Saccadic characteristics in autistic children

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Summary

Some studies suggest that individuals with autism present abnormal saccadic eye movements due to an altered strategy for exploration of the surrounding environment. In this study, potential early abnormalities of saccadic movements were explored in 14 male children with autism (5- to 12-year-olds) and in 20 age-matched normal males. Only one patient showed clear abnormalities of the "main sequence"; all the other patients, although showing slight changes in saccadic eye movements, did not present classic deficits. Therefore our results did not confirm the presence of saccadic movement alterations in the early stage of autism. Nonetheless, tracts of saccadic initiation failure, continuous changes in saccadic velocity profiles, and instability of fixation were often observed in the autistic population. These findings could be the expression of an early brainstem impairment in autism.

KEY WORDS: autism, saccades, premotor system

Introduction

Autism is a developmental disorder characterised by social communication problems, difficulties with reciprocal social interactions, and unusual patterns of repetitive behaviour. These manifestations cover a wide spectrum, ranging from individuals with severe impairment (who may be silent, mentally disabled, and locked into hand-flapping and rocking behaviours) to less impaired individuals who have active but distinctly odd social approaches, narrowly focused interests, and a verbose, pedantic communication style.

Autism appears to result from brain maldevelopment affecting various cerebral systems. In this regard, structural magnetic resonance imaging (MRI) and histopathological studies have consistently documented abnormalities in the frontal and parietal cortex, cerebellum, and limbic system (1,2). In particular, total brain, parietal-temporal lobe, and cerebellar hemisphere volumes are often increased. In addition, functional imaging studies have reported abnormalities in the frontal and parietal cortex. Event-related functional MRI (fMRI) is now used to investigate the working of the superior temporal sulcus, as well as the other brain structures that have been linked to social cognition and social perception (3).

Most MRI studies in autism reported negative findings for size abnormalities in the cerebellar vermis, brainstem, basal ganglia, and fourth ventricle, but the absence of volumetric abnormalities does not exclude the existence of functional impairments.

The brainstem, in particular, is difficult to investigate; however, since this is where the centres of eye movement generation (in particular the generation of saccades) are located, studying saccadic eye movement can help to further knowledge of brainstem involvement in autism. Eye tracking technology is already used in individuals with disorders of the autism spectrum to investigate gaze behaviour, in particular the strategies used during tasks involving social information processing (4). Eye tracking allows an objective, quantitative evaluation of visual behaviour during observation of the environment and, allowing analysis of fixation patterns, can indicate which information from a scene is available to the brain. The most common stimuli used for this purpose are pictures of human faces, but videotapes of social interactions, human voices, and abstract animations have also been employed. Despite some negative findings, most studies have shown that individuals with autism look at social stimuli differently from normal subjects, and in particular that they look less at the eye region of the face (5).

As far as saccadic eye movements are concerned, the parameters amplitude, duration and peak velocity are measured to calculate the "main sequence" consisting of two relationships: the one between amplitude and duration, and the one between amplitude and peak velocity. These relationships are relatively fixed in normal saccades. The "main sequence" thus provides a means of investigating the working of the premotor system, i.e., of investigating whether the burst cells are working correctly to produce the recorded saccade, independently of the correctness of the eye tracking in terms of direction, amplitude and timing. The "main sequence"

also makes it possible to understand whether all saccades were correctly generated by the premotor system, and in particular, whether they were generated with adequate velocity. Slowed saccades are usually due to lesions of motoneurons, or premotor burst or omnipause neurons (6).
Accuracy is the ability to execute saccades of correct amplitude: a saccade with insufficient amplitude is defined hypometric, whereas a hypermetric saccade is one with excessively high amplitude. Saccades of incorrect amplitude can be the consequence of a cerebellar lesion (6). Latency is the time that elapses between the appearance of a target and the onset of a saccade in response to that target. Increased latencies can be the consequence of a lesion of the frontal eye fields (6).
Indeed, many nervous structures are involved in the generation of saccades. Some areas of the parietal and (perhaps) the temporal cortex are involved in visuospatial attention. The selection of targets and the decision to execute a fast eye movement take place mainly in the frontal eye fields and in the superior colliculus; the premotor system, which produces the saccade (pulse generator), is located in the brainstem reticular formation, in particular in the pontine paramedian reticular formation (PPRF) for horizontal movements, and in the mesencephalic reticular formation for vertical saccades. The premotor command, controlled by the cerebellum (vermis), is sent to the ocular motor nuclei from which the three ocular motor nerves (III, IV and VI) originate. These nerves command the six extraocular muscles which move each eye and the levator muscle of the upper lid (6).
Despite contradictory results in the literature (7,8), most studies indicate abnormal saccadic eye movements in individuals with autism (9-13). In several of these studies, a visually-guided saccade task was used in conjunction with intentional saccade tasks, such as memory-guided, predictive, and anti-saccade tasks. In the first study of basic ocular motor function in autism (14), a non-predictive (visually-guided) saccade task was employed and saccadic eye movements were recorded by means of an electro-oculographic device. Saccadic velocity, latency, and accuracy were evaluated. Although abnormalities were found in only six of the 11 children with autism, most of the autistic children showed reduced accuracy and lower peak velocity compared with the control group. No differences in latency were found. In a second, similar study by Minshew et al. (15), no difference was found between a group of autistic (26 high-functioning) individuals and a control group in terms of accuracy, velocity, or latency. However, in a later study involving a larger sample (46 high-functioning individuals with autism), Takarae et al. (16) found subtle, yet statistically significant, saccadic dysmetria (consistent with reports of histological abnormalities in the cerebellum) (7,8).
Abnormalities in the frequency of saccades and in visual search behaviour have been shown in autistic patients, especially during memory-guided or predictive tasks. Atypical characteristics of fast eye movements have also been detected in some cases. These findings suggest that some basic oculomotor abnormalities may be present early in the course of the disease. In fact, unlike attention systems related to the oculomotor function, which undergo prolonged development throughout childhood, saccadic eye movements, which are basic components of oculomotor behaviour, are already present in infancy. If impaired, these early and basic oculomotor components could subsequently affect the development of sensorimotor, attentional, and cognitive functions (17).
The present study assessed saccades in autistic children in order to verify Brenner's (17) assumption that some alterations of saccadic movements are present at an early stage of the disease.

Materials and methods

Patients

The saccadic eye movements of 14 male children with DSM-IV autism, aged 5 to 12 years (average 8.1 years), were recorded. Diagnoses were made according to the Autism Diagnostic Observation Schedule (ADOS) administered in Italian by a certified psychologist. The Childhood Autism Rating Scale (CARS) was also applied to determine disease severity; all the autistic children recruited in this study had a CARS score > 40, suggesting a high severity. They all had a developmental quotient or an IQ > 60, as determined by the Leiter-R or the Griffiths scale. None of the patients had comorbid attention-deficit hyperactivity disorder, seizures, or any other associated disorder known to cause autism.
In all patients, the ophthalmological examination, performed by an ophthalmologist and an orthoptist, showed a monocular visual acuity of at least 16/20 without optical correction, with hyperopia not exceeding +1.50 dioptres and maximum astigmatism of 0.50 dioptres; no case of myopia was present. In all patients the orthoptic examination excluded the presence of heterotropia for far and near distance vision, and limitations of eye rotation.
The control group consisted of 20 male children, with ages in the same range as those of the autistic patients (range 5-12 years; mean 8 years). All the control children had a normal ophthalmological examination (hyperopia not exceeding +1.50 dioptres) and none of them suffered from any major medical, neuropsychiatric or developmental problems, as determined by clinical examinations performed by a child neuropsychiatrist.
None of the children, in either the autistic or the control group, were taking or had ever taken psychotropic medications.
This research was approved by the ethics committee of the IRCCS "Burlo Garofolo", Trieste. Informed consent was obtained from the parents of all the patients and controls.

Eye movement recording

Saccadic movements of both eyes were recorded by means of an infrared bi-channel probe based on the *limbus tracking* technique, which uses the infrared reflection on the eye to estimate the eye position (18). In this study, we did not investigate smooth visual pursuit, but monitored only saccadic eye movements. The signal was low-pass filtered at 100 Hz and sampled at 500 Hz with a resolution greater than 0.2 deg. The acquisition was performed with the subject sitting one metre

from a horizontal semicircular stimulation bar containing 255 red LEDs, with his head on a chin rest. The stimulus was randomly moved in time and position in a visual range of +/- 20 deg with amplitudes of 5, 10, 15, 20 and 25 deg, producing a sequence of 75 displacements which were pursued in binocular vision without optical correction.

Saccadic processing

Following semiautomatic identification of saccades on the basis of a velocity threshold (set at 5 deg/s), for each identified saccade the following parameters were evaluated: amplitude (A), duration (D), latency, and peak velocity (Vp). A/D and A/Vp relationships ("main sequence") were calculated. The A/D relationship was calculated as a linear regression (D = m*A+q), while for the A/Vp relationship the fitting curve was derived from the function $Vp = 1/(\alpha+\beta/A)$, where $1/\alpha$ (in deg/s) represents the velocity saturation value for $A \rightarrow \infty$ and $1/\beta$ (in s^{-1}) corresponds to the slope of the best-fit curve for $A \rightarrow 0$. Furthermore, alterations in the eye movement velocity profiles, such as slowing down and oscillations, were investigated.
Two other parameters were also calculated (19-21): K (mean velocity/peak velocity ratio) and skewness (saccadic rise time/duration ratio), which provided a description of velocity responses. The value of K is related to the velocity waveform of saccades, ranging from triangular to rectangular. Skewness (or asymmetry), the ratio of the time to reach maximum velocity (the acceleration phase) to the total duration of the saccade, normally ranges from 0.5 (for small saccades) to 0.2 (for the largest saccades), but increases also for anti-saccades, saccades made to remembered targets, and saccades made under fatigue or decreased vigilance.

Statistical analysis

The parameters observed in the autistic and normal children were compared using a two-tailed Student's t-test.

Results

On initial examination of the acquired traces, it was observed that most of the patients (n=10, 71%) did not follow correctly and with constancy the light target appearing in a random and unpredictable fashion within their visual field. Visual analysis of the tracking profile showed that the children with typical development consistently and correctly followed the stimulus with some rare blinks, whereas in the children with autism there were some tracts characterised by continuous blinks, some characterised by stillness (similar to the saccadic initiation failure of oculomotor apraxia), and others still by gross errors in movement direction (Fig.s 1 and 2) and by fixation instability (Fig. 3, see over) (6). Abrupt changes in the velocity profiles (Fig. 4, see over) were often seen in the largest saccades (18% of saccades of 20-25 deg amplitude) recorded in the normal subjects, while in the autistic children they were much more frequent (37% at 20-25 deg) and also present in saccades of small amplitude (15% at 10-15 deg).
With regard to the "main sequence", only one case, examined at the age of 12 years, showed a clear peak velocity reduction (Fig. 5, see over; Table 1, see over) which was confirmed by the results of a second test. Table 1 (see over) shows the intersubject mean values and SDs for each of the four parameters necessary for calculation of the main sequence (see Methods) in the autistic children (13, having left the 12-year-old child out) and in the control group. Table 1 also displays latency, K and skewness mean values in the two groups. On the Student's t-test, all parameters were similar in both groups.

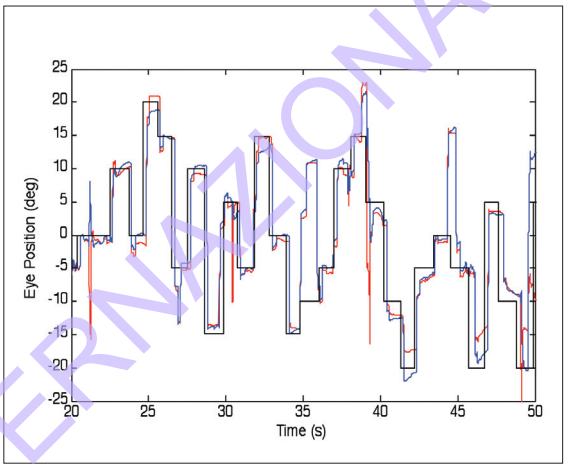

Figure 1 - Example of good tracking: only some blinks and few errors are present.
Stimulus position (black), right- (red) and left-eye position (blue). Y-axis: 0 corresponds to the primary position of the eyes (straight ahead), the positive numbers indicate the positions to the right and the negative ones the positions to the left (the numbers, in degrees, represent the distance from the primary position). X-axis: the time (in seconds) since the beginning of the test.

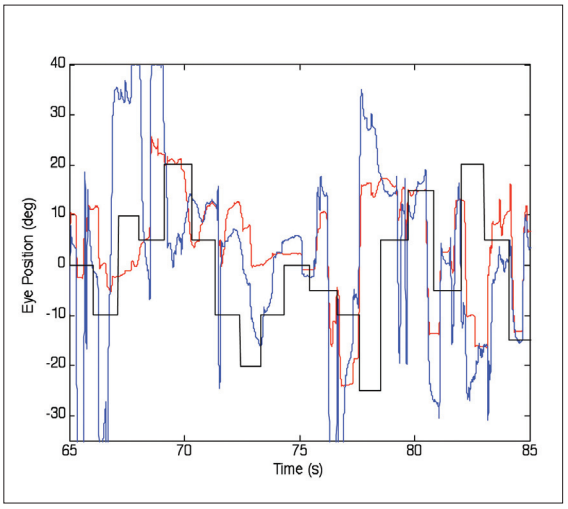

Figure 2. Example of very poor tracking showing evidence of many blinks and some tracts of saccade initiation failure.

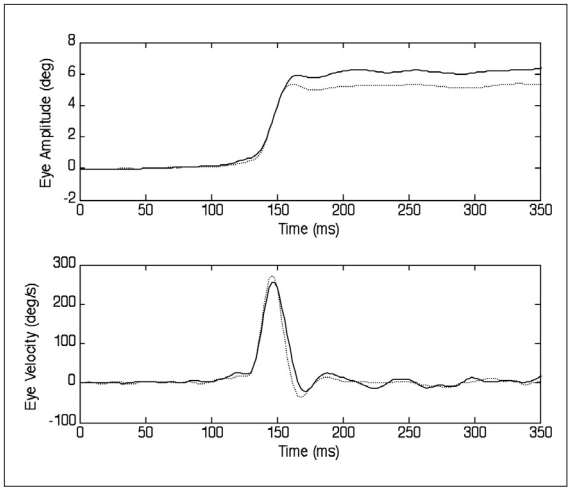

Figure 3. Example of fixation instability.
At the end of the saccade, velocity fluctuates for at least 200 ms. Upper traces: eye position: right eye (dashed line), left eye (continuous line). Bottom: corresponding eye velocities. This example shows a saccade from the primary position (0) to a new eye position around 5 degrees to the right (+5). Its peak velocity is around 250 deg/s.

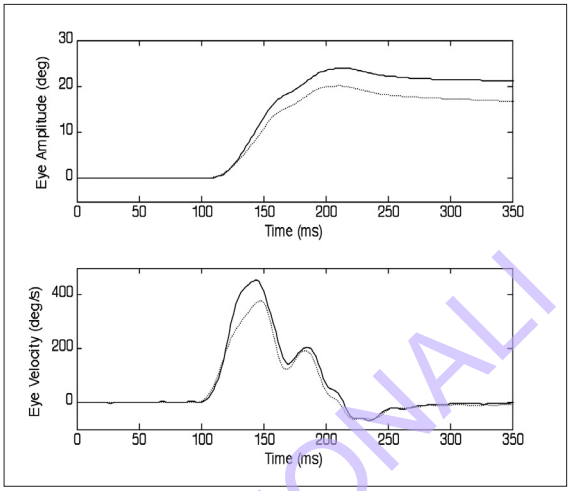

Figure 4. Example of altered saccadic velocity profile.
Abnormal intrasaccadic slowing, typical of a saccade interrupted in mid-flight. Upper traces: eye position; right eye (dashed line), left eye (continuous line). Bottom: corresponding eye velocities. This example shows a saccade from the primary position (0) to a new eye position around 20 degrees to the right (+20). Its peak velocity is around 400 deg/s.

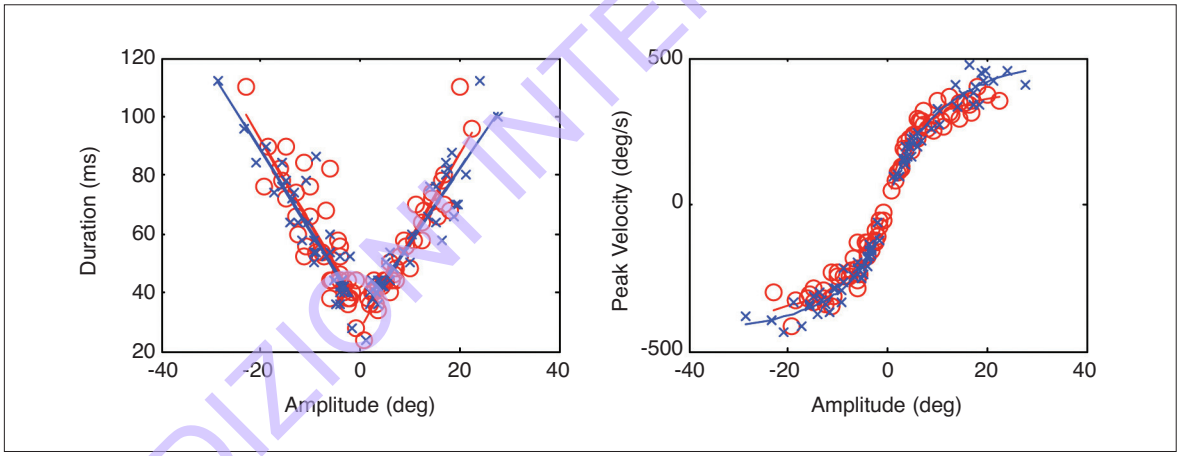

Figure 5. First examination of the autistic child aged 12 years who presented a clear peak velocity reduction.
Both A/D and A/Vp relationships are shown ("main sequence"): eye movements are divided depending on their direction (to the left for negative amplitudes, to the right for positive ones) and on the eye (right eye in red and left eye in blue). Peak velocity saturations slightly exceed 500 deg/s (normally over 700 deg/s).

Discussion

Several studies indicate abnormal saccadic eye movements in individuals with autism, certainly linked to an altered strategy for exploration of the surrounding environment. Brenner et al. (17) proposed that the attentional functions of these patients could be impaired by early oculomotor alterations, in particular of the generation of saccades. But, while Rosenthal et al. (22) pointed out some saccadic abnormalities and lower peak velocity in autistic children, Minshew et al. (15) found no differences between a group with autism and a control group in terms of accuracy, velocity, or latency, suggesting that the basic dynamics of saccades is intact in individuals with autism. In a subsequent study, Takarae et al. (16) found subtle but statistically significant saccadic dysmetria, consistent with reports of histological abnormalities in the cerebellum.

In the present study, regardless of the tracking strategy adopted (often incorrect), the recorded saccades were used to evaluate the saccadic features, in particular the "main sequence" which provides an indication of the functioning of the fast eye movement premotor system. In fact, the "main sequence" describes the norm for each saccade in relation to its own amplitude, independently of the direction and amplitude required by the test.

Table I - Saccadic eye movement parameters in children with autism and healthy controls.

	Autistic patients (n=13)		Controls (n=20)		12-year-old child (n=1)
	mean	SD	mean	SD	
A/D m (ms/deg)	2.01	0.36	1.82	0.52	2.73
A/D q (ms)	37	10	32	7	32
A/Vp 1/α (deg/s)	1061	325	1042	322	536
A/Vp 1/β (1/s)	58	14	60	15	68
Latency (ms)	210	23	192	22	225
K	0.52	0.02	0.51	0.03	0.54
Skewness (asymmetry)	1.02	0.12	1.03	0.17	0.99

Abbrevations: see text (*Saccadic processing*)
All parameters were similar in the normal controls and the autistic children (differences not significant on the Student's t-test). The parameters of the boy presenting the clear peak velocity reduction are shown separately.

It is well known that inattention can reduce the velocity of saccades; for this reason, throughout the test the children received constant stimulation, being required to follow, with their gaze, the illuminated LEDs.

In our study, only one case (out of 14) presented classic alterations of the saccadic features; the fact that these involved the "main sequence" allowed us to diagnose a functional lesion of the PPRF. Indeed, we used a non-predictive visually-guided saccadic task only in the horizontal plane. In the presence of slow saccades, the first consideration is always a possible lesion at the level of motoneurons or of the PPRF, including the omnipause neurons (6). Normal eye rotation was documented in this case, which meant that there had to be a lesion superior to the level of the oculomotor nuclei. Furthermore, the number of saccades interrupted in mid-flight (attributable to incorrect function of pause neurons) and the frequent fixation instability increased the likelihood that the lesion was located in the brainstem premotor system.

The other cases must be considered normal, both with regard to saccadic velocity and latency (Table 1). These findings are in contrast with those of Rosenthal et al. (22), but in line with those of Minshew et al. (15). The only child who presented "main sequence" alterations was aged 12 years. This finding, together with the lower ages of most of the other children, does not enable us to validate Brenner's hypothesis of the presence of early classic saccadic alterations in children with autism (17). However, the "main sequence" alteration observed in this 12-year-old child suggests that there may be involvement of the brainstem in at least some cases of autism.

With regard to the tracking strategy, most of the patients did not follow the light target correctly: blinks, periods of stillness, errors in the movement direction and instability of fixation were often noticed. Some of these abnormalities could be due to the very young age of our children, as similar tracts were observed in some of the youngest of the normal children (5-6 years), albeit markedly less frequently.

Even though the children were encouraged and prompted throughout the test, periods of stillness were nevertheless often observed. Indeed, we recorded periods of saccadic initiation failure and increases in the number of blinks before and during fast eye movements, as already seen in patients with storage diseases, like Gaucher disease, in cases in which the storage also takes place in the central nervous system (20). This evidence could indicate a functional pulse generator alteration. Moreover, the ability of the autistic children to sustain attention throughout the duration of the test was greatly impaired when compared to the control group, and fixation at the end of each movement appeared more difficult (Fig. 5).

It should also be noted that in this study we did not use social stimuli, which are often associated with oculomotor abnormalities in autism (13). However, it is not known whether these alterations are linked only to social stimuli, or whether they are also due to subtle saccadic system alterations, which may still be undetectable by conventional semeiotic examinations. In this regard, we deliberately used non-structured stimuli and in this way were able to evaluate only the features of the generation of saccadic movements, independently of the exactness (with regard to the stimuli) of the visual pursuit. Also, prior studies were mostly conducted in adolescents or adults suffering from autism. Indeed, the acquisition of eyetracking in children is difficult, particularly in those suffering from developmental disorders. Therefore, innovative techniques, such as video-oculography, should be implemented to explore contemporaneously eye movement features and exploration of the environment in a sizeable number of children with autism.

In conclusion, our autistic children did not show clear alterations of the saccadic features, as evaluated by the "main sequence", but they did produce more blinks than normal children and show some tracts of saccadic initiation failure and irregularities of saccadic velocity profiles that could be due to a functional alteration of the PPRF. Further studies are needed to prove that slight premotor alterations are present in young autistic children. In particular, MRI studies (23,24) are expected to provide a reliable means of investigating the brainstem and thus to further understanding of the role of the oculomotor system in autism.

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References

1. Brambilla P, Hardan A, di Nemi SU, Perez J, Soares JC, Barale F. Brain anatomy and development in autism: review of structural MRI studies. Brain Res Bull 2003;61:557-569
2. Brambilla P, Hardan AY, di Nemi SU et al. The functional neuroanatomy of autism. Funct Neurol 2004;19:9-17
3. Pelphrey KA, Morris JP, McCarthy G. Neural basis of eye gaze processing deficits in autism. Brain 2005;128:1038-1048
4. Boraston Z, Blakemore SJ. The application of eye-tracking technology in the study of autism. J Physiol 2007;581:893-898
5. Pelphrey KA, Sasson NJ, Reznick JS, Paul G, Goldman BD, Piven J. Visual scanning of faces in autism. J Autism Dev Disord 2002;32:249-261
6. Leigh RJ, Zee DS. The Neurology of Eye Movements. Fourth Edition. Oxford University Press 2006
7. Nowinski CV, Minshew NJ, Luna B, Takarae Y, Sweeney JA. Oculomotor studies of cerebellar function in autism. Psychiatry Res 2005;137:11-19
8. Takarae Y, Minshew NJ, Luna B, Krisky CM, Sweeney JA. Pursuit eye movement deficits in autism. Brain 2004;127:2584-2594
9. Kemner C, Verbaten MN, Cuperus JM, Camfferman G, van Engeland H. Abnormal saccadic eye movements in autistic children. J Autism Dev Disord 1998;28:61-67
10. van der Geest JN, Kemner C, Camfferman G, Verbaten MN, van Engeland H. Eye movements, visual attention, and autism: a saccadic reaction time study using the gap and overlap paradigm. Biol Psychiatry 2001;50:614-619
11. Goldberg MC, Lasker AG, Zee DS, Garth E, Tien A, Landa RJ. Deficits in the initiation of eye movements in the absence of a visual target in adolescents with high functioning autism. Neuropsychologia 2002;40:2039-2049
12. Mercadante MT, Macedo EC, Baptista PM, Paula CS, Schwartzman JS. Saccadic movements using eye-tracking technology in individuals with autism spectrum disorders: pilot study. Arq Neuropsiquiatr 2006;64:559-562
13. Fletcher-Watson S, Leekam SR, Benson V, Frank MC, Findlay JM. Eye-movements reveal attention to social information in autism spectrum disorder. Neuropsychologia 2009;47:248-257
14. Rosenhall U, Johansson E, Gillberg C. Oculomotor findings in autistic children. J Laryngol Otol 1988;102:435-439
15. Minshew NJ, Luna B, Sweeney JA. Oculomotor evidence for neocortical systems but not cerebellar dysfunction in autism. Neurology 1999;52:917-922
16. Takarae Y, Minshew NJ, Luna B, Sweeney JA. Oculomotor abnormalities parallel cerebellar histopathology in autism. J Neurol Neurosurg Psychiatry 2004;75:1359-1361
17. Brenner LA, Turner KC, Müller RA. Eye movement and visual search: are there elementary abnormalities in autism? J Autism Dev Disord 2007;37:1289-1309
18. Eggert T. Eye movement recordings: methods. Dev Ophthalmol 2007;40:15-34
19. Accardo AP, Pensiero S, Da Pozzo S, Perissutti P. Some characteristics of saccadic eye movements in children of primary school age. Doc Ophthalmol 1992;80:189-199
20. Accardo AP, Pensiero S, Perissutti P. Saccadic analysis for early identification of neurological involvement in Gaucher disease. Ann N Y Acad Sci 2005;1039:503-507
21. Pensiero S. Accardo A, Pittis MG, Ciana G, Bembi B, Perissutti P. Saccade testing in the diagnosis and treatment of type 3 Gaucher disease. Neurology 2005;65:1837
22. Rosenthal J, Massie H, Wulff K. A comparison of cognitive development in normal and psychotic children in the first two years of life from home movies. J Autism Dev Disord 1980;10:433-444
23. Bastianello S, Pezzella FR, D'Angelo E. Non-invasive imaging of brain structure and function in neural connectivity analysis. Funct Neurol 2008;23:169-170
24. Bastianello S, Luccichenti G, Giugni E, Pezzella FR, Calliada F. Splitting the technology: functional imaging between open and high-field magnetic resonance. Funct Neurol 2009;24:69-70