social interaction and in general linked with human social life etc.). In support of the fact that autism has a completely nervous origin and not a "psychological" one, see the paper of Porges[13]. He, according to a point of view which goes back to Charles Darwin, claims that social interaction is due to the vagus nerve and this in the whole class Mammalia[14]. This position is also supported by Paul MacLean[15].

Let us summarize: we have reduced the result of many experiments (Courchesne, Gillberg and Rodier) to only one: autism (or chronic inflammation) is a disease which affects the nervous system through brain, cerebellum

[12]See the pathways which connect the cerebellum with the motor cortex
http://en.wikipedia.org/wiki/Motor_cortex
http://en.wikipedia.org/wiki/Primary_motor_cortex
http://en.wikipedia.org/wiki/Premotor_cortex
http://en.wikipedia.org/wiki/Supplementary_motor_area
and with the spino-cerebellar tract:
http://en.wikipedia.org/wiki/Spinocerebellar_tract
http://en.wikipedia.org/wiki/Mossy_fiber_%28cerebellum%29
http://en.wikipedia.org/wiki/Purkinje_cell
http://en.wikipedia.org/wiki/Vestibular_nervehttp://en.wikipedia.org/wiki/
Dentate_nucleus

[13]Porges S.W.: The polyvagal theory: phylogenetic contribution to social behaviour - Physiology and Behavior 79, 503-513 (2003)

[14]Darwin C.: The expression of emotions in man and animals. London: John Murray. 1.st edition (1872)- Look for instance p. 69
Or
http://darwin-online.org.uk/contents.html

[15]see
http://en.wikipedia.org/wiki/Paul_D._MacLean

and XII cranial nerves.

But now we have to discuss the nature of this disease: is it genetic or what? Fortunately this problem has been solved in the last 30 years.

Michael Rutter has solved this problem applying a well known procedure of experimental technique[16]. He was able to show that, taken two identical twins, neither are autistic or both are. This kind of measurement is based on the principle "all or nothing". The idea was originally due to physicists in XIX century by which Eötvös measured the torsion of a wire in 1908 which allowed Einstein to found the theory of General Relativity[17]. The difficulty with such measurements is that one has to do with human beings (the twins) who have almost an infinity of variables (not only one i.e. the torsion on a wire!). Rutter repeated many times this measurement overcoming many difficulties and the results were invariably the same. His results will be taken as a point of departure for this paper and autism must be considered a genetic disease even if certain facets make it slightly different from what we understand as a genetic disease.

Coming back to the results by Courchesne (see Courchesne' s papers) we said that the inflammation slightly reduces with age in autistic people. This doesn't mean that an autistic person, becoming older, can recover completely (such cases are absent from scientific literature and this fact is in agreement with the fact that autism is genetic) but what can happen is that an autistic person improves slightly. This behaviour finds an explanation in the data of fMRI and the growth curves of cerebral matter.

The main contributions given by Rodier and Gillberg are to have brought to light the fact that many syndromes (thalidomide poisoning, syndrome of Möbius, valproic acid poisoning etc.) have in common with autism certain autistic symptoms. This means that the autistic syndrome has its origin in the formation of the nervous system which appears at the beginning of gestation.

Research in this sense has begun by a group of italian researchers in collaboration with other groups[18]

Particularly interesting is the first paper in which the authors find an

[16]See for Rutter's work my site
http://xoomer.alice.it/bioresautism/padre.html

[17]See
http://en.wikipedia.org/wiki/Equivalence_principle

[18]M. Elia et al.: A genetic variant that disrupts MET transcription is
associated with autism - PNAS (Proceedings of the National Academy of Sciences of the USA)- 1 September 2006

M. Conciatori et al.: Association between the HOXA1 A218G plymorphism and increased head circumference in patients with autism - Biol. Psychiatry **55**, 413-419 (2004)

association with autism of MET, which is an oncogenetic factor called mesenchymal epithelial transition. This receptor has an important rôle in various functions among which there is a gastrointestinal repair and the growth of the cerebellum. Considering the importance of cerebellum in the research on autism we shall call this factor MET factor to underline the importance that this gene could have in the pursuit of the gene (or genes) of autism. In my paper this "MET factor" will be responsible for various troubles in the interactions of brain, cerebellum and 12 cranial nerves.

Apropos of the diction "MET factor" we must make some very important clarifications. With these words we don't mean in general that particular oncogenetic factor taken into account in the paper of E.Elia et al. but we mean the gene, still not known, responsible for autism. Therefore the words "MET factor" remain in general for this gene we are looking for. So for example in the paper by D.M.Sikore et al.[19] the authors, taking into account the Smith-Lemli-Opitz syndrome[20] , which turns up through a deficency in cholesterol metabolism linked to the 7-dehydrocholesterol (7-DHC) reductase, note that this syndrome is associated with the majority of symptoms of autism. This situation is much similar to the syndromes observed by Gillberg for thalidomide and Rodier for valproic acid. The deficiency of 7-DHC for cholesterol gives similar symptoms in autism but it does not coincide with autism itself. Therefore the words "MET factor", in my draft, can include also 7-DHC reductase as a first "approximation" toward the identification of the autism gene. In fact I am considering in a forthcoming paper the possible links between autism and the chemistry and biology of cholesterol: in this work I am still using the words "MET factor".

A consequence of this new outlook is that many theories on autism , sometimes very bizarre indeed, are no longer sustainable. Here I give one example of this kind of theory which, though not bizarre, must be discarded applying the so called "Occam's razor"[21]

Recently Pierce et al.[22] used fMRI to examine the behaviour of autistic

[19]Sikora D.M., Pettit-Kekel K., Penfield J., Merkens L.S., Steiner R.D. 2006. The near universal presence of autism spectrum disorders in children with Smith-Lemli-Opitz syndrome. Am. J. Med. Genet. Part A 140A:1511-1518.

[20]See for example

http://www.geneclinics.org/profiles/slo/details.html

http://en.wikipedia.org/wiki/Smith-Lemli-Opitz_syndrome

[21]This principle is due to William of Occam (c. 1288 - c. 1347) an English Franciscan friar and scholastic philosopher. In explaining some phenomenon one must be very careful to eliminate everything that make no difference in the observable prediction. In Latin is "entia non sunt multiplicanda praeter necessitatem", or "entities should not be multiplied beyond necessity".

[22]Pierce et al.: The brain response to personally familiar faces in autism: findings of

children compared with normal children. They were shown the faces in pictures of family members (mother, father etc.): the answers of autistic children were lacking in activity of the frontal lobe (see figure 8 pag. 161 of the quoted paper). The absence of a response from autistic children to optical stimuli has been explained by Courchesne and co-workers to the partial absence in the cortex structure of minicolumns, which are particular structures in primate primary visual cortex[23]. The introduction of further structures (like the "mirror neurons") for explaining the lack of recognition of the faces of the members of the family is typically an assumption which must be abolished applying the "Occam razor": the assumption of "mirror neurons" becomes completely useless.

Our next task in the following of this draft will be

1) autism can be explained with the anatomy of cranial nerves in the presence of a still unknown gene.

2) there is a particular test which is based on Rutter' s experiments which, if improved, can replace fMRI for a rapid and safe diagnosis of autism.

3) if all the assumptions are correct, we shall have a clue for looking in the right place to discover the still unknown gene.

3 Autism and theory of cranial nerves

We will fix our attention on that part of the human brain which contains the cerebellum that is rhombencephalon.

The rhombencephalon contains, besides cerebellum, also the medulla oblongata and the pons Varolii.

Now we' ll give a concise explanation of the figures which are useful to localize the anatomical site where autism takes place.

In figure 1 at page 8 we' ll get a glance at the human brain.

We' ll look at that part of the brain called rhombencephalon (figure 2 at page 9). Moreover, in this part, we shall consider that part which is beneath the cerebellum and is between pons Varolii and medulla oblonga (figure 3 at page 10). In this area the majority of 12 cranial nerves have their origin (some of these nerves are show in figure 4 at page 11).

Going from the cranial part to the caudal part we meet the XII cranial nerves in this succession:

I – olfactory nerve

II– optical nerve

fusiform activity and beyond. Brain, 127,2703-2716 (2004)

[23]See

http://en.wikipedia.org/wiki/Cortical_minicolumn

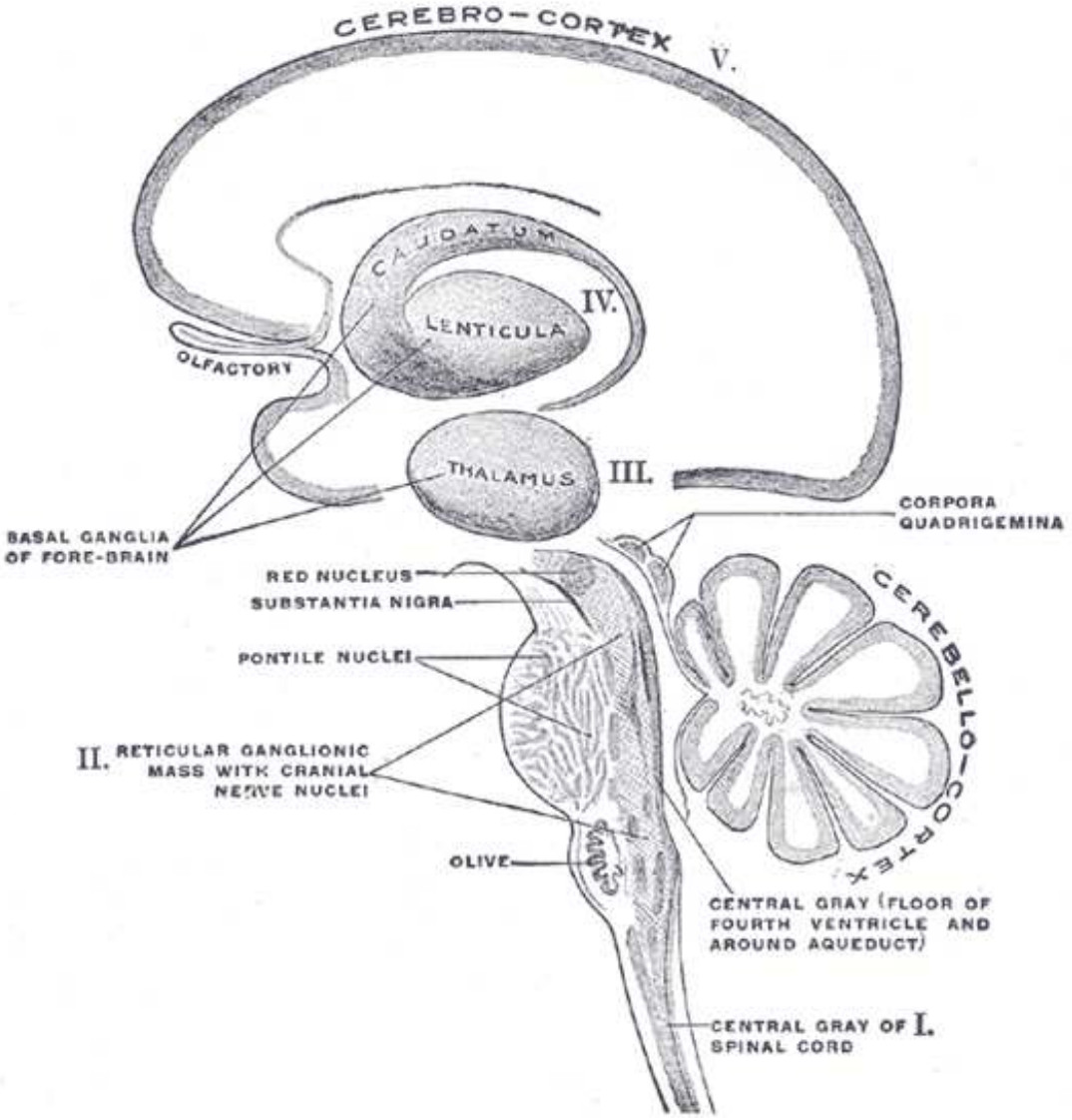

Figure 1: In this figure there are the various parts of the brain. The rhombencephalon is in the lower part of this figure. There are highlighted the pons, medulla oblongata and the cerebellum. (Gray678.eps)

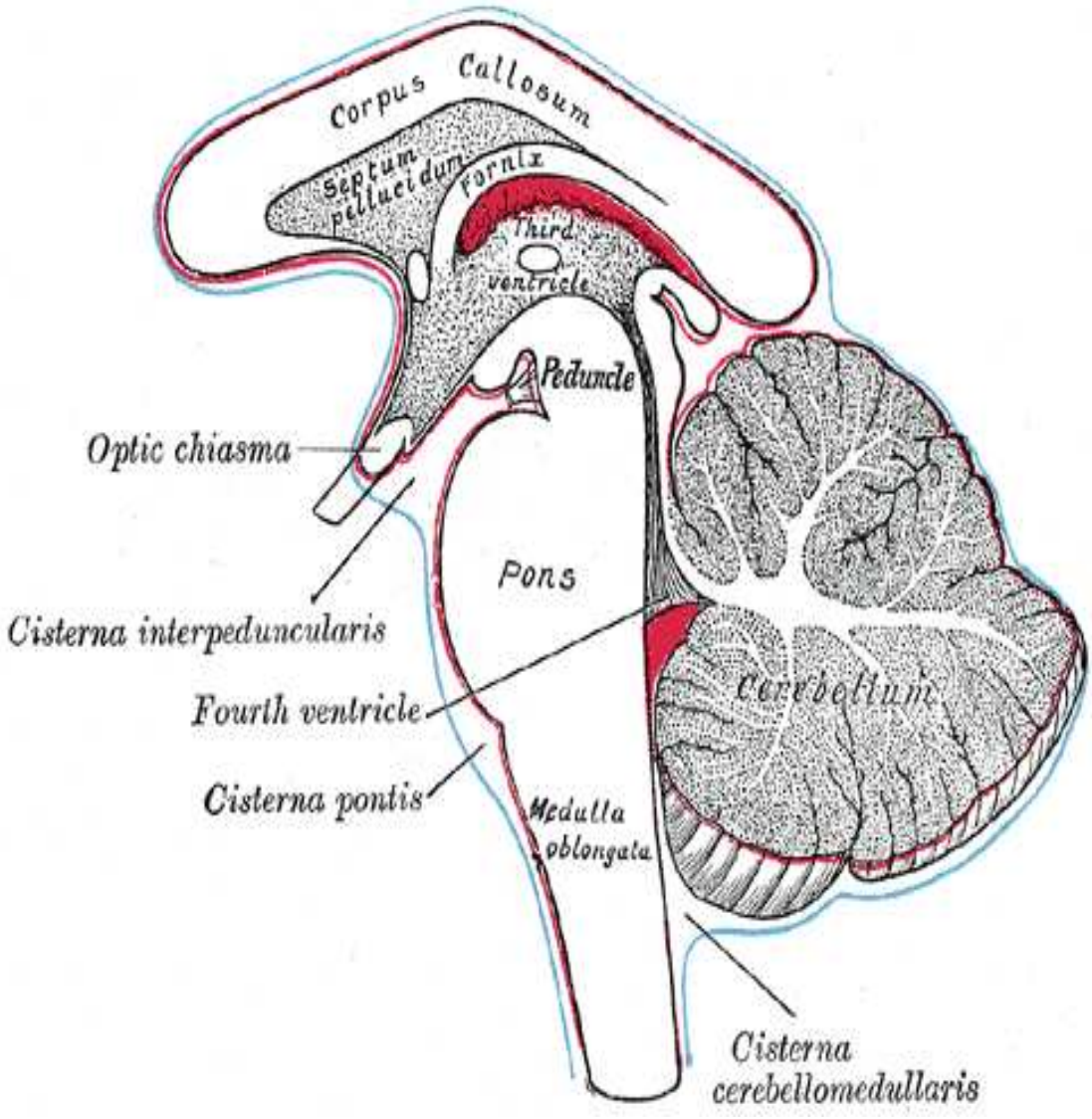

Figure 2: In this figure there is the rhombencephalon more enlarged (the lower part of the preceding figure).(Gray768.eps)

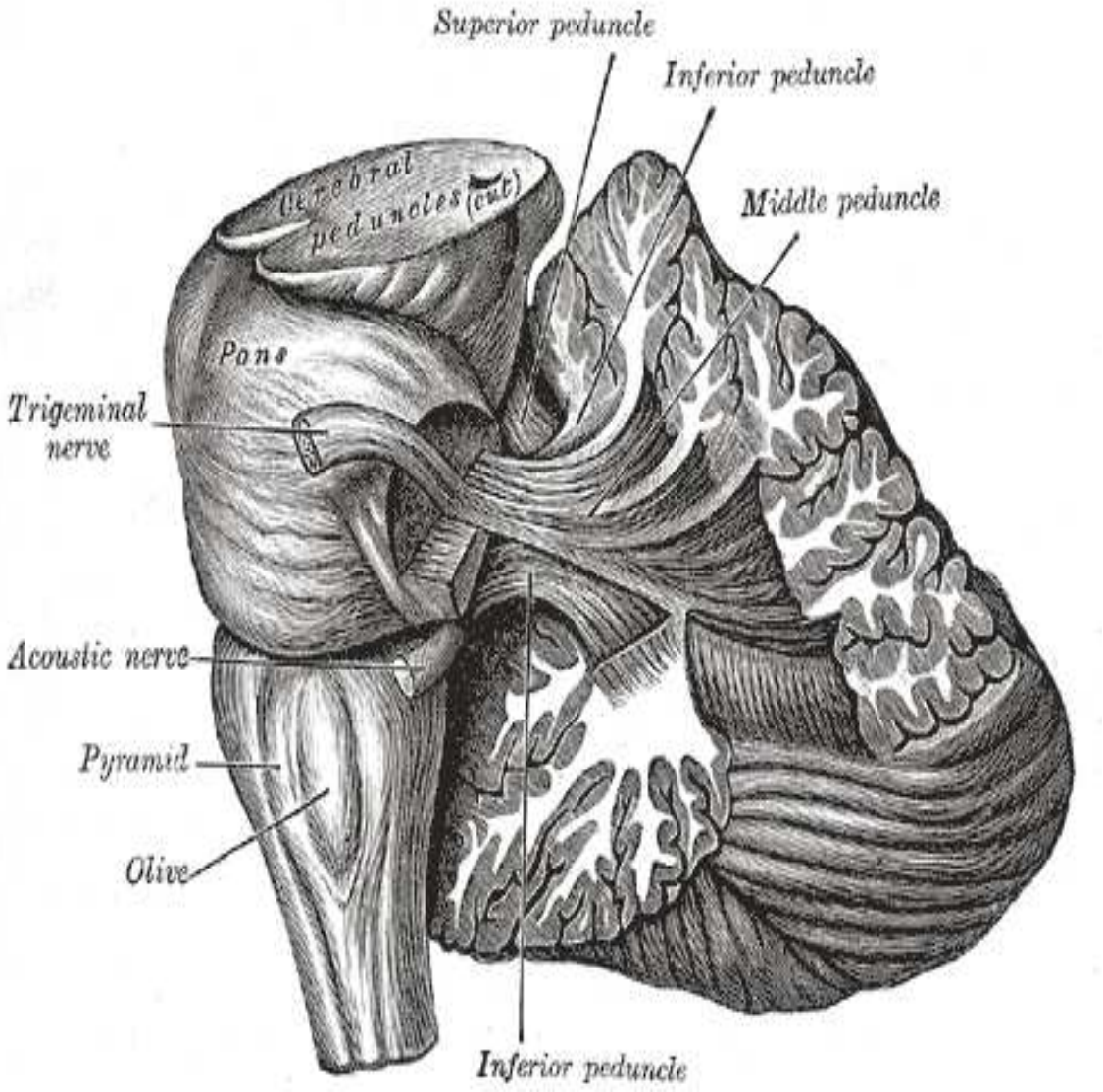

Figure 3: In this figure there are the origins of the cranial nerves once the cerebellum has been moved from its position where it covered the stem of the brain.(Gray705.eps)

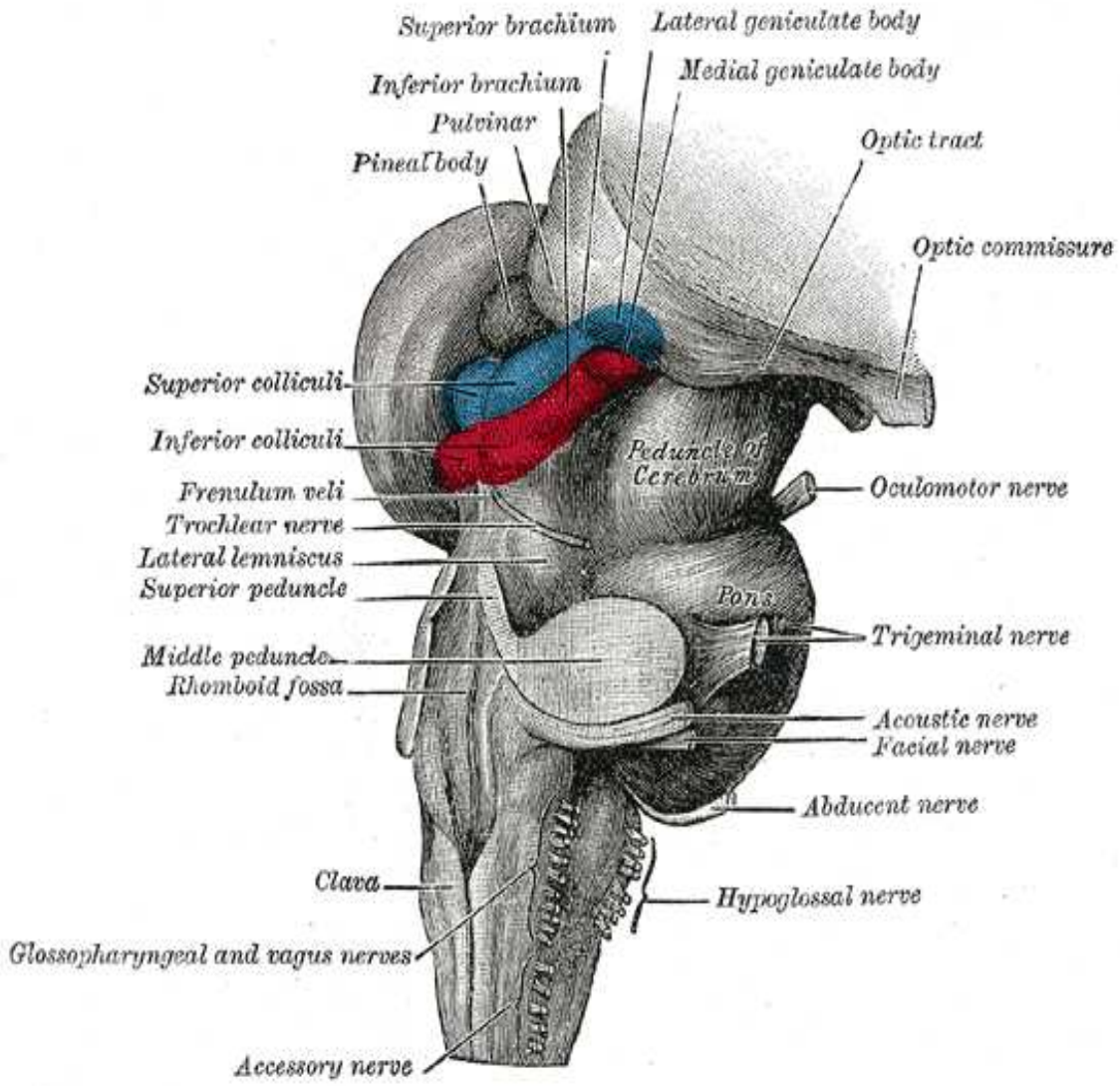

Figure 4: In this figure the cerebellum was completely removed; in this way the origin of some of 12 cranial nerves are highlighted.(Gray719.eps)

III– oculomotor nerve
IV – trochlear nerve
V – trigeminal nerve
VI – abducens nerve
VII – facial nerve
VIII – acoustic nerve or vestibulocochlear nerve
IX – glossopharyngeal nerve
X – vagus nerve or pneumogastric nerve
XI – spinal accessory nerve
XII – hypoglossal nerve

As we shall see in the next section, the nerves from VI to X are the nerves which are more important in our considerations: the other nerves are involved in autism but take part in the inflammation indirectly. We say they are "dragged" because of topographic proximity of nerves belonging to neighbouring zones (from V up and from XI down).

Now we shall examine which kind of disorders can be explained with the theory of cranial nerves.

3.1 Abducens nerve (VI) - Other nerves depending on it: II,III,IV

This nerve concerns the autistic disorder which affects the eye; more exactly we refer to the muscular apparatus which moves the eye by means of the extra-ophthalmic six muscles. As we shall see in the following, the autistic disorder is essentially more motorial than sensorial in nature i.e., in general, the MET factor concerns mainly the conjunction of nerve with the muscle.

In figure 5 at page 13 the six ocular muscles are shown; the lateral rectus muscle (fifth in the figure) is the only one which is innervated by the abducens nerve; the other muscles are innervated by nerves II, III e IV.

According to our assumptions, the others nerves (II,III,IV) have not been particularly hit by the MET factor and only the VI nerve was hit. This means that the movement, by which the autistic person looks laterally, is, in a certain measure, prevented. At this level of our diagnosis we are obliged to use sentences of the kind "in a certain way" waiting for the analysis made by means of sophisticated devices i.e. using PET or MRI, now completely lacking. These apparati are necessary to measure the ability of the abducens nerve in behaving normally because the way of looking of small autistic children is definitely dysfunctional.

In fact small children (of the age of about 3-4 years) have a strange way of looking which upsets parents and in general adults. This "strange way of

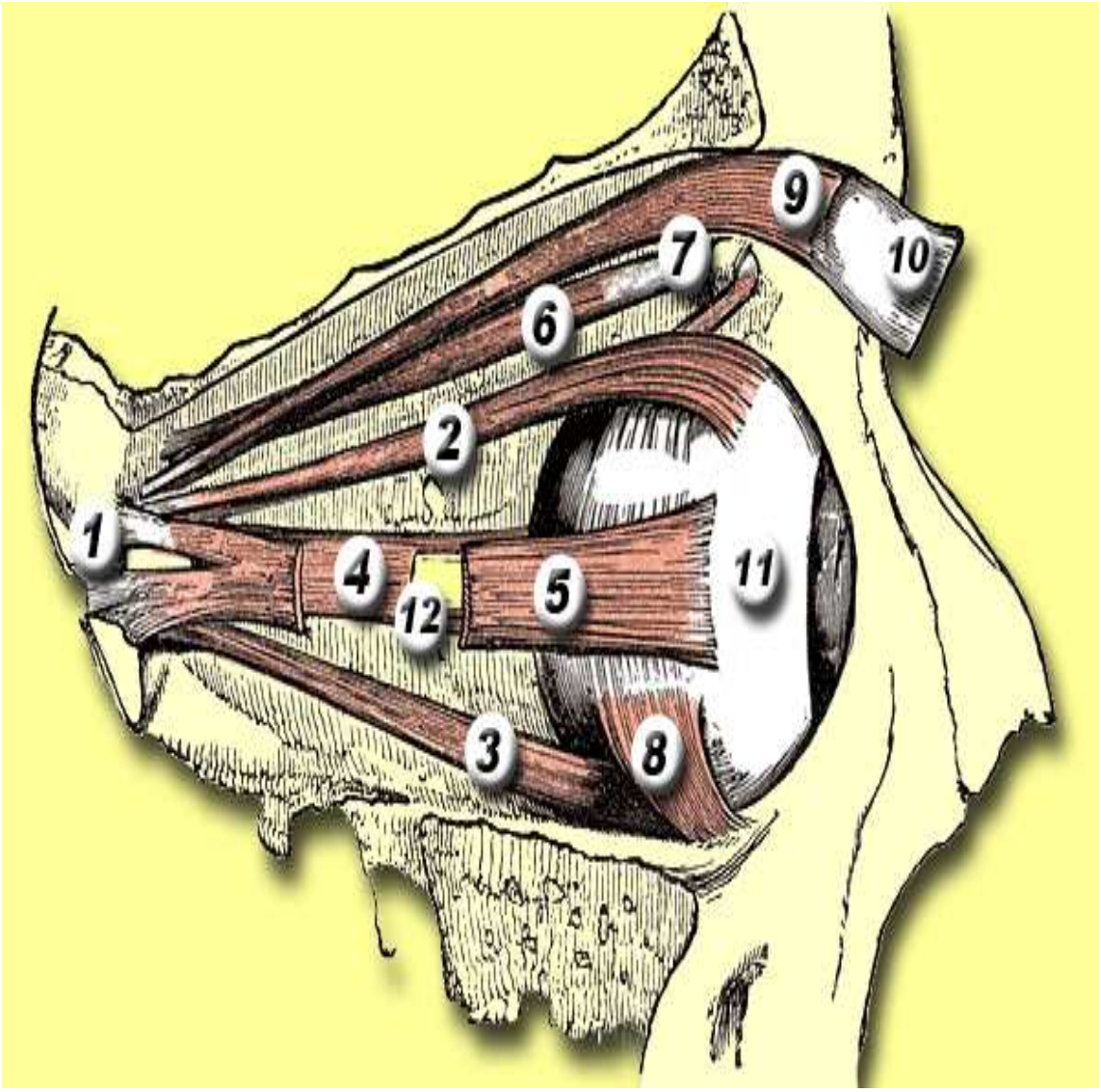

Figure 5: Muscles: 2-higher;3-lower;4-median;5- **lateral**. Other muscles:9-lift of the eyelid. Other structures: 1-Zinn's ring;7-trochlea;10-higher tarsus;11-sclera;12-optical nerve. (Eyemuscles.eps)

behaving" consists in running to and fro very near a wall trying to look in the opposite directions of their motion. The more obvious explanation of this behaviour is that the child, who is not able to speak, sees the objects having a non natural placement in space and so he/she tries to find, subconsciously of course, a different solution to this problem. He/she is trying to rotate the eyes sideways accompanying them with the mouvement of the head; in this way he/she gets over the difficulty of rotating the eyes sideways.

When the optical system tends to normalize because of development with age, as we have seen previously, there is always, in the autistic way of observing, a strong incapacity of looking sideways. Therefore the autistics, if called by a person at their side, find it difficult to make this movement: keeping their head still rotates the eyes to look but he finds it better to do it this way: rotating their head keeping his eyes looking straight in front.

To this end we notice that the complete interruption of the VI nerve causes a diplopia (i.e. a double vision) due to the lack of the action of the lateral rectus muscle: the eye is compelled to stay in a median position in the orbit. This situation is very similar to the autistic's way of looking. The difference to normal people is however that the autistic person is not able to tell other people the discomfort of his situation. So, I suppose, he is running along a wall trying to correct this "double vision" as mentioned above.

We notice that the abducens (VI), facial (VII), oculomotor (III) and trochlear (VI) nerves are very close in a very small area. This area is therefore particularly crowded with nuclei of nerves. So it would be enough for the "MET factor" to cause the inflammation of a single nerve that such an inflammation would also affect other nerve nuclei nearby (see figure 6 at page 15).

3.2 Facial nerve (VII). Other nerves depending on it: V, VIII

If one looks at the figures 7, 8, at pages 16, 17 one realizes that in the auditory canal we have three nerves i.e. facial, trigeminal and acoustic. If even only one of these nerves is inflamed by the "MET factor" one expects an escalation of autistic pain in this area.

In fact there are a further three typical syndromes besides the one we saw previously due to abducent nerve.

1 - Autistic people plug up their ears with their hands when they "judge" there is a strong noise. We shall see in a moment there is another cranial nerve (vagus nerve) responsible of inflaming the area near the auditory canal.

2 - The principal function of the motor part of the facial nerve is to control

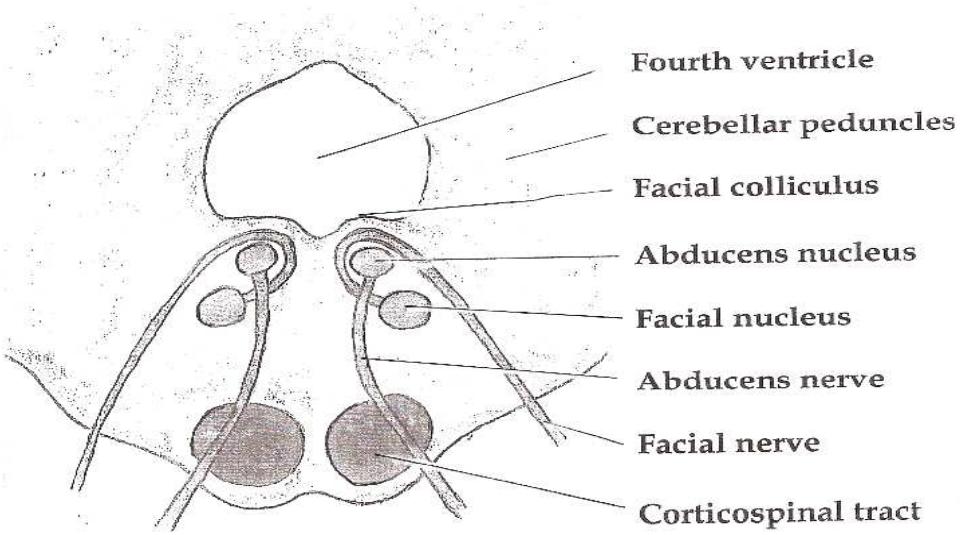

Figure 6: The nuclei which give origin to the abducens and facial nerves.(Brainstem_Abducens.eps)

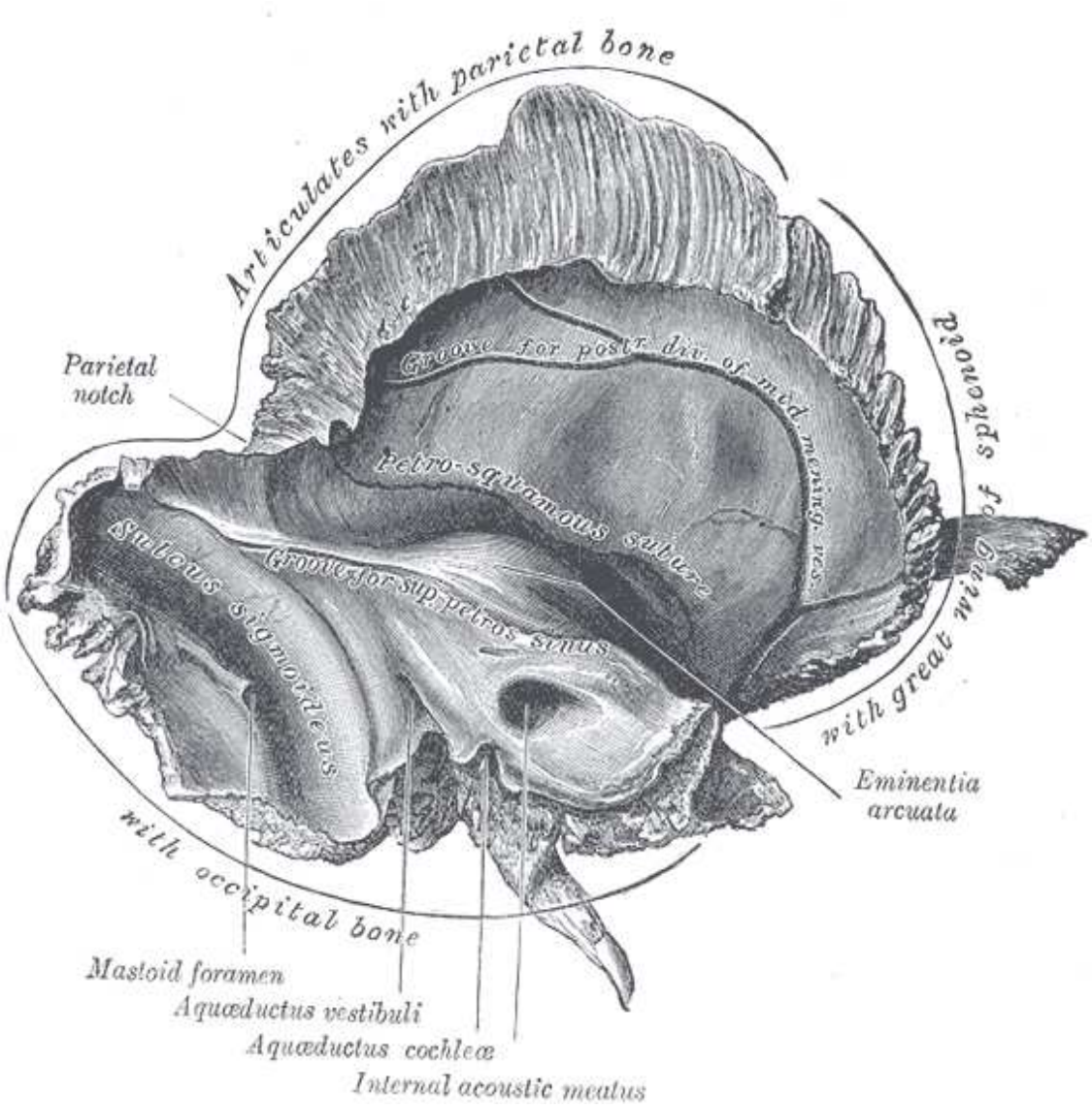

Figure 7: Part of the auditory canal; next figure shows the internal of the auditory canal with the nerves.(Gray138.eps)

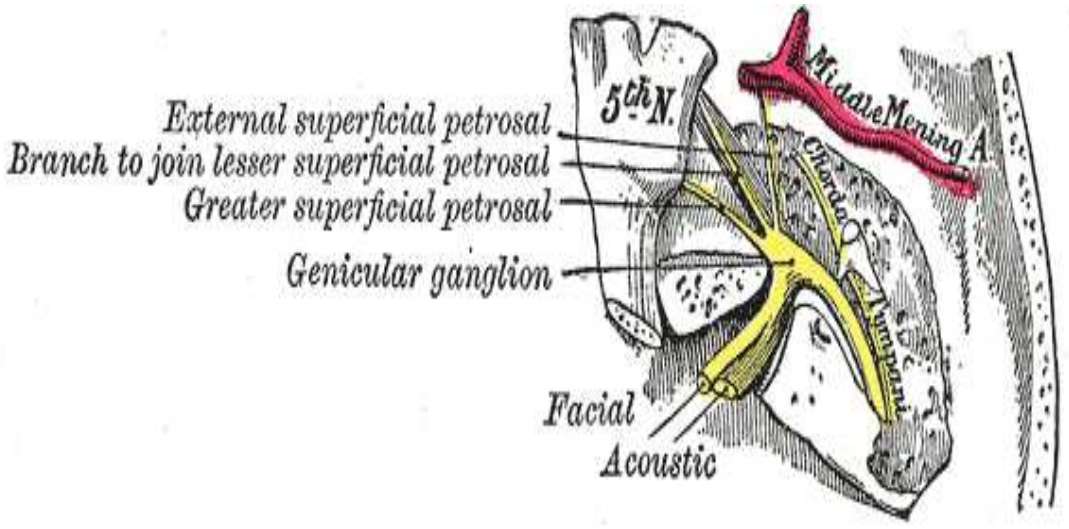

Figure 8: Trigeminal (V), facial (VI) and acoustic (VIII) stay together in the auditory canal.(Gray789.eps)

the muscles of the face in order to give other people a measurement of their emotional state. It is well known that autistic people cannot convey their emotional state outside i.e. they cannot carry information from SNC outside and therefore their faces are like blank masks.

3 - Similarly the sensorial part of the facial nerve is deputy to carry the sense of taste toward the SNC. It is very common for autistic people to show very "strange taste" towards certain foods and besides many autistics have very serious problems to nourish themselves.

3.3 Vagus nerve (X). Other nerves depending on it: IX, XI

These three nerves, coming out from the skull through the jugular foramen, influence each other as far as the "MET factor" is concerned. So if the "MET factor" has affected the accessory nerve, the person is unable to lift both shoulders; the only difficulty is to get any kind of collaboration from an autistic, even for such simple gestures, so this test is almost useless to exploit.

The other two nerves are extremely important. In fact as for the glossopharyngeal nerve we note that it has motor fibres which open and close the pharynx; if the glossopharyngeal nerve is affected by the "MET factor", it is understandable why the pronunciation of words is so seriously compromised.

This situation is even worse because of the presence of the vagus nerve. This nerve in fact has a branch going to the larynx and the other going to the pharynx. If the "MET factor" prevents these branches to operate correctly, together with the glossopharyngeal nerve, it is obvious that it becomes almost impossible to pronounce words so that autism is a typical disease affecting "dumb people".

4 Vagus nerve and gastrointestinal tract

As it is well known the vagus nerve is responsible for a lot of innervations. Are due to the vagus nerve the heartbeat, gastrointestinal peristalsis, perspiration, movements of some muscles of the mouth etc. Besides this the vagus nerve receives sensations from the external ear by means of Alderman's nerve.

The most important branches of the vagus nerve are: 1 innervation of the heart and 2 innervation of the intestine.

4.1 Innervation of the heart

It is well known that the innervation of the heart, though being due to the vagus nerve, forms a subsystem of the nerve itself for the following reasons: 1 the cardiac muscle is more similar to a skeletal muscle; 2 the action potential which is responsible for the heartbeat is generated inside the heart itself; 3 the transfer of these impulses happens for the whole cardiac muscle causing in this way a synchronous wave which goes from auricles to ventricles.

For these reasons the cardiac muscle cannot behave like the rest of other muscles. So certain cardiac dysfunctions can be detected by means of the pulmonary system which is similarly innervated by the same branch of the vagus nerve.

In our italian association of parents (Angsa: Associazione Nazionale Genitori Soggetti Autistici), one year ago a case came to light which can be probably explained by means of our theory. An 24 year old autistic boy died in this way: one month before his feet swelled up and his outer ear swelled too assuming a blue colour, then he went to an emergency unit and there he died. The post-mortem examination showed a pulmonary cardiac oedema.

These facts put together, can be explained, I suppose, assuming that, according to our theory, the vagus system was inflamed. I know quite well that a single case is not enough to have the absolute certainty that something is going wrong. However one must be very cautious and always alert in the case of autistics who are not able to convey their state of health. As far

as I know both parents and doctors give no importance to the health of the hearts of autistic people they are so much concerned only by the psychological problems. For the same reason we lack statistical data on heart disease of autistic people so that anything can happen like what happened to that Italian autistic boy.

There is another disorder, linked to the vagus system, that is a kind of intestinal trouble which is considered by medical doctors as one unimportant colitis. The man who stressed the importance of this kind of colitis for autistic people was Prof. Kalle Reichelt of the University of Oslo: it is due, as we shall see according to the present theory, to the particular conformation of the intestinal nervous system.

4.2 Enteric nervous system (ENS)

It is well known that the autonomic nervous system (ANS) is formed by the sympathetic system and the parasympathetic system: the sympathetic ganglions are near the backbone and the parasympathetic ganglions are near the organ of which they are targets (heart, salivary gland etc.)(see figure 9 page 20).

Research in gastroenterology came recently to the conclusion that the relative part to the vagus nerve, which innervates the intestine, must be separate from the ANS and was called enteric nervous system (ENS). Such a system is endowed of so many peculiarities that it is also called "second brain"[24].

In particular it is able to: 1 - regulate the endocrine function of the intestine in a completely independent way to other parts of nervous system. 2 - regulate the nerve-muscle relationship within the intestine. 3 - secrete various very important neurotransmitters, as for instance serotonin.

4.3 Vagus nerve and intestine: some observational results

Let us remember briefly the path of the vagus nerve. From figure 10 page 22 we can see that this nerve goes from the skull to the stomach running parallel to the oesophagus (let me call this part "superior vagus") and then goes from the duodenum to the second half of the transverse colon (let me call this part "inferior vagus").

[24] See
http://en.wikipedia.org/wiki/Enteric_nervous_system

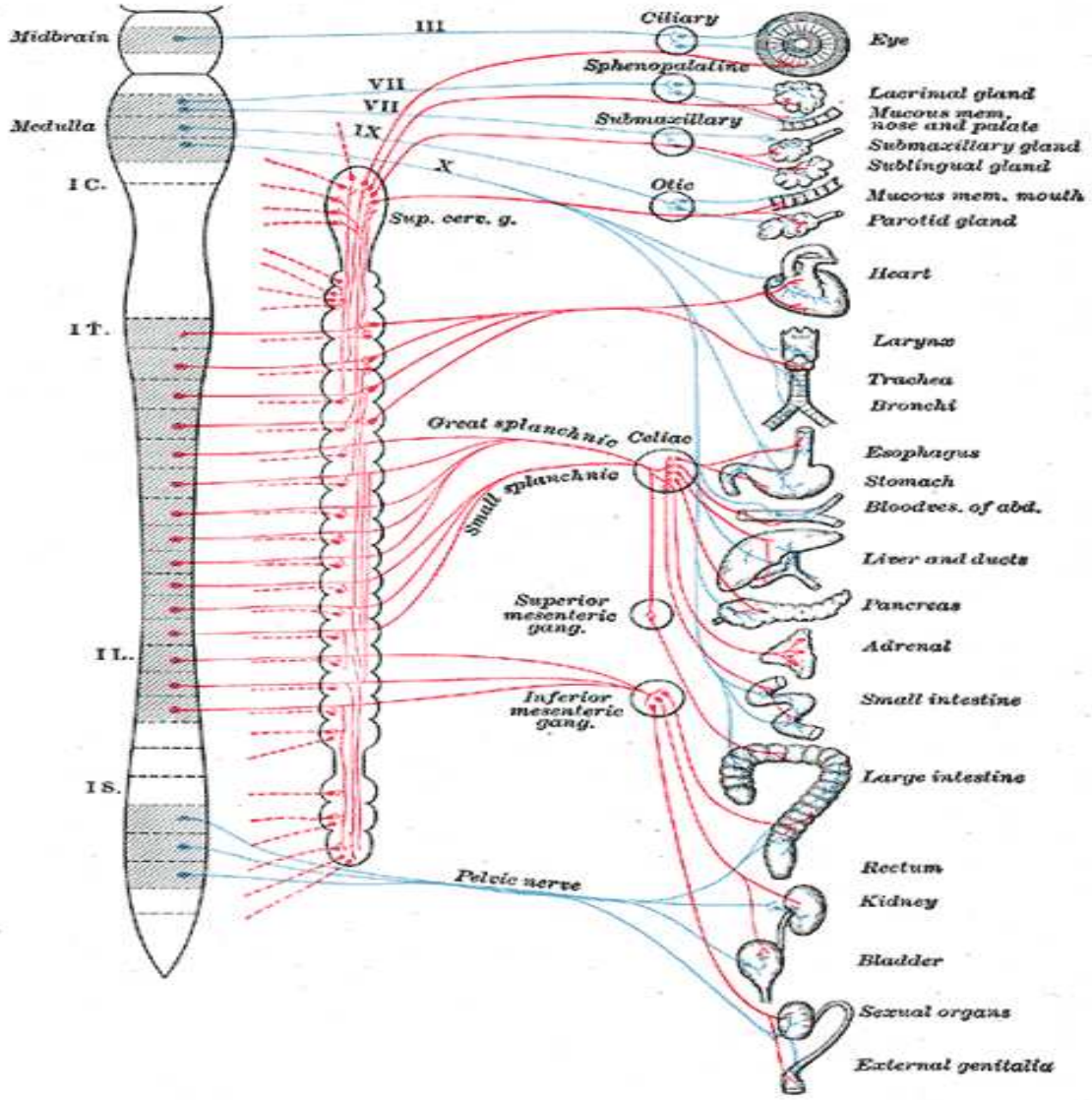

Figure 9: Autonomic nervous system. Blue: parasympathetic ; Red: sympathetic . The vagus is drawn in various branches. The vagus which innervate the intestine is drawn in blue with the colon icon.(Gray839.eps)

From this point down to the anus the innervation is due to the pelvic nerve.

Dr. Wakefield was the first to examine colonscopies of autistic children and found the intestinal tube inflamed. As this inflammation was of unknown origin, he called this "autistic enterocolitis". During the same period he made the hypothesis that autism was due to a great extent to measles vaccination. In a recent paper[25] both Wakefield's hypotheses (1 - autistic enterocolitis; 2 - measles vaccination) turned out to be false. The first in particular was not a colitis at all but the origin of this inflammation remains a mystery. Here we bring forward the following assumption: the inflammation is caused by the "MET factor" which can be studied where the vagus nerve is visible i.e. in the intestinal tube.

In the paper by Balzola Federico et al.[26] you can see the first pictures of this mysterious inflammation which has the following characteristics (see for instance figure 11 page 23):

1 - From some gastroscopies it turns out that the oesophagus is inflamed down to the duodenum

2 - the same situation is present in the ileum-colon tract. This inflammation stopped before the middle transverse colon.

3 - the descendant colon down to the anus was without inflammation.

Of course we need further confirmation.

5 Conclusions and expectations

In the end we must draw some important observations.

Autism is a genetic disease

It has been clear since '70 that autism is a genetic disease (as we said at the beginning) but we have no clue as to the particular gene to investigate (see measurements by Rutter). If we however believe in the present theory, we have some ideas to look at. It is very important to repeat **the measurements by Rutter in the light of our theory** i.e. we must use gastroscopies and colonscopies to carry out the measurements of the intestines in identical twins. If the intestines are "identical" (i.e. the inflammations of the

[25]Gillian Baird et al. Measles vaccination and antibody response in autism spectrum disorders - Arch.Dis.Child published online 5 Feb.2008

[26]Balzola R. et alii: Autistic enterocolitis: further confirmation in Italian autistic childen. Meeting on "Digestive and liver disease" - (P02.87, S137, vol. 37 Suppl. 1) - March 2005

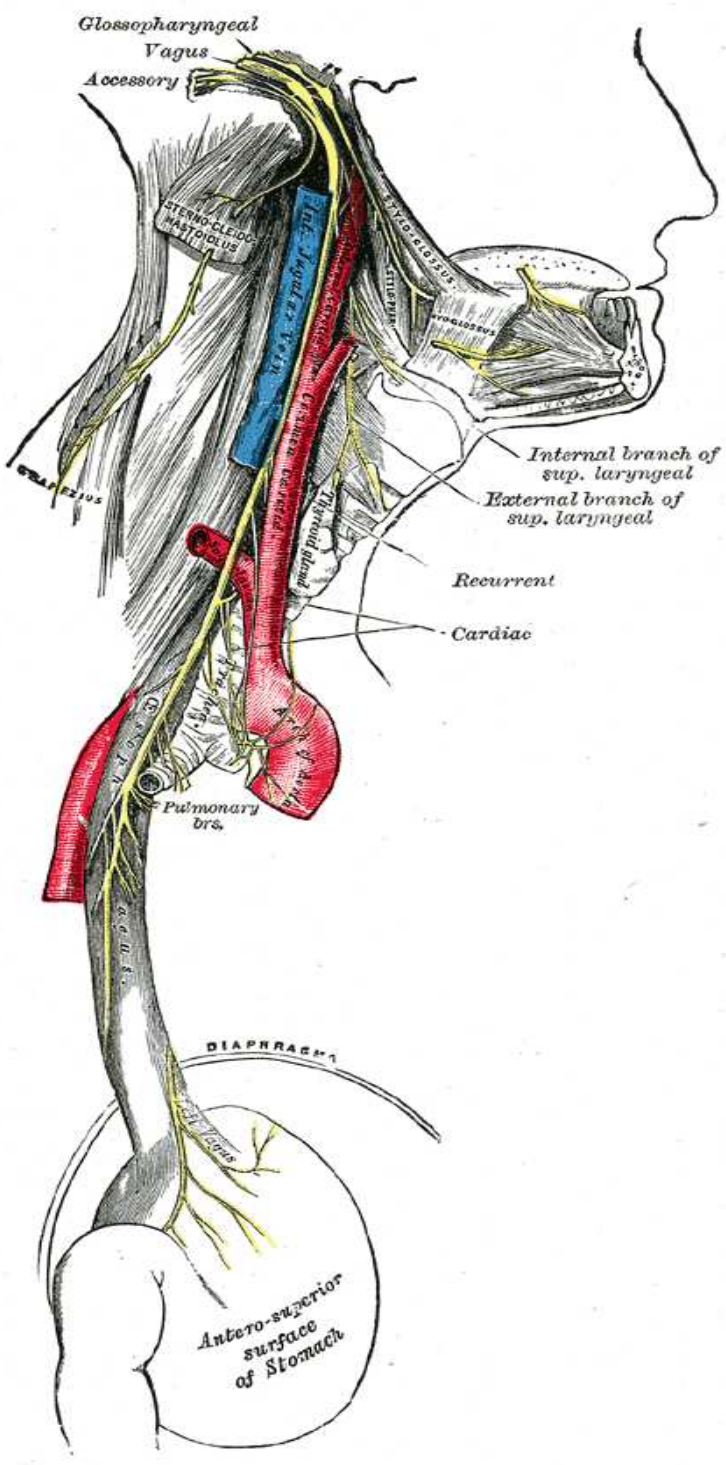

Figure 10: Vagus path between skull and stomach.(Gray793)

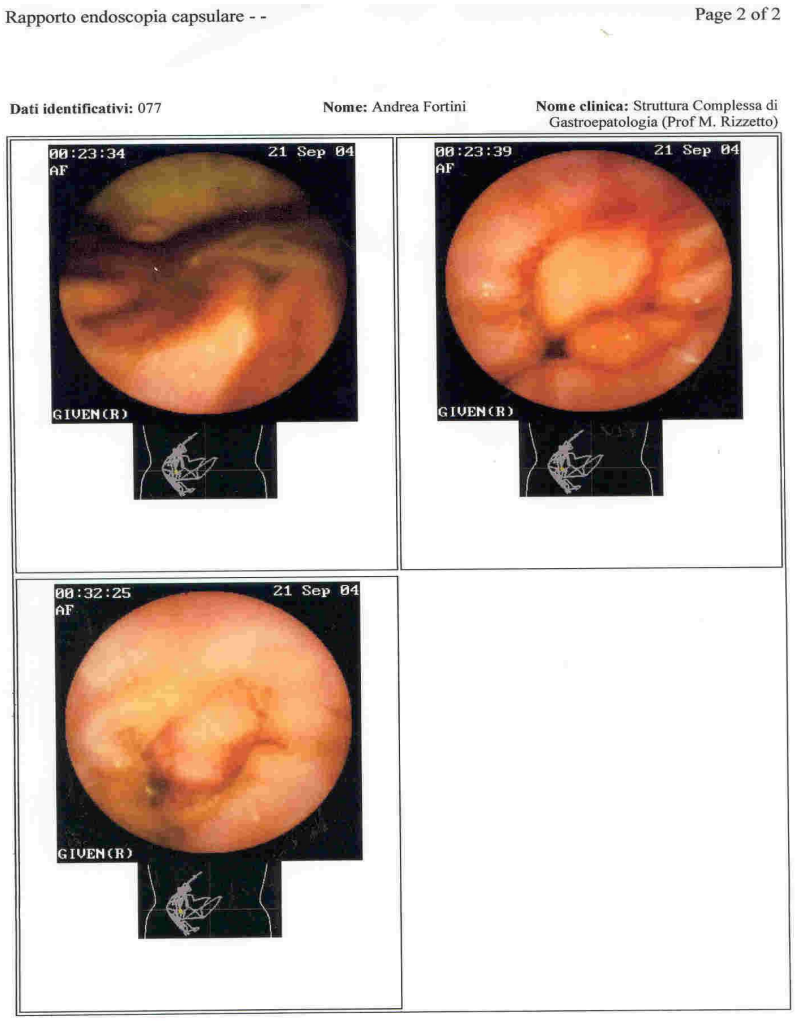

Figure 11: Tract of an intestine of a 30 years old autistic

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intestines are identical) one can draw the following conclusions: 1 - autism is genetic and one can discard other places to look for the gene and concentrate on the intestine; 2 - if one accepts the present theory one can focus on the vagus nerve and therefore on the XII cranial nerves.

Autism is not a mental disease

Autism is a disease of the motor system linked to 1 - the XII cranial nerves and 2 - the motor system of the brain but not to the cerebral cortex. In fact referring to mental disorders we usually intend a sickness which affects the cerebral cortex, according the theory of my paper. But in our case autism affects only the motor system of the brain, leaving undamaged the cerebral cortex in its functions.

In my opinion, if this is really the situation (i.e. autism is not a mental disease) it can be seen from these further following considerations.

A) In 1985 the child psychiatrist Michele Zappella, who is working at the Hospital of Siena (Italy), tried to release the ability of speaking using the following approach called "holding". The child is laid down and immobilized by other people while another person, blocking the mouth of the child, is speaking to him/her; from time to time the mouth is freed in order to see his/her reactions. Some parents who tried this approach gave a positive report but the majority of them were unable to stand their son/daughter in a such piteous situation and the "holding" was quickly abandoned. The positive results were: 1 - the releasing of speech started a) pronouncing very few words and b) complicating the sentences and 2 - in a few months the child learnt to read and write.

B) From what precedes we can fairly be sure that autism is not a mental disease: 1 - the releasing of speech means that "stimulating" the vagus nerve we were able to soften the inflammation and the system larynx-pharynx was partly unblocked allowing the words to be formed. 2 - after the inflammation was partly relieved, the very refined mechanism of reading and writing began. At the same time the neural apparatus proved to be undamaged when the cerebellum and/or brain gave the ok to the cerebral cortex.

C) Autism must not be mistaken with mental disease as there is no cerebral lesion in the superior hemispheres of the brain. No one has been able to demonstrate that such a lesion exists; only Courchesne has proved that the brain has a smaller volume but this does not prove that a "piece of brain" is lacking (as was claimed by people sponsoring of the theory of "mirror neurons").

Conclusion: autism is not a mental disease

Treatment of autism: what can be done?

If we are right then: 1 - autism must not be treated as a mental disease; 2 - autism is a genetic disease but "sui generis". Autism is a kind of dysfunction which acts directly on the motor part of the nervous system and generates movements not well-coordinated. In fact all functions are undamaged but it was as if they were plunged into a "ground noise" or, said in other words, they are inflamed. As a consequence it is necessary to use drugs against inflammation of the nervous system. One must take into account also that this inflammation is spread over the whole organism (the XII nerves practically are everywhere because of the vagus nerve), so it is not enough to give a small dose of drug but the dose must be proportional to the body weight. From this simple consideration one sees that autism is an important area of research for the pharmaceutical industry.

Nowadays lacking drugs for autism, we must recur to the only drug existing which soften the symptom of autism i.e. **bromelain**. It is a natural compound derived from fruits of pineapples formed by 10 or 20 enzymes (the exact composition of bromelain is not yet known; see[27]). Bromelain is lacking harmful effects on human beings at the dose of 2.5-3.0 grams/die which should be taken to get a positive effect on autism. We point out that, at a much smaller dose, bromelain is used in dentistry for the treatment of the nerves of teeth irritated by infection.

As a last topic I wish to recall that a particular diet was prescribed for autistic people by Prof. Kalle Reichelt of the University of Oslo. According to this diet foods containing gluten and casein should be prohibited. In Italy over the last 20 years many people have tried this diet (essentially because of my intervention as President of ANGSA) with good results. But this diet is more widespread in the USA and in 2008 (or 2009) the National Institute of Health (NIH) is expected to publish the following experimental question: Is Reichelt's diet effective in weakening the symptom of autism?

In any case it is not at all clear why a diet of any kind should work. In my opinion the only answer to this question comes from the present theory. In fact if one believes that autism is a mental disease there is no way to answer the question, while if one believes that autism is produced by the XII nerves a hint to a solution of this puzzle is possible. What I mean is the rôle of the vagus nerve which is 1) present in the whole intestine as a unique nerve

[27] http://xoomer.alice.it/bioresautism/theory-app-A.html.
See also: http://xoomer.alice.it/bioresautism/theory-int.html;
http://xoomer.alice.it/bioresautism/theory-1.html and
http://xoomer.alice.it/bioresautism/theory-2.html
for discussions with Rimland Association and Reichelt's hypotesis

and 2) if this nerve has some dysfunction of a genetic nature then what can happen is 3) the digestion of particular foods can be made difficult or even act as a poison for the intestine.

Personally I "believe" in this diet simply because it has saved my son from going into a mental hospital. Obviously a single case cannot be generalized (so we must wait for the results of the NIH) so medical interventions must be applied even if they only bring benefit to the single person.

Conclusion: apart from the psychological interventions the biological interventions are: 1 - use of bromelain; 2 - Reichelt's diet (after favourable opinion of NIH); 3 - the "holding" (where possible). All the three points are in agreement with the present theory.