

Finding the causes of Autism Spectrum Disorders: the Trigeminal Factor

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February 2010

Emerging clinical evidence indicates that jaw malignment is a major factor in the development of autism. In addition, review of the medical literature strongly supports this conclusion.

Current working model for the development of autism:

Preliminary clinical evidence supports the following findings:

1. the mother has a cranio-mandibular disorder that evidence shows is likely due to multigenerational dietary insufficiencies.
2. cranio-mandibular disorder causes a shift in neuropeptides with subsequent compromised neurodevelopment and epigenetic shifts.
3. mother gestates infant in an altered neurochemical environment.
4. baby is born with elevated neuropeptide levels| neuroplasticity shifts, and altered epigenetic functions.
5. baby inherits poor cranio-mandibular relationship, perhaps further degraded than mothers by modern diet, which contributes further toward developmental abnormalities.
6. when teeth erupt, traumatic cranio-mandibular dysfunction causes shifts in tonicity of reticular formation, altered neuropeptide levels, shifts in immune function, and alterations in endocrine function, contributing to overt onset of autistic symptoms.

Note: cranio-mandibular dysfunction manifests as a multitude of disorders, affecting everyone differently. The breadth of pathology created by cranio-mandibular dysfunction is best viewed from the perspective of “chaos theory”(see [Dental Physician, Fonder, 1976](#)).

The evidence in medical literature that cranio-mandibular dysfunction contributes significantly to the development of autism is indirect but extensive. The following list includes many, but not all associations between cranio-mandibular dysfunction and autism.

1. Somatic sensory abnormalities are common to both temporomandibular disorders (TMJ) and autism spectrum disorders (ASD)ⁱ. Bite abnormalities found in TMJ cause the trigeminal nerve to become hypertonic leading to a number of conditions that promote hyper sensitization. Some of those mechanisms include:
 - a. The trigeminal nerve is anatomically and functionally a spinal nerve, hence sitting atop the spine it has the ability to modulate the ascending spinal signal (that is why biting the bullet works). Judith Bluestone in her work with autism believed that the primary defect in autism was a hypersensitization of the trigeminal nerve.

- b. Bite dysfunction impacts autonomic tone leading to acidosis, which increases production of pain neuropeptides production.
 - c. Elevated trigeminal tonicidity leads to increase production of substance P. The trigeminal nerve has an enormous density of C fibers which produce substance P; substance P is known to systemically sensitize all sensory neurons.
2. Hyperacusis (noise hypersensitivity) is common in both ASD and cranio-mandibular disorders.ⁱⁱ The¹ purpose of the tensor tympani muscle in the ear is to dampen sounds. It is innervated by the trigeminal nerve. Hence, trigeminal nerve hypertonicity from jaw malalignment can cause the muscle to malfunction, thus causing hyperacusis.
 3. Hearing loss is common to both ASD and cranio-mandibular disorders.ⁱⁱⁱ The relationship between temporomandibular joint dysfunction and hearing disorders has long been recognized by some healthcare providers. Fonder reported that "chronic low-grade otitis media is a constant finding in patients who have a disturbance of the stomatognathical structures due to malocclusion"
 4. Increased otitis media is common to both ASD and cranio-mandibular disorders and the severity of the otitis media matches age onset of ASD.^{iv} Multiple studies have found that bite correction through posterior build up of primary teeth is approximately 95% effective at eliminating otitis media.
 5. Both ASD and cranio-mandibular disorders are associated with sleep disturbance.^v The trigeminal nerve is a major input into the brain stem (reticular activating system) which controls activity level of the brain. Hence, over stimulation of the trigeminal nerve can cause sleep disturbance.
 6. Both ASD and cranio-mandibular disorders are associated with oculomotor dysfunction.^{vi} The primary afferent cell somata subserving extraocular muscle proprioception are located within the medial portion of the ipsilateral trigeminal ganglion. Hence, eye muscle coordination is easily influenced by trigeminal disturbance as found in cranio-mandibular dysfunction.
 7. Both ASD and cranio-mandibular disorders are associated with pigment disorders.^{vii} My clinical observations indicate that facial pigmentation disorders are very common with cranio-mandibular dysfunction, though I have found no published accounts of my observations. This I suspect is due to the common embryological origin of trigeminal proprioception cells and melanocytes from neural crest cells.
 8. Both ASD and cranio-mandibular disorders have altered plasma levels of amino acids.^{viii} Research has shown that the trigeminal nerve has the ability to modulate nutrient levels in the blood. This manifests clinically with increased stability in blood sugar, calcium, etc. levels with bite therapy.
 9. Both ASD and cranio-mandibular disorders are associated with seizures.^{ix} The connection with jaw alignment and seizures is one that I happened on twenty years ago. I published an article on it which is included. The mechanism of action I suspect is likely through the impact of bite on neuropeptides levels. To date I have over 60 cases of seizures that have resolved with bite therapy.

10. Both ASD and cranio-mandibular disorders are associated with elevated neuropeptides.^x In particular, substance P levels are elevated with cranio-mandibular dysfunction. This is manifested by the large number of neurogenic inflammatory disorders that occur with cranio-mandibular disorders, and that respond to bite therapy. With an elevation in substance P, many other neuropeptides levels will be altered as well as levels of neurotrophins and neurotransmitters.
11. Both ASD and cranio-mandibular disorders are associated with elevated familial history of autoimmune disorders.^{xi} The trigeminal nerve is known to modulate sensory input into the limbic brain, hence has the ability to modulate the neuroimmune complex. Levels of a neuropeptide co-secreted with substance P (“calcitonin gene related peptide”) is known to correlate with autoimmune disorders.
12. Cranio-mandibular disorders are known to have a high incidence of thyroid dysfunction; ASD is hypothesized to have been associated with thyroid dysfunction.^{xii} Alread Fonder in his book *The Dental Physician*, found thyroid dysfunction to be a constant finding with cranio-mandibular dysfunction.
13. Dopamine disregulation is found in both ASD and cranio-mandibular disorders.^{xiii} In persons with craniomandibular disorders there will be an elevated substance P, whose primary effect on the brain is the stimulation of dopamine levels.
14. Both ASD and cranio-mandibular disorders are associated with abnormalities in the inflammatory response system.^{xiv} Substance P, which becomes elevated with cranio-mandibular dysfunction, has two primary effects on the body: increased inflammatory response and hypersensitization of all sensory neurons.
15. ^{xv}In autism it is hypothesized that over activity of the amygdale could account for much of the behavioral changes. The trigeminal nerve is known to direct neural effects on the amygdale, as well as possible modulatory effects through neuropeptides.
16. Rimland in 1964 hypothesized that there was a relationship between the cognitive dysfunction in autism and the reticular formation of the brain stem. Griffin (1964) demonstrated that the trigeminal proprioceptors were a major influence on tonicity of the reticular formation. Recent advances in effective treatment of Parkinsons symptoms has demonstrated that jaw orthopedic therapy is effective at impacting the reticular formation (Jennings 2008, 2010).
17. It has been thought that the observed excess affect on twins implied a genetic link to autism, but I believe this may have been misinterpreted. I believe it in fact supports the idea that the mother has elevated substance P, which is known to regulate cell division (i.e. the mothers elevated substance P is the cause of twins).^{xvi}

Treatment:

Assuming the foregoing to be somewhat relevant, the treatment for the autistic condition would benefit from optimal biomechanical repositioning of the lower jaw. This treatment is generally

understood by dentists that do TMJ or functional jaw orthopedic therapy, though my 30 years experience in pain management indicates that the current dental protocol for this type of treatment fails to understand a few significant nuances.

Case Histories:

Generally what is found is that the vertical dimension is the one off the most (excess freeway space), though the other dimensions are off significantly. Treatment has been through orthopedic repositioning of the mandible with twin block appliances on light wire crozat appliances and craniosacral support as needed. The mandible has been repositioned to criteria set forth in Biomechanical Principles of Occlusion (Jennings 2007).

Of the limited number of autism cases that I have treated, I have seen a very favorable response. Generally, they very rapidly improve in executive function (i.e. ability to hear and respond). I have seen many forms of movement disorders correct and multiple forms of hypersensitivity resolve (food texture, noise hypersensitivity, etc.). Their ability to socially interact typically significantly improves.

Case History (s.d.): 5 year old Downs Syndrome with major autistic symptoms: impaired gait and balance, no speech, no eye focus, limited response to commands, nonresponsive to surrounding noises, constant rocking, microcephalic, retruded occlusion. Due to presence of sleep apnea and microcephalia, he was fitted with a removable Herbst appliance which placed his mandible in a class III relationship. Within 3 months he reacted to the noise of an airplane flying over for the first time in his life, and rocking had stopped. At 6 months his balance and strength had significantly improved so as he could open heavy doors. At 12 months he had developed fantastic eye contact, able to make multiple sounds on command, give high five immediately on request, and was being commended daily at school for his attentiveness. At 13 months he was able to say bye-bye.

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ⁱ J Autism Dev Disord. 2007 May;37(5):894-910.

Describing the sensory abnormalities of children and adults with autism.

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Patterns of sensory abnormalities in children and adults with autism were examined using the Diagnostic Interview for Social and Communication Disorders (DISCO). This interview elicits detailed information about responsiveness to a

wide range of sensory stimuli. Study 1 showed that over 90% of children with autism had sensory abnormalities and had sensory symptoms in multiple sensory domains. Group differences between children with autism and clinical comparison children were found in the total number of symptoms and in specific domains of smell/taste and vision. Study 2 confirmed that sensory abnormalities are pervasive and multimodal and persistent across age and ability in children and adults with autism. Age and IQ level affects some sensory symptoms however. Clinical and research implications are discussed.

PMID: 17016677

[Rogers SJ](#), [Ozonoff S](#).

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BACKGROUND: Unusual responses to sensory stimuli are seen in many children with autism. Their presence was highlighted both in early accounts of autism and in more recent first-person descriptions. There is a widespread belief that sensory symptoms characterize autism and differentiate it from other disorders. This paper examines the empirical evidence for this assumption. METHOD: All controlled experimental laboratory investigations published since 1960 were identified through systematic searches using Medline/PubMed and PsycInfo search engines. A total of 48 empirical papers and 27 theoretical or conceptual papers were reviewed. RESULTS: Sensory symptoms are more frequent and prominent in children with autism than in typically developing children, but there is not good evidence that these symptoms differentiate autism from other developmental disorders. Certain groups, including children with fragile X syndrome and those who are deaf-blind, appear to demonstrate higher rates of sensory symptoms than children with autism. In reviewing the evidence relevant to two theories of sensory dysfunction in autism, over- and under-arousal theory, we find that there is very little support for hyper-arousal and failure of habituation in autism. There is more evidence that children with autism, as a group, are hypo-responsive to sensory stimuli, but there are also multiple failures to replicate findings and studies that demonstrate lack of group differences. CONCLUSIONS: The use of different methods, the study of different sensory modalities, and the changing scientific standards across decades complicate interpretation of this body of work. We close with suggestions for future research in this area.

PMID: 16313426

Autism and hearing loss.

Rosenhall U, Nordin V, Sandström M, Ahlsén G, Gillberg C.

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A group of 199 children and adolescents (153 boys, 46 girls) with autistic disorder was audiotologically evaluated. Mild to moderate hearing loss was diagnosed in 7.9% and unilateral hearing loss in 1.6% of those who could be tested appropriately. Pronounced to profound bilateral hearing loss or deafness was diagnosed in 3.5% of all cases, representing a prevalence considerably above that in the general population and comparable to the prevalence found in populations with mental retardation. Hearing deficits in autism occurred at similar rates at all levels of intellectual functioning, so it does not appear that the covariation with intellectual impairment per se can account for all of the variance of hearing deficit in autism. Hyperacusis was common, affecting 18.0% of the autism group and 0% in an age-matched nonautism comparison group. In addition, the rate of serous otitis media (23.5%) and related conductive hearing loss (18.3%) appeared to be increased in autistic disorder. The study emphasizes the need for auditory evaluation of individuals with autism in order to refer those with pronounced to profound hearing loss for aural habilitation and to follow those with mild to moderate hearing loss because of the risk of deterioration.

Publication Types:

Research Support, Non-U.S. Gov't

PMID: 10587881

[Otolaryngol Head Neck Surg.](#) 1980 Jul-Aug;88(4):361-7.

Myofascial pain-dysfunction syndrome: the role of nonmasticatory muscles in 91 patients.

[Curtis AW.](#)

Ninety-one new patients with myofascial pain-dysfunction (MPD) syndrome were studied prospectively. The patients experienced aural fullness, tinnitus, vertigo, odynophagia, and headache in addition to the

cardinal symptoms of otalgia, muscle tenderness, temporomandibular joint (TMJ) click, and trismus. Some nonmasticatory muscles were found to be tender as frequently as the masticatory muscles. It is proposed that MPD syndrome as seen clinically involves more than just the masticatory musculature and is a composite of several head and neck myofascial pain syndromes including tensor tympani syndrome, muscle tension headache, cervical syndrome, and hyoid syndrome.

[Med Oral Patol Oral Cir Bucal.](#) 2007 Mar 1;12(2):E96-100.

Tensor tympani muscle: strange chewing muscle.

[Ramírez LM](#), [Ballesteros LE](#), [Sandoval GP](#).

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This work seeks to alert medical and odontological staff to understanding and using interdisciplinary handling for detecting different pathologies common otic symptoms. It offers better tools for this shared symptomatology during therapy's conservative phase. Tensor tympani muscle physiology and function in the middle ear have been veiled, even when their dysfunction and anatomical relationships may explain a group of confused otic symptoms during conventional clinical evaluation. Middle ear muscles share a common embryological and functional origin with chewing and facial muscles. This article emphasizes that these muscles share a functional neurological and anatomical dimension with the stomatognathic system; these muscles increased tonicity ceases to be a phenomenon having no logical connections. It offers functionality and importance in understanding referred otic symptoms in common with other extra-otical symptom pathologies. Tinnitus, vertigo, otic fullness sensation, hyperacusia, hypoacusia and otalgia are not only primary hearing organ symptoms. They should be redefined and related to the neighboring pathologies which can produce them. There is a need to understand temporomandibular disorders and craniofacial referred symptomatology from neurophysiologic and muscle-skeletal angles contained in the stomatognathic system. Common symptomatology is frequently observed in otic symptoms and temporomandibular disorders during daily practice; this should be understood by each discipline from a broad, anatomical and clinical perspective.

Tensor tympani

From Wikipedia, the free encyclopedia

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Tensor tympani



[Malleus](#)

Tensor Tympani

[Incus](#)

[Stapedius](#)

[Labyrinth](#)

[Stapes](#)

[Auditory Canal](#)

[Tympanic Membrane](#)
(Ear Drum)

[Eustachian Tube](#)

[Tympanic cavity](#)

Bones and muscles in the tympanic cavity
in the middle ear

Latin

*musculus
tensor
tympani*

Gray's

subject #231
1046

<u>Origin:</u>	auditory tube
<u>Insertion:</u>	handle of the malleus
<u>Artery:</u>	superior tympanic artery
<u>Nerve:</u>	medial pterygoid nerve from the mandibular nerve (V)

Action:

Dorlands/Elsevier

m 22/12551096

The **tensor tympani**, the larger of the two muscles of the [tympanic cavity](#), is contained in the bony canal above the osseous portion of the [auditory tube](#), from which it is separated by the [septum canalis musculotubarii](#).

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Origin and insertion

It arises from the cartilaginous portion of the [auditory tube](#) and the adjoining part of the [great wing of the sphenoid](#), as well as from the osseous canal in which it is contained.

Passing backward through the canal, it ends in a slender tendon which enters the tympanic cavity, makes a sharp bend around the extremity of the septum, and is inserted into the [manubrium](#) of the [malleus](#), near its root.

Function

When tensed, the action of the muscle is to pull the malleus medially, tensing the [tympanic membrane](#), damping [vibration](#) in the ear [ossicles](#) and thereby reducing the [amplitude](#) of sounds. This muscle is contracted primarily to dampen the noise produced by chewing. (Compare to the more general dampening function of the [stapedius](#) muscle.)

[\[edit\]](#) Innervation

Innervation of the muscle is from branches of the [mandibular division](#) of the [trigeminal nerve](#) (V), by way of the [Otic ganglion](#).

iii J Autism Dev Disord. 1999 Oct;29(5):349-57.

Autism and hearing loss.

Rosenhall U, Nordin V, Sandström M, Ahlsén G, Gillberg C.

Department of Audiology, Karolinska Hospital, Karolinska Institute, Stockholm, Sweden. uro@ent.ks.se

A group of 199 children and adolescents (153 boys, 46 girls) with autistic disorder was audiologically evaluated. Mild to moderate hearing loss was diagnosed in 7.9% and unilateral hearing loss in 1.6% of those who could be tested appropriately. Pronounced to profound bilateral hearing loss or deafness was diagnosed in 3.5% of all cases, representing a prevalence considerably above that in the general population and comparable to the prevalence found in populations with mental retardation. Hearing deficits in autism occurred at similar rates at all levels of intellectual functioning, so it does not appear

that the covariation with intellectual impairment per se can account for all of the variance of hearing deficit in autism. Hyperacusis was common, affecting 18.0% of the autism group and 0% in an age-matched nonautism comparison group. In addition, the rate of serous otitis media (23.5%) and related conductive hearing loss (18.3%) appeared to be increased in autistic disorder. The study emphasizes the need for auditory evaluation of individuals with autism in order to refer those with pronounced to profound hearing loss for aural habilitation and to follow those with mild to moderate hearing loss because of the risk of deterioration.

Publication Types:

Research Support, Non-U.S. Gov't

PMID: 10587881

[Am J Orthod Dentofacial Orthop.](#) 2003 Jun;123(6):620-3.

Prevalence of otologic complaints in patients with temporomandibular disorder.

[Tuz HH](#), [Onder EM](#), [Kisnisci RS](#).

Department of Oral and Maxillofacial Surgery, Ankara University, Faculty of Dentistry, Turkey.

The prevalence and rank of order of 4 otologic complaints in 200 temporomandibular disorder (TMD) patients, as well as the relationship between the complaints and TMD subgroups, were investigated and compared with an asymptomatic control group. No subjective otologic complaints were reported by 45 (22.5%) TMD patients; the remaining 155 (77.5%) patients had at least 1 otologic complaint. Otalgia, tinnitus, vertigo, and hearing loss were reported by 63.6%, 59.1%, 50%, and 36.4%, respectively, of the subjects with myofascial pain and dysfunction; by 46.1%, 44.2%, 32.5%, and 22% of the patients with internal derangement; and by 62.5%, 45.8%, 41.6%, and 20.8% of the patients with both myofascial pain and dysfunction and internal derangement. However, the incidence of otalgia (8%), tinnitus (26%), vertigo (14%), and hearing loss (14%) was found to be lower for the control group. Statistically, the control group had fewer otologic complaints. Patients in the TMD groups had high incidences of otologic complaints compared with the control subjects without TMD signs or symptoms. Aural symptoms in patients with internal derangement or myofascial pain and dysfunction, or their combination, were nonspecific.

[Funct Orthod.](#) 1995 Jan-Feb;12(1):26-9.

Documented instance of restored conductive hearing loss.

Bubon MS.

The relationship between temporomandibular joint dysfunction and hearing disorders has long been recognized by some healthcare providers (1,2). Fonder reports that "chronic low-grade otitis media is a constant finding in patients who have a disturbance of the stomatognathical structures due to malocclusion" (3). Fingeroth stated that "a constricted maxillary dental arch frequently results in a decrease in nasal permeability...and within this environment a conductive hearing loss may be present" (4). Histological studies confirm the intimate relationship between the TMJ, the tympanic cavity and the eustachian tube (5,6). Nevertheless, craniomandibular origins are frequently overlooked in the medical profession as possible causes for hearing problems. The following case illustrates this point.

^{iv} J Dev Behav Pediatr. 2006 Apr;27(2 Suppl):S120-7.

Early medical history of children with autism spectrum disorders.

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Previous studies have suggested that children with autism spectrum disorders (ASD) may have different medical histories than nonspectrum children in several areas: their reactions to vaccinations, number of ear infections, chronic gastrointestinal problems, and use of antibiotics. Furthermore, some studies have found associations between regressive autism and gastrointestinal (GI) symptoms. The present study analyzes the medical records from birth to the age of 2 years of 99 children (24 typically developing; 75 with ASD, of whom 29 had parent-reported regression). Data were coded in the following areas: frequency and purpose of pediatrician visits, frequency and type of illnesses and medications, type and chronicity of GI complaints, date of vaccinations, growth data, and whether the pediatrician noted behaviors indicative of an ASD before the age of 2 years. Children with ASD were found to have significantly more ear

infections than the typically developing children as well as to use significantly more antibiotics. Typically developing children had significantly more illness-related fevers. There was a nonsignificant trend toward the ASD group having more chronic gastrointestinal problems. There were no significant differences between the groups for the age of vaccination or for number of pediatrician visits. Finally, pediatricians noted symptoms of onset of possible autism, including language delay, for 44 of the 75 children with ASD and 2 of the 24 typical children. Results are discussed in terms of needs for future research.

Publication Types:

Multicenter Study
Research Support, N.I.H., Extramural

PMID: 16685178

J Autism Dev Disord. 1987 Dec;17(4):585-94.

Ear infections in autistic and normal children.

Konstantareas MM, Homatidis S.

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The frequency of ear infections, ear tube drainage, and deafness was examined through parental reports in autistic and yoke-matched, normal children. For the autistic group these difficulties were additionally examined as a function of the children's cognitive and communication abilities, verbal versus nonverbal status, sex, and degree of autistic symptomatology. Autistic children had a greater incidence of ear infections than matched normal peers. Lower-functioning children had an earlier onset of ear infections than their higher-functioning autistic peers. Ear infections coexisted with low-set ears, and with a higher autistic symptomatology score. The findings are discussed in terms of greater CNS vulnerability in the autistic children, which is likely present since embryogenesis. The possible adverse consequences of intermittent hearing loss on language, cognitive, and socioaffective development are considered.

Publication Types:

Research Support, Non-U.S. Gov't

PMID: 3680158

[Cranio.](#) 1991 Apr;9(2):169-73.

The relationship between craniomandibular disorders and otitis media in children.

[Youniss S.](#)

Most of the literature written about temporomandibular joint (TMJ) or craniomandibular dysfunction has looked at the problem in adults, probably because most of the patients we see with problems are adults. This article first establishes the fact that young children also exhibit signs and symptoms of craniomandibular dysfunction, almost at the same percentage as seen in adults. A review of otitis media with effusion (OME) in children establishes that malfunction of the eustachian tube is the underlying cause of this disease process. Because of the close anatomical and embryological relationship between the TMJ and the middle ear, there exists the possibility that a dysfunctioning TMJ may initiate the bout of OME, primarily by its relationship to the tensor veli palatini muscle. This muscle controls the function of the eustachian tube. This author feels that we might be able to decrease the incidence of OME by improving the function of the eustachian tube. This could be done by altering the relationship between the TMJ and the muscles of mastication, similar to the way we treat craniomandibular (TMJ) dysfunction in adults.

PMID: 1802427

^v [Child Psychiatry Hum Dev.](#) 2006 Winter;37(2):179-91.

Sleep disturbances and correlates of children with autism spectrum disorders.

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This study examined sleep patterns, sleep problems, and their correlates in children with autism spectrum disorders (ASD). Subjects consisted of 167 ASD children, including 108 with autistic disorder, 27 with Asperger's syndrome, and 32 with other diagnoses of ASD. Mean age was 8.8 years (SD = 4.2), 86% were boys. Parents completed a self-administered child sleep questionnaire. Results showed that average night sleep duration

was 8.9 h (SD = 1.8), 16% of children shared a bed with parent. About 86% of children had at least one sleep problem almost every day, including 54% with bedtime resistance, 56% with insomnia, 53% with parasomnias, 25% with sleep disordered breathing, 45% with morning rise problems, and 31% with daytime sleepiness. Multivariate logistic regression analyses indicated that younger age, hypersensitivity, co-sleeping, epilepsy, attention-deficit/hyperactivity disorder (ADHD), asthma, bedtime ritual, medication use, and family history of sleep problems were related to sleep problems. Comorbid epilepsy, insomnia, and parasomnias were associated with increased risk for daytime sleepiness. Results suggest that both dyssomnias and parasomnias are very prevalent in children with ASD. Although multiple child and family factors are associated with sleep problems, other comorbid disorders of autism may play a major role.

PMID: 17001527

[BMC Psychiatry](#). 2006 Apr 28;6:18.

Insomnia in school-age children with Asperger syndrome or high-functioning autism.

[Allik H](#), [Larsson JO](#), [Smedje H](#).

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BACKGROUND: Asperger syndrome (AS) and high-functioning autism (HFA) are pervasive developmental disorders (PDD) in individuals of normal intelligence. Childhood AS/HFA is considered to be often associated with disturbed sleep, in particular with difficulties initiating and/or maintaining sleep (insomnia). However, studies about the topic are still scarce. The present study investigated childhood AS/HFA regarding a wide range of parent reported sleep-wake behaviour, with a particular focus on insomnia. **METHODS:** Thirty-two 8-12 yr old children with AS/HFA were compared with 32 age and gender matched typically developing children regarding sleep and associated behavioural characteristics. Several aspects of sleep-wake behaviour including insomnia were surveyed using a structured paediatric sleep questionnaire in which parents reported their children's sleep patterns for the previous six months. Recent sleep patterns were monitored by use of a one-week sleep diary and actigraphy. Behavioural characteristics were surveyed by use of information gleaned from parent and teacher-ratings in the High-Functioning Autism Spectrum Screening Questionnaire, and in the Strengths and Difficulties Questionnaire. **RESULTS:** Parent-reported difficulties initiating sleep and daytime sleepiness were more common in children with AS/HFA than in controls, and 10/32 children with AS/HFA (31.2%) but none of the controls fulfilled our definition of paediatric insomnia. The parent-reported insomnia corresponded to the findings obtained by actigraphy. Children with insomnia

had also more parent-reported autistic and emotional symptoms, and more teacher-reported emotional and hyperactivity symptoms than those children without insomnia. CONCLUSION: Parental reports indicate that in childhood AS/HFA insomnia is a common and distressing symptom which is frequently associated with coexistent behaviour problems. Identification and treatment of sleep problems need to be a routine part of the treatment plan for children with AS/HFA.

PMID: 16646974

[Dent Clin North Am.](#) 2001 Oct;45(4):701-13.

Disordered sleep in fibromyalgia and related myofascial facial pain conditions.

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Myofascial pain and fibromyalgia have a recognized relationship to sleep disturbances. Understanding the comorbidity of these entities helps the practitioner, physician and dentist alike, be better prepared to manage the causative factors related to these conditions rather than treating only the symptoms. The increasing recognition of the coexistence of fibromyalgia, myofascial pain in the head and neck region, and the presence of temporomandibular disorders further increases the need for the dentist to be aware of sleep as a contributory factor from the diagnostic and the therapeutic aspects. This awareness results in more comprehensive management and an improved opportunity for optimal patient management as well as improved sleep and diminished pain levels.

PMID: 11699237

^{vi} J Laryngol Otol. 1988 May;102(5):435-9.

Oculomotor findings in autistic children.

Rosenhall U, Johansson E, Gillberg C.

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Eleven children with infantile autism or autistic-like conditions were examined

with oculomotor tests and with auditory brainstem response audiometry. Measurements of voluntary, horizontal non-predictable saccades showed that the eye motor function was abnormal in six (55 per cent) of the eleven patients. The saccades were hypometric in all six instances and the saccadic velocity was reduced in four instances. The abnormalities observed are consistent with brain dysfunction, in most cases probably indicating pontocerebellar involvement. In five instances ABR was found to be abnormal which indicates brainstem dysfunction. Oculomotor dysfunction and/or ABR abnormality was observed in eight (73 per cent) of the patients studied.

Publication Types:

Research Support, Non-U.S. Gov't

PMID: 3397639

[Neuroscience](#). 1991;43(2-3):473-81.

The anatomical substrate for cat extraocular muscle proprioception.

Porter JD, Donaldson IM.

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Lexington 40536-0084.

The localization of cell bodies and of the central terminal projections of extraocular muscle afferent neurons was examined in adult cats using transport of horseradish peroxidase. The results confirm that primary afferent cell somata subserving extraocular muscle proprioception are located within the medial portion of the ipsilateral trigeminal ganglion. Occasional labeling of cell bodies in the mesencephalic nucleus of the trigeminal nerve occurred only in association with evidence of spread of tracer beyond the eye muscles. These results, taken together with work of others, make it unlikely that the trigeminal mesencephalic nucleus participates significantly in eye muscle proprioception. The central projections of extraocular muscle afferent neurons were found consistently in a restricted area in the ventral portion of the pars interpolaris of the spinal trigeminal nucleus. This corresponds exactly with their site of termination in the monkey [Porter (1986) J. comp. Neurol. 247, 133-143]. Terminal labeling was restricted to this area in cases in which there was no evidence of spread of the tracer beyond the extraocular muscles. In contrast to previous findings in the monkey, the cat did not exhibit a second muscle afferent representation in the cuneate nucleus. Though it is known that extraocular muscle afferent signals interact with both retinal and vestibular signals, and thus probably are involved in both visual processing and oculomotor control, the details of their roles in these processes are not yet clear. (ABSTRACT TRUNCATED AT 250 WORDS)

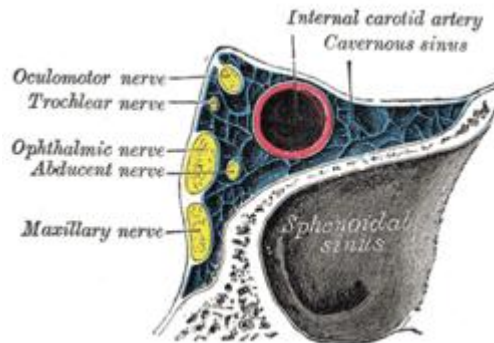
Ophthalmic nerve

From Wikipedia, the free encyclopedia

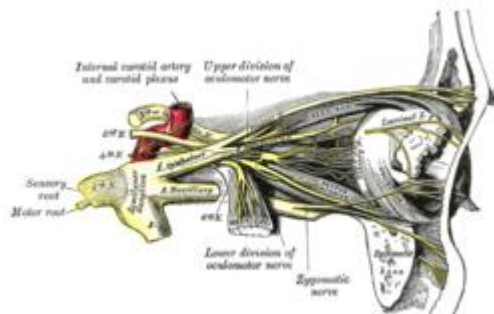
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Jump to: [navigation](#), [search](#)

Nerve: Ophthalmic nerve



Oblique section through the [cavernous sinus](#).



Nerves of the orbit, and the [ciliary ganglion](#). Side view.

Latin *n. ophthalmicus*

Gray's [subject #200 887](#)

From [trigeminal nerve](#)

MeSH [Ophthalmic+Nerve](#)

The **ophthalmic nerve** is one of the three branches of the [trigeminal nerve](#), the fifth [cranial nerve](#). Like the [maxillary](#) branch of the trigeminal nerve, the ophthalmic branch carries sensory fibers only. The ophthalmic nerve passes through the [cavernous sinus](#) and its

nasociliary branch exits the [skull](#) through the [superior orbital fissure](#).

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- 2 [Path](#)
- 3 [Additional images](#)
- 4 [External links](#)

[\[edit\]](#) Branches

- [Nasociliary nerve](#)
 - [sensory root of ciliary ganglion](#)
 - [posterior ethmoidal nerve](#)
 - [long ciliary nerve](#)
 - [infratrochlear nerve](#)
 - [anterior ethmoidal nerve](#)
- [lacrimal nerve](#)
- [frontal nerve](#)
 - [supratrochlear nerve](#)
 - [supraorbital nerve](#)

[\[edit\]](#) Path

The ophthalmic nerve supplies branches to the [cornea](#), [ciliary body](#), and [iris](#); to the [lacrimal gland](#) and [conjunctiva](#); to the part of the [mucous membrane](#) of the [nasal cavity](#); and to the skin of the [eyelids](#), [eyebrow](#), [forehead](#), and [nose](#).

It is the smallest of the three divisions of the trigeminal, and arises from the upper part of the [semilunar ganglion](#) as a short, flattened band, about 2.5 cm. long, which passes forward along the lateral wall of the cavernous sinus, below the [oculomotor](#) and [trochlear nerves](#); just before entering the orbit, through the [superior orbital fissure](#), it divides into three branches, lacrimal, frontal, and nasociliary.

The ophthalmic nerve is joined by filaments from the [cavernous plexus](#) of the sympathetic, and communicates with the [oculomotor](#), [trochlear](#), and [abducent](#) nerves; it gives off a recurrent filament which passes between the layers of the [tentorium](#).

^{vii} Eur J Neurol. 2006 Aug;13(8):842-51.

Neurocutaneous syndrome with mental delay, autism, blockage in

intracellular
vesicular trafficking and melanosome defects.

Buoni S, Zannolli R, de Santi M, Macucci F, Hayek J, Orsi A, Scarinci R,
Buscalferri A, Cuccia A, Zappella M, Miracco C.

Section of Pediatric Neurology, Department of Pediatrics, Policlinico
Le Scotte,
University of Siena, Siena, Italy.

We evaluated a 11-year-old male patient with mental delay, autism and
brownish
and whitish skin spots. The former resembled those of
neurofibromatosis, the
latter those of tuberous sclerosis. The patient received a complete
clinical
work-up to exclude neurofibromatosis, tuberous sclerosis, or any other
known
neurocutaneous disease, with biochemistry, chromosome analysis and
analysis of
skin specimens. Being all the other tests not significant, two main
ultrastructural defects were observed. The first was a blockage in
intracellular
vesicular trafficking with sparing of the mitochondria; the second an
aberrant
presence of melanosomes in vacuoles of several cell lines and abnormal
transfer
of these organelles to keratinocytes. This patient presented with a
unique
clinical picture distinct from neurofibromatosis or tuberous sclerosis
or any
other known neurocutaneous disease. The ultrastructural abnormalities
suggested a
defect in cell trafficking involving several cell lines and
compartments.

Publication Types:

Case Reports
Evaluation Studies
Research Support, Non-U.S. Gov't

PMID: 16879294

Dev Med Child Neurol. 1993 Sep;35(9):826-32.

Autism and hypomelanosis of Ito in twins.

Zappella M.

Department of Child Neuropsychiatry, USL 30, Siena, Italy.

A pair of monozygotic and a pair of dizygotic twins with autism and
hypomelanosis
of Ito skin-abnormalities are described. These observations are further

evidence of the frequent association between these two conditions, already demonstrated in the literature, and suggest a possibly higher incidence of single gene associations among cases of autism with known genetic basis.

Publication Types:
Case Reports

PMID: 8354433

Neural crest

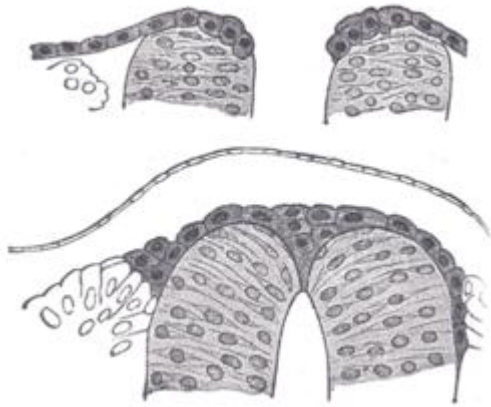
From Wikipedia, the free encyclopedia

(Redirected from [Neural crest cells](#))

- *Have questions? [Find out how to ask questions and get answers.](#)* •

Jump to: [navigation](#), [search](#)

Neural crest



Two stages in the development of the **neural crest** in the human [embryo](#).

[Gray's](#) [subject #184 736](#)

[Carnegie stage](#) [9](#)

Precursor	ectoderm
---------------------------	--------------------------

MeSH	Neural+Crest
----------------------	------------------------------

The **neural crest**, a transient component of the [ectoderm](#), is found at in between the [neural tube](#) and the epidermis (or the free margins of the [neural folds](#)) of an embryo during neural tube formation. Neural crest cells quickly leave this during or shortly after [neurulation](#).

It has been referred to as the fourth [germ layer](#), due to its great importance. The neural crest can give rise to neurons and glia of the [peripheral nervous system](#) (PNS); some skeletal elements, tendons and

smooth muscle; chondrocytes, osteocytes, melanocytes, chromaffin cells, and supporting cells and hormone producing cells in certain organs.

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Clinical significance

Diseases due to defects in the neural crest induction, formation or migration are referred to as **neurocristopathies**, and genes that cause some of these like [piebaldism](#) and [Hirschprung's disease](#) have been cloned in mice models.

History and Nomenclature

In 1868 His described Neural Crest as "*zwischenstrang*"- a strip of cells lying between the dorsal ectoderm and the neural tube.^[1]

From this time till almost 1950s most of the work on this structure was done on amphibian embryos, eg a 1950 comprehensive review in a monograph by Hörstadius.^[2] Newth (who also studied it in fishes)^[3] in 1951 described it as such by "a remarkable embryonic structure" and till another decade its origin still remained an enigma!

In 1960s with the invent of cell labeling with tritiated thymidine by Chibon^[4] and Weston^[5] gave rise to a major breakthrough in this field through amphibian and avian studies. But this was a transient method of cell labeling and the field had to wait till the chick-quail transfer studies were devised for a definitive confirmation of those results. These extensive works in 1970s was reviewed extensively in "the Neural Crest" by Nicole Le Douarin first published in 1982 (and second ed in 1999).^[6]

The nomenclature of these cells derives from amphibian and avian studies which demonstrate migration from the *neural crest* which forms

on the rostral region of the neurulating ectoderm in the trilaminar disc. In humans, the cells actually migrate from the lateral margins of the neural tube however the use of 'crest cells' in this regard is retained.

Induction

Cells fated to become neural crest tissue are induced by [BMP](#), [Wnt](#) and [FGF](#) signaling to express the proteins [Fox3D](#), [RhoB](#) and [Slug](#), and to lose expression of [E-cadherin](#).

- RhoB is likely to signal cytoskeletal changes required for migration. [\[7\]](#)
- Slug is a repressor [\[8\]](#) that leads to an activation of factors that dissociate tight junctions.

Categories

There are several main categories of neural crest based upon function: [\[9\]](#)

Cranial neural crest

- The **cranial neural crest** arises in the anterior and populates the face and the pharyngeal arches giving rise to bones, cartilage, nerves and connective tissue.

Other Migration Locations:

- Into the pharyngeal arches and play an inductive in [thymus](#) development.
- Into the pharyngeal arches and form the [parafollicular cell](#) or [ultimobranchial bodies](#) of the [thyroid gland](#).
- Into the pharyngeal arches and play an inductive role in [parathyroid gland](#) development.
- Facial [ectomesenchyme](#) of the [pharyngeal arches](#) forming skeletal muscle, bone, and cartilage in the face.
- [Odontoblasts](#) ([dentin](#)-producing cells) of the [teeth](#).
- Into the [optic vesicle](#) and the developing [eye](#) and contributes to many anterior eye elements such the cornea, sclera, and ciliary muscle. It also contributes to the attaching skeletal muscles of the eye.
- Into the otic placode and participates in the [inner ear](#) development.
- [Sensory ganglia](#) of the fifth, seventh, ninth and tenth [cranial nerves](#).

Vagal and sacral neural crest

- The **vagal and sacral neural crest** arises in the neck and tail and populates the gut, forming the [parasympathetic](#) neurons that regulates peristalsis and control blood vessel dilation.

Other Migration Locations:

- Walls of the viscera to become [enteric ganglia](#).

Trunk neural crest

- The **trunk neural crest** lies between the vagal and sacral neural crest and gives rise to two groups of cells. One group migrates dorsolateral and populates the skin, forming [pigment cells](#) and the other migrates ventrolateral through the anterior [sclerotome](#) to become the epinephrine-producing cells of the [adrenal gland](#) and the neurons of the [sympathetic nervous system](#). Some cells remain in the sclerotome to form the [dorsal root ganglia](#)

Other Migration Locations:

- Proximal to the spinal cord and line up symmetrically to form the [dorsal root ganglia](#).
- Into the skin to form [melanocytes](#) and [Merkel cells](#).
- [Chromaffin cells](#) of the [adrenal medulla](#).
- Near the vertebral column and become [sympathetic chain ganglia](#).

Cardiac neural crest

- The **cardiac neural crest** overlaps the vagal neural crest and migrates to populate the [pharyngeal arches](#) 3, 4 and 6 (producing structures in the head) and to the [heart](#), forming connective tissue that separates the great vessels of the heart.

Other Migration Locations:

- Into the [pharyngeal arches](#) and [Truncus arteriosus \(embryology\)](#), forming the [aorticopulmonary septum](#) and the [smooth muscle](#) of [great arteries](#).
- Anterior of the aorta to become the four pre-aortic ganglia ([celiac ganglion](#), [superior mesenteric ganglion](#), [inferior mesenteric ganglion](#) and [aortical renal ganglia](#))

Migration

Neural crest cells require extracellular matrix to migrate through interactions between [integrins](#) and [fibronectin](#) and [laminin](#). Migration is directed by inhibitory and attractive signals from cells. [Ephrin](#) is an inhibitory [ligand](#) in posterior sclerotome that affects ventral pathway trunk neural crest cells and causes them to migrate through the anterior sclerotome instead. [Thrombospondin](#) promotes migration through the anterior sclerotome. Another signal, stem cell factor is involved in specifying the destination of migration. If expressed in the wrong locations, pigment cells migrate to that site and proliferate there.

Plasticity

Neural crest cells show varying degrees of plasticity. Some trunk neural crest cells are [pluripotent](#). Cranial neural crest cells can give rise to trunk neural crest cells if transplanted. However, heart neural crest cells are committed before migration. Individual neural crest cells can take on a new fate, however groups of neural crest cells cannot.

viii Invest Clin. 1996 Jun;37(2):113-28.

Plasma excitatory amino acids in autism.

Moreno-Fuenmayor H, Borjas L, Arrieta A, Valera V, Socorro-Candanoza L.

Servicio de Medicina Genética Perinatal, Hospital Chiquinquirá, Maracaibo, Venezuela.

Plasma amino acid levels were measured by high pressure liquid chromatography (HPLC) in fourteen autistic children, all below 10 years of age. Mean glutamic and aspartic acid values were elevated (169 +/- 142 uM and 22.1 +/- 13 uM respectively) together with taurine (90.1 +/- 78.7 uM) ($p > 0.1$). All affected children had low levels of glutamine (241 +/- 166 uM; $p < 0.01$) and asparagine (22.9 +/- 12.9 uM; $p < 0.01$) as compared to normal values (585 +/- 25 and 59.2 +/- 4.2 uM respectively); eleven children had increased aspartic acid and eight children had high levels of glutamate; seven of these children had a concomitant increment of taurine. The increment of the three above mentioned compounds was observed at the same time only in five children. These findings demonstrate that abnormal plasmatic levels of neurotransmitter amino acids may be found in some autistic children. Increased glutamatermia may be dietary in origin or may arise endogenously for several reasons, among others, metabolic derangements in glutamate metabolism perhaps involving vitamin B6, defects or blockage of the glutamate receptor at the neuronal compartment, or alterations in the function of the neurotransmitters transporters. Increments of taurine, an inhibitor, is likely compensatory and calcium dependent.

Publication Types:

Research Support, Non-U.S. Gov't

PMID: 8718922

^{ix} Brain Dev. 2007 Feb 23; [Epub ahead of print]

Autism and epilepsy: A retrospective follow-up study.

Hara H.

Yokohama Central Area Habilitation Center for Children, Yokohama,
Japan; Kanagawa
Day Treatment & Guidance Center for Children, Japan.

So-called "idiopathic" autism, which exhibited no major complications before diagnosis is well-known as one of the risk factors for epilepsy. This retrospective follow-up study aimed to clarify the characteristics of epilepsy in the autism; onset of seizure, seizure types, EEG findings and epilepsy outcome and the differences as a group between the autism with epilepsy and those without epilepsy. One hundred thirty individuals with autistic disorder or atypical autism diagnosed in childhood were followed up over 10years and were evaluated almost every year up to 18-35years of age. Their medical records related to perinatal conditions, IQ, social maturity scores and several factors of epilepsy were reviewed in October 2005. Thirty-three of the follow-up group (25%) exhibited epileptic seizures. The onset of epilepsy was distributed from 8 to 26years of age. Two types of seizure were observed; partial seizure with secondarily generalized seizure and generalized seizure. Twenty of the epileptics (61%) showed the partial seizure. Although 18% of the non-epileptic group exhibited epileptic discharges on EEG, 68% of the epileptic group revealed epileptiform EEG findings before the onset of epilepsy. No differences were observed concerning the sex ratio, autistic disorder/atypical autism and past history of febrile seizures between the epileptic and non-epileptic groups. Lower IQ, lower social maturity score and higher frequency of prescribed psychotropics were observed in the epileptic group compared to the non-epileptics.

Idiopathic
autism was confirmed as the high risk factor for epilepsy. Epileptiform
EEG
findings predict subsequent onset of epileptic seizures in adolescence.
Epilepsy
is one of negative factors on cognitive, adaptive and
behavioral/emotional
outcomes for individuals with autism.

PMID: 17321709

Epilepsy Behav. 2007 Mar;10(2):344-7. Epub 2007 Feb 14.

Effects of vagus nerve stimulation in a patient with temporal lobe
epilepsy and
Asperger syndrome: case report and review of the literature.

Warwick TC, Griffith J, Reyes B, Legesse B, Evans M.

Department of Internal Medicine, University of California, San
Francisco, University Medical Center, 445 South Cedar Avenue, Fresno, CA
93702,
USA. Twarwick@fresno.ucsf.edu

Seizures are a common comorbidity of autism and occur in as many as 30%
of
patients. This case report describes a 23-year-old man diagnosed with
both
Asperger syndrome and bitemporal epilepsy. The patient had behavioral
regression
that correlated with worsening of his intractable seizures. He
subsequently
underwent implantation of a vagus nerve stimulation therapy device for
his
refractory epilepsy. Both his seizures and his behavior were monitored
for 6
months. We describe the efficacy of vagus nerve stimulation therapy in
reducing
seizure severity as well as improving the behavioral components of his
Asperger
syndrome. We also review the current literature regarding epilepsy in
autistic
spectrum disorders.

Publication Types:
Clinical Trial

PMID: 17300990

* Autism. 2002 Sep;6(3):315-28.

Urinary peptides in Rett syndrome.

Solaas KM, Skjeldal O, Gardner ML, Kase FB, Reichelt KL.

Institute of Pediatric Research, The National Hospital, University of Oslo,
Norway.

Rett syndrome is a neuro-developmental disorder related to autistic behavior. Persons with autism have previously been found to have hyperpeptiduria. We here report a significantly higher level of peptides in the first fasting morning urine from 53 girls with Rett syndrome (both classical and congenital) compared with 53 healthy girls. This elevation in urinary peptides was similar to that in 35 girls with infantile autism. As in persons with autism, the individual levels of urinary peptides in the Rett syndrome group varied, and about a fifth were within the normal range. Levels of peptides were lower in girls with classic Rett syndrome than in girls with congenital Rett syndrome. This may be due to different etiological causes or to active and stagnant phases of the disease. Urine from girls with Rett syndrome was found to have higher frequency and higher levels of some urinary peptides that may cause inhibition of brain maturation and epilepsy

Publication Types:

Research Support, Non-U.S. Gov't

PMID: 12212921

Ann Neurol. 2001 May;49(5):597-606.

Neuropeptides and neurotrophins in neonatal blood of children with autism or mental retardation.

Nelson KB, Grether JK, Croen LA, Dambrosia JM, Dickens BF, Jelliffe LL, Hansen RL, Phillips TM.

National Institute of Neurological Diseases and Stroke, Bethesda, MD 20892-1447,
USA. knelson@helix.nih.gov

There has been little exploration of major biologic regulators of cerebral development in autism. In archived neonatal blood of children with autistic spectrum disorders (n = 69), mental retardation without autism (n =

60), or cerebral palsy (CP, n = 63) and of control children (n = 54), we used recycling immunoaffinity chromatography to measure the neuropeptides substance P (SP), vasoactive intestinal peptide (VIP), pituitary adenylate cyclase-activating polypeptide (PACAP), calcitonin gene-related peptide (CGRP), and the neurotrophins nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin 3 (NT3), and neurotrophin 4/5 (NT4/5). Neonatal concentrations of VIP, CGRP, BDNF, and NT4/5 were higher (ANOVA, all p values < 0.0001 by Scheffe test for pairwise differences) in children in the autistic spectrum and in those with mental retardation without autism than in control children. In 99% of children with autism and 97% with mental retardation, levels of at least one of these substances exceeded those of all control children. Concentrations were similar in subgroups of the autistic spectrum (core syndrome with or without mental retardation, other autistic spectrum disorders with or without mental retardation) and in the presence or absence of a history of regression. Among children with mental retardation, concentrations did not differ by severity or known cause (n = 11, including 4 with Down syndrome). Concentrations of measured substances were similar in children with CP as compared with control subjects. SP, PACAP, NGF, and NT3 were not different by diagnostic group. No measured analyte distinguished children with autism from children with mental retardation alone. In autism and in a heterogeneous group of disorders of cognitive function, overexpression of certain neuropeptides and neurotrophins was observed in peripheral blood drawn in the first days of life.

Publication Types:

Research Support, Non-U.S. Gov't

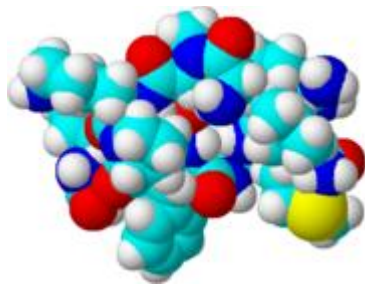
Research Support, U.S. Gov't, P.H.S.

PMID: 11357950

Substance P

From Wikipedia, the free encyclopedia

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Spacefilling [model](#) of substance P
tachykinin, precursor 1

Identifiers	
Symbol	TAC1
Alt. Symbols	TAC2, NKNA
Entrez	6863
HUGO	11517
OMIM	162320
RefSeq	NM_003182
UniProt	P20366
Other data	
Locus	Chr. 7 q21-q22

Substance P	
Identifiers	
CAS number	33507-63-0
PubChem	36511
MeSH	Substance+P
Properties	
Molecular formula	C ₆₃ H ₉₈ N ₁₈ O ₁₃ S
Molar mass	1347.63 g/mol

Except where noted otherwise, data are given for materials in their [standard state](#) (at 25 °C, 100 kPa)
[Infobox disclaimer and references](#)

In [neuroscience](#), **Substance P** is a [neuropeptide](#): a short-chain [polypeptide](#) that functions as a [neurotransmitter](#) and as a [neuromodulator](#). It belongs to the [tachykinin](#) neuropeptide family.

It is an 11-[amino acid](#) polypeptide with the sequence: Arg Pro Lys Pro Gln Gln Phe Phe Gly Leu Met NH₂.

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- [3 Substance P in gastrointestinal infection](#)
- [4 Animals without substance P](#)
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Receptor

The [endogenous receptor](#) for Substance P is [neurokinin 1](#) receptor (NK1-receptor, NK1R). It belongs to the [tachykinin](#) receptor sub-family of [GPCRs](#).

Functions

In the [central nervous system](#), substance P has been associated in the regulation of [mood disorders](#), [anxiety](#), [stress](#), [reinforcement](#), [neurogenesis](#), [respiratory rhythm](#), [neurotoxicity](#), [nausea](#) / [emesis](#) and [pain](#).

Vomiting

The [vomiting](#) center in the [brainstem](#) contains high concentrations of substance P and its receptor, in addition to other neurotransmitters such as [choline](#), [histamine](#), [dopamine](#), [serotonin](#), and [opioids](#). Their activation stimulates the vomiting reflex. Different emetic pathways exist, and substance P/NK1R appears to be within the final common pathway to regulate vomiting. ^[1]

Substance P antagonist (SPA) [aprepitant](#) is available in the market in the treatment of [chemotherapy](#)-induced nausea / emesis.

Pain

Substance P is involved in the transmission of [pain](#) impulses from peripheral receptors to the [central nervous system](#). It has been theorized that it plays a part in [fibromyalgia](#). [Capsaicin](#) has been shown to reduce the levels of Substance P probably by reducing the number of [C-fibre](#) nerves or causing these nerves to be more tolerant.

Stimulating cellular growth

Substance P has been shown to stimulate cellular growth in cell culture [\[2\]](#), and it was shown that Substance P could promote wound healing of non-healing [ulcers](#) in humans. [\[3\]](#) It has also been shown to reverse diabetes in mice. [\[4\]](#)

Vasodilation

It also has effects as a potent [vasodilator](#). This is caused by the release of [nitric oxide](#) from the [endothelium](#). Its release can cause [hypotension](#).

Substance P in gastrointestinal infection

[Entamoeba histolytica](#) is a single-celled parasitic [protozoan](#) that infects the lower gastrointestinal tract of humans, producing symptoms of [diarrhea](#), [constipation](#), and [abdominal pain](#).[\[5\]](#)[\[6\]](#) This protozoan was found to secrete [serotonin](#)^[7], as well as substance P and [neurotensin](#).[\[8\]](#)

^{xi} J Autism Dev Disord. 2006 Apr;36(3):317-24.

Familial autoimmune thyroid disease as a risk factor for regression in children with Autism Spectrum Disorder: a CPEA Study.

Molloy CA, Morrow AL, Meinzen-Derr J, Dawson G, Bernier R, Dunn M, Hyman SL, McMahon WM, Goudie-Nice J, Hepburn S, Minshew N, Rogers S, Sigman M, Spence MA, Tager-Flusberg H, Volkmar FR, Lord C.

Center for Epidemiology and Biostatistics, Cincinnati Children's Hospital Medical Center, University of Cincinnati College of Medicine, Ohio 45229-3039, USA.
cynthia.molloy@cchmc.org

A multicenter study of 308 children with Autism Spectrum Disorder (ASD)

was conducted through the Collaborative Programs of Excellence in Autism (CPEA), sponsored by the National Institute of Child Health and Human Development, to compare the family history of autoimmune disorders in children with ASD with and without a history of regression. A history of regression was determined from the results of the Autism Diagnostic Interview-Revised (ADI-R). Family history of autoimmune disorders was obtained by telephone interview. Regression was significantly associated with a family history of autoimmune disorders (adjusted OR=1.89; 95% CI: 1.17, 3.10). The only specific autoimmune disorder found to be associated with regression was autoimmune thyroid disease (adjusted OR=2.09; 95% CI: 1.28, 3.41).

Publication Types:
Multicenter Study

PMID: 16598435

^{xii} J Autism Dev Disord. 2006 Apr;36(3):317-24.

Familial autoimmune thyroid disease as a risk factor for regression in children with Autism Spectrum Disorder: a CPEA Study.

Molloy CA, Morrow AL, Meinzen-Derr J, Dawson G, Bernier R, Dunn M, Hyman SL, McMahon WM, Goudie-Nice J, Hepburn S, Minshew N, Rogers S, Sigman M, Spence MA, Tager-Flusberg H, Volkmar FR, Lord C.

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results of the Autism Diagnostic Interview-Revised (ADI-R). Family history of autoimmune disorders was obtained by telephone interview. Regression was significantly associated with a family history of autoimmune disorders (adjusted OR=1.89; 95% CI: 1.17, 3.10). The only specific autoimmune disorder found to be associated with regression was autoimmune thyroid disease (adjusted OR=2.09; 95% CI: 1.28, 3.41).

Publication Types:
Multicenter Study

PMID: 16598435

^{xiii} Med. Hypotheses. 2007;68(1):46-60. Epub 2006 Sep 7.

Prenatal influences on brain dopamine and their relevance to the rising incidence of autism.

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fprevic@sbcglobal.net

The incidence of autism has risen 10-fold since the early 1980s, with most of this rise not explainable by changing diagnostic criteria. The rise in autism is paradoxical in that autism is considered to be one of the most genetically determined of the major neurodevelopmental disorders and should accordingly either be stable or even declining. Because a variety of epigenetic influences, particularly those occurring during the prenatal period, can override or masquerade as genetic influences, these should be considered as prime contributors to the recent increase of autism. Prenatal influences on dopamine activity are especially well-documented, including the effects of maternal psychosocial stress, maternal fever, maternal genetic and hormonal status, use of certain medications, urban birth, and fetal hypoxia. All of these factors have been implicated in the genesis of autism, which is characterized by a "hyperdopaminergic" state based on evidence from monkey and human behavioral studies, pharmacological studies in humans, and a left-hemispheric predominance

of both dopamine and autistic-like symptoms. Chronically high maternal levels of dopamine caused by the pressures of increasingly urbanized societies and by changing maternal demographics such as increased workforce participation, educational achievement level, and age at first birth, may be especially significant epigenetic contributors to the recent autism rise.

PMID: 16959433 [PubMed - indexed for MEDLINE]

Brain Dev. 2006 Mar;28(2):99-103. Epub 2005 Sep 15.

Administration of secretin for autism alters dopamine metabolism in the central nervous system.

Toda Y, Mori K, Hashimoto T, Miyazaki M, Nozaki S, Watanabe Y, Kuroda Y, Kagami S.

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We evaluated the clinical effects of intravenously administered secretin in 12 children with autism (age range: 4-6 years, median age: 9 years, boy:girl=8:4). In addition, we investigated the association between improvement in symptoms and changes in the cerebrospinal fluid (CSF) homovanillic acid (HVA), 5-hydroxyindole-3-acetic acid (5-HIAA), and 6R-5,6,7,8-tetrahydro-L-biopterin (BH(4)) levels after administration. After administration of secretin, the Autism Diagnostic Interview-Revised (ADI-R) score improved in 7 of the 12 children. However, the score deteriorated in 2 of the 12 children (in the item of 'restricted and repetitive, stereotyped interests and behaviors'). The HVA and BH(4) levels in CSF were increased in all children with improvement in the ADI-R score. In contrast, no patient without the elevation of the BH(4) level showed improvement in the score. These findings suggest that secretin activated metabolic turnover of dopamine in the central nervous system via BH(4), improving symptoms.

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Clinical Trial
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Tachykinin 1 (TAC1) gene SNPs and haplotypes with autism: A case-control study.

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Autism (MIM 209850) is a severe neurodevelopmental disorder characterized by disturbances in social interaction and communication, by repetitive body movements and restricted interests, and by atypical language development. Several twin and family studies have shown strong evidence for genetic factors in the etiology of autism. Glutamate is a major excitatory neurotransmitter in the human brain. Glutamate systems are involved in the pathophysiology of autism. There are many similarities between the symptoms evoked by glutamate antagonist treatment and symptoms of autism found in several human and animal studies. To elucidate the genetic background of autism, we analyzed the relationship between three single nucleotide polymorphisms (SNPs) of the Tachykinin 1 gene (TAC1) and autism, because TAC1 is located in the candidate region for autism and produces substance P and neurokinins. These products modulate glutamatergic excitatory synaptic transmission and are also involved in inflammation. Many different inflammation-related mechanisms could be involved in the autistic brain. Therefore, TAC1 may have some functions associated with the presumable pathophysiology of autism. We compared the allele and haplotype frequencies between autistic patients (n=170) and normal controls (n=214) in the Japanese population, but no significant difference was observed. Thus, the TAC1 locus is not likely to play a major role in the development of autism.

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Substance P and cholecystokinin regulate neurochemical responses to cocaine and methamphetamine in the striatum.

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The mechanism of action of drugs of abuse like cocaine and amphetamines has been studied extensively in the dopamine terminal field areas of the caudate-putamen (CPu) and the nucleus accumbens (NAc) of the rodent brain. These brain regions contain several neuropeptides that must play important roles in the normal physiological functions of these brain regions. The study of neuropeptide physiology in the context of the neurobiological responses to drugs of abuse may shed some light on the intrinsic mechanism of action of neuropeptides of the CPu and the NAc. The neuropeptides substance P (SP) and cholecystokinin (CCK) are present in the striatum where they could play an important role regulating the effects of psychostimulants like cocaine and amphetamines (methamphetamine [METH] is a long acting derivative of d-amphetamine). These highly addictive agents induce the release of dopamine (DA) (and other catecholamines) from dopaminergic terminals of the striatum. The excessive release of DA in the striatum and the NAc has been implicated in the habit-forming properties of these drugs. In order to study the contribution of SP and CCK in the striatum during psychostimulant treatment, we employed selective non-peptide neurokinin-1 (NK-1) and cholecystokinin-2 (CCK-2) receptor antagonists that readily cross the blood brain barrier. We infused the neurokinin-1 receptor (NK-1R) antagonist, L-733,060, into the striatum of freely moving rats via a microdialysis probe in order to assess the effects of SP on cocaine-induced DA overflow in the striatum. Infusion of the NK-1R antagonist prior to a systemic injection of cocaine (10 mg/kg i.p.) significantly attenuated DA overflow in the striatum. Conversely, infusion of a CCK-2 receptor (CCK-2R) antagonist, L-369,293, through the microdialysis probe evoked DA overflow in the striatum in the absence of cocaine and potentiated DA overflow after a single injection of cocaine (10 mg/kg i.p.). Exposure to METH (10 mg/kg 4x at two-hour intervals) produced deficits of dopamine transporters (DAT) in mice striatum that are detectable three days after the treatment and are long lasting. Pre-treatment (i.p. injections) with the NK-1R antagonist, WIN-51,708 30 minutes before the 1st and 4th injections of METH prevented the loss of DAT in the striatum. Moreover, pre-treatment with the NK-1R antagonist prevents METH-induced cell death. Taken together, these results demonstrate that the NK-1R and the CCK-2R are important modulators of the actions of the psychostimulants cocaine and METH. Neuropeptide receptors represent an important control point mediating the effects of the neurotransmitter DA in the striatum of the rodent brain.

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Dopamine control of striatal gene expression during development: relevance to knockout mice for the dopamine transporter.

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The aim of this study was to determine at which developmental stage and how dopamine regulates the expression of striatal dopamine receptor and neuropeptide mRNAs. For this, we studied the expression of these mRNAs, in relation to dopamine innervation, in normal mice from gestational day 13 (G13) to adult. Particularly, we investigated the adaptive changes in the expression of these markers in mice lacking the dopamine transporter during development. We detected tyrosine hydroxylase, by immunohistochemistry, in the ventral mesencephalon and the striatal anlage in both genotypes at G13, whereas the dopamine transporter appeared in the striatum of normal mice at G14. By in situ hybridization, we detected striatal dopamine D1, D2, D3 receptor, and substance P mRNAs at G13, preproenkephalin A mRNA at G14 and dynorphin mRNA at G17 in normal mice. Although the time of initial detection and the distribution were not affected in mutant mice, quantitative changes were observed. Indeed, D1 and D2 receptor as well as preproenkephalin A mRNA levels were decreased from G14 on, and dynorphin mRNA level was increased from G17 on. In contrast, substance P mRNA level was unaffected. Our data demonstrate that the influence of dopamine on striatal neurons occurs early during the development of the mesostriatal system as quantitative changes appeared in mutant mice as soon as G14. These findings bring new insights to the critical influence of dopamine on the expression of striatal dopamine receptor and neuropeptide mRNAs during development, and suggest that mesostriatal dopamine transmission functions from G14 on.

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Activation of the inflammatory response system in autism.

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BACKGROUND/AIM: There is now some evidence that autism may be accompanied by abnormalities in the inflammatory response system (IRS). Products of the IRS, such as proinflammatory cytokines, may induce some of the behavioral symptoms of autism, such as social withdrawal, resistance to novelty and sleep disturbances.

The main aim of the present study was to examine whether autism is accompanied by an activation of the IRS. METHODS: We measured the production of interleukin

(IL)-6, IL-10, the IL-1 receptor antagonist (IL-1RA), interferon (IFN)-gamma and tumor necrosis factor (TNF)-alpha by whole blood and the serum concentrations of IL-6, the IL-2 receptor (IL-2R) and IL-1RA. RESULTS: This study showed a significantly increased production of IFN-gamma and IL-1RA and a trend toward a significantly increased production of IL-6 and TNF-alpha by whole blood of autistic children. There were no significant differences in the serum concentrations of IL-6, IL-2R and IL-1RA between autistic and normal children.

CONCLUSIONS: These results suggest that autism may be accompanied by an activation of the monocytic (increased IL-1RA) and Th-1-like (increased IFN-gamma) arm of the IRS. It is hypothesized that increased production of proinflammatory cytokines could play a role in the pathophysiology of autism.

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Voluntary control of saccadic and smooth-pursuit eye movements in children with learning disorders.

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Eye movement is crucial to humans in allowing them to aim the foveae at objects of interest. We examined the voluntary control of saccadic and smooth-pursuit eye movements in 18 subjects with learning disorders (LDs) (aged 8-16) and 22 normal controls (aged 7-15). The subjects were assigned visually guided, memory-guided,

and anti-saccade tasks, and smooth-pursuit eye movements (SPEM). Although, the LD subjects showed normal results in the visually guided saccade task, they showed more errors in the memory-guided saccade task (e.g. they were unable to stop themselves reflexively looking at the cue) and longer latencies, even when they performed correctly. They also showed longer latencies than the controls in the anti-saccade task. These results suggest that they find it difficult to voluntarily suppress reflexive saccades and initiate voluntary saccades when a target is invisible. In SPEM using step-ramp stimuli, the LD subjects showed lower open- and closed-loop gains. These results suggest disturbances of both acceleration of eye movement in the initial state and maintenance of velocity in minimizing retinal slip in the steady state. Recent anatomical studies in LD subjects have suggested abnormalities in the structure of certain brain areas such as the frontal cortex. Frontal eye movement-related areas such as the frontal eye fields and supplementary eye fields may be involved in these disturbances of voluntary control of eye movement in LDs.

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Amygdala volume and nonverbal social impairment in adolescent and adult males with autism.

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BACKGROUND: Autism is a syndrome of unknown cause, marked by abnormal development of social behavior. Attempts to link pathological features of the amygdala, which plays a key role in emotional processing, to autism have shown little consensus. **OBJECTIVE:** To evaluate amygdala volume in individuals with autism spectrum disorders and its relationship to laboratory measures of social behavior to examine whether variations in amygdala structure relate to symptom severity. **DESIGN:** We conducted 2 cross-sectional studies of amygdala volume, measured blind to diagnosis on high-resolution, anatomical magnetic resonance images. Participants were 54 males aged 8 to 25 years, including

23 with autism and 5 with Asperger syndrome or pervasive developmental disorder not otherwise specified, recruited and evaluated at an academic center for developmental disabilities and 26 age- and sex-matched community volunteers. The Autism Diagnostic Interview-Revised was used to confirm diagnoses and to validate relationships with laboratory measures of social function. MAIN OUTCOME MEASURES: Amygdala volume, judgment of facial expressions, and eye tracking. RESULTS: In study 1, individuals with autism who had small amygdalae were slowest to distinguish emotional from neutral expressions ($P=.02$) and showed least fixation of eye regions ($P=.04$). These same individuals were most socially impaired in early childhood, as reported on the Autism Diagnostic Interview-Revised ($P<.04$). Study 2 showed smaller amygdalae in individuals with autism than in control subjects ($P=.03$) and group differences in the relation between amygdala volume and age. Study 2 also replicated findings of more gaze avoidance and childhood impairment in participants with autism with the smallest amygdalae. Across the combined sample, severity of social deficits interacted with age to predict different patterns of amygdala development in autism ($P=.047$). CONCLUSIONS: These findings best support a model of amygdala hyperactivity that could explain most volumetric findings in autism. Further psychophysiological and histopathological studies are indicated to confirm these findings.

PMID: 17146016

[Psychopharmacology \(Berl\)](#). 2007 Mar;191(1):107-18. Epub 2007 Feb 3.

From anxiety to autism: spectrum of abnormal social behaviors modeled by progressive disruption of inhibitory neuronal function in the basolateral amygdala in Wistar rats.

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RATIONALE: Social behaviors are disrupted in several psychiatric disorders. The amygdala is a key brain region involved in social behaviors, and amygdala pathology has been implicated in disease states ranging from social anxiety disorder to autism. OBJECTIVE: To test the effects of progressive disruption of the inhibitory function within the basolateral nucleus of the amygdala (BLA) on conspecific social interaction in rats and investigate functional networks from the ventral medial prefrontal cortex (mPFCv) to the BLA. MATERIALS AND METHODS: BLA inhibitory tone was disrupted by priming it with the stress-peptide corticotrophin releasing factor (CRF) receptor agonist urocortin 1 (Ucn 1, 6 fmol), or by selective lesioning of a subset of BLA-GABAergic interneurons containing neurokinin 1 receptors using the targeted toxin SSP-

Saporin. The effects of the disruption of GABAergic tone in the BLA were examined using a repeated exposure and habituation paradigm of social interaction (SI/h). Lesions and selectivity of lesions were confirmed postmortem. Additionally, effects of stimulating mPFCv on cFos activity in interneurons of the BLA were examined. RESULTS: Rats primed with Ucn 1 showed persistent social inhibition, which could be overcome with habituation, putatively modeling social anxiety. Rats with a selective lesioning of a subset of GABAergic interneurons in the BLA exhibited persistent social inhibition that was not reversed by SI/h paradigm. We also demonstrate selective functional inputs to this subset of interneurons when mPFCv was activated. CONCLUSIONS: These models with different gradations of disrupted BLA inhibition could help to study social dysfunction in disorders ranging from social anxiety to autism spectrum disorders.

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[Peptides](#). 1983 Jul-Aug;4(4):525-41.

Organization and interrelationship of neuropeptides in the central amygdaloid nucleus of the rat.

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The organization and interactions of neuropeptides in the central nucleus of the amygdala (Ce) were studied using single and double label immunocytochemical techniques. Immunocytochemical localization of substance P (SP), neurotensin (NT), met-enkephalin (m-ENK), somatostatin (SS) and vasoactive intestinal polypeptide (VIP) revealed all of these peptides within discrete regions of the Ce. The regions differed from the classical medial and lateral anatomical divisions reported for the Ce. Instead, three easily recognizable neuropeptidergic subdivisions were evident: a medial zone, a central zone and a lateral capsular zone. Two types of interrelationships between peptides were noted. The first involved a peptidergic fiber in apposition to a peptidergic perikarya. The most prevalent peptidergic interaction of this type occurred between SP and NT. The second interrelationship involved two different peptidergic fibers in apposition to an immunonegative cell. Two interactions of this type were commonly observed. The first involved NT and m-ENK fibers simultaneously apposed to an unstained cell. The second involved SP and m-ENK fibers adjacent to the same immunonegative cell. The interactions between peptidergic systems may suggest a role of these substances in the regulation of autonomic functions in the Ce.

[Chem Senses](#). 2007 May;32(4):343-53. Epub 2007 Feb 17.

Cerebral activation to intranasal chemosensory trigeminal stimulation.

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Although numerous functional magnetic resonance imaging (fMRI) studies have been performed on the processing of olfactory information, the intranasal trigeminal system so far has not received much attention. In the present study, we sought to delineate the neural correlates of trigeminal stimulation using carbon dioxide (CO₂) presented to the left or right nostril. Fifteen right-handed men underwent fMRI using single runs of 3 conditions (CO₂ in the right and the left nostrils and an olfactory stimulant-phenyl ethyl alcohol-in the right nostril). As expected, olfactory activations were located in the orbitofrontal cortex (OFC), amygdala, and rostral insula. For trigeminal stimulation, activations were found in "trigeminal" and "olfactory" regions including the pre- and postcentral gyrus, the cerebellum, the ventrolateral thalamus, the insula, the contralateral piriform cortex, and the OFC. Left compared with right side stimulations resulted in stronger cerebellar and brain stem activations; right versus left stimulation resulted in stronger activations of the superior temporal sulcus and OFC. These results suggest a trigeminal processing system that taps into similar cortical regions and yet is separate from that of the olfactory system. The overlapping pattern of cortical activation for trigeminal and olfactory stimuli is assumed to be due to the intimate connections in the processing of information from the 2 major intranasal chemosensory systems.

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xvi [Am J Hum Genet](#). 2001 Nov;69(5):1062-7. Epub 2001 Oct 2.

Excess of twins among affected sibling pairs with autism: implications for the etiology of autism.

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It is widely accepted that genes play a role in the etiology of autism. Evidence for this derives, in part, from twin data. However, despite converging evidence from gene-mapping studies, aspects of the genetic contribution remain obscure. In a sample of families selected because each had exactly two affected sibs, we observed a remarkably high proportion of affected twin pairs, both MZ and DZ. Of 166 affected sib pairs, 30 (12 MZ, 17 DZ, and 1 of unknown zygosity) were twin pairs. Deviation from expected values was statistically significant ($P < 10^{-6}$ for all twins); in a similarly ascertained sample of individuals with type I diabetes, there was no deviation from expected values. We demonstrate that to ascribe the excess of twins with autism solely to ascertainment bias would require very large ascertainment factors; for example, affected twin pairs would need to be, on average, approximately 10 times more likely to be ascertained than affected non-twin sib pairs (or 7 times more likely if "stoppage" plays a role). Either risk factors (related to twinning or to fetal development) or other factors (genetic or nongenetic) in the parents may contribute to autism.

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