

# Autism and genius: is there a link?

## The involvement of central brain loops and hypotheses for functional testing

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### Summary

**Mental processing is the product of the huge number of synaptic interactions that occur in the brain. It is easier to understand how brain functions can deteriorate than how they might be boosted. Lying at the border between the humanities, cognitive science and neurophysiology, some mental diseases offer new angles on this problematic issue. Despite their social deficits, autistic subjects can display unexpected and extraordinary skills in numerous fields, including music, the arts, calculation and memory. The advanced skills found in a subgroup of people with autism may be explained by their special mental functioning, in particular their weak central coherence (CC), one of the pivotal characteristics of the disorder. As a result of the increasing interest in autistic talent, there has recently emerged a tendency to screen any eccentric artist or scientist for traits of the autistic spectrum. Following this trend, we analyze the eccentricity of the popular pianist Glenn Gould and briefly discuss the major functional hypotheses on autistic hyperfunctioning, advancing proposals for functional testing. In particular, the potential involvement of rhythm-entrained systems and cerebro-cerebellar loops opens up new perspectives for the investigation of autistic disorders and brain hyperfunctioning.**

*KEY WORDS: ASD, autism, brain connectivity, cerebro-cerebellar loops, music*

### Mental functions, autism and genius

#### *The neurophysiological context*

The processing of brain cognitive functions depends on a continuous crosstalk between analysis and synthesis: signals are analyzed in detail in all their biophysically discernible components and then the results of this analysis are synthesized into high-level percepts or concepts (1). One leading hypothesis on how this system might work is that multiple local computations are dynamically synchronized: at neurophysiological level, this would be reflected in the ability of the brain to generate a complex system of rhythms that can entrain the network modules into coherent oscillations (2). While local processing in small modules would be responsible for detailed analysis, dynamic binding of several such modules would determine a coherent multi-factorial representation of the ensemble. This continuous activity, by exploiting brain internal memories and representations, is thought to generate a virtual reality that is then compared with the actual world (3). This comparison is assisted by subcortical loops involving the cerebellum, which acts as a comparator for sensorimotor and cognitive processing – these probably share a common computational architecture (4) – and then informs the cortex about the correctness of the predictions (5). These cortico-cerebellar loops, by improving the identification of errors and novelty, trigger automatic corrections, promote learning and redirect attention (6). In the complex case of autism, not only is the analysis of details dissociated from the whole, but also the relationship between internal representations and reality is weakened. These aspects are considered in this paper in which we evaluate the remarkable talents often shown by autistic patients and present a hypothesis on their potential neurophysiological correlates.

#### *Autism, genius and the weak central coherence hypothesis*

One of the most fascinating and mysterious features of autism is the remarkable talent frequently found in people affected by this severe neurodevelopmental disorder that impairs interaction and communication (7). Despite their social deficits, autistic subjects may display unexpected and extraordinary skills in numerous fields, including music, the arts, calculation/mathematics and memory (8). Since Asperger's first investigations in 1944, several autistic talents have been described (9-12). Treffert (12) studied savant skills at different levels of achievement, distinguishing between talented savants and prodigious savants. He described the talented savant as a cognitively impaired person with a special ability that is conspicuous and in contrast to his/her overall disability. When the special skill is spectacular and out-

standing, Treffert (12) speaks of a prodigious savant. Interestingly, these peculiar areas of giftedness and interest, musical giftedness in particular, may be positively exploited within rehabilitation programs in autism to promote social interactions, communicative behavior and emotional responsiveness (13,14,15).

The exceptional skills found in autistic subjects may be explained by their special mental functioning, in particular the weak central coherence (CC), demonstrated in various domains and at different levels, including the perceptual, visuospatial, constructional, and verbal semantic ones (16-18). Weak CC is one of the pivotal features of autism. Normally, the brain forms concepts that impart automatic judgment and confer intuition, but hide details from conscious awareness. This results in an individual seeing the whole more than the parts. Conversely, the autistic mind, being literal and appreciating the parts more than the whole, may access details that are not normally considered. Happé (18) stresses the role of weak CC in the organization of cerebral functioning in people with autism and highlights the advantages they derive from it; rather than a deficit, these subjects' weak CC seems to represent a peculiar cognitive style. Accordingly, autistic subjects may be able to generate unexpected connections between the diverse parts of disparate systems, finding novelty within a familial space (19). In other words, autistic creativity is a way of thinking that retains elements of domain-specific knowledge and protects them from normal integrative processes (19).

Hans Asperger (20), who clearly described autistic intelligence, argued that the presence of a dash of autism is essential to be successful in science or art. As a result of the increasing interest in autistic talent, there has recently emerged a tendency to screen any eccentric artist or scientist for traits of autism or Asperger's syndrome (AS). Accordingly, worldwide, mathematicians, philosophers and artists, including Newton, Einstein and Wittgenstein, are now believed to have shown some autistic traits (21). Following this recent trend, we here present and analyze the eccentricity of a popular pianist, Glenn Gould. Subsequently, we briefly discuss the major functional hypotheses on autistic hyperfunctioning and some proposals for functional testing.

#### *Variations on autism and humanity: Glenn Gould, eccentric and musical genius*

The Canadian pianist Glenn Gould (born Glenn Herbert Gold) was a musical genius who revolutionized the way people hear, perceive and appreciate classical music. His troubled, eccentric mix of exceptional musical talents and unusual behaviors makes him one of the most fascinating and celebrated figures in all of music and prompts reflection on his complex personality.

Gould was born in Toronto, Ontario, on September 25, 1932, into a musical family which included his father, an amateur violinist, and his mother, a pianist and organist; Edvard Grieg was a distant relative as well. Even at the age of three, Gould's prodigious skills were evident. In addition to his absolute pitch, he was already able to read staff notation, and just two years later wrote his first compositions (22). At the age of 14, Gould made his debut as a soloist at a Royal Conservatory orchestral performance of Beethoven's Fourth Piano Concerto.

In early 1955, Gould made his American debut, with recitals in Washington and New York, choosing a very unorthodox program (Gibbons, Sweelinck, Bach, late Beethoven, Berg, Webern). His first recording, a performance of Bach's Goldberg Variations, released in 1956, was a popular success, and brought him international attention. For the next nine years Gould toured throughout North America, and between 1957 and 1959 made three overseas tours, playing in the USSR, Western Europe, Israel and England. In 1964, with no advance warning, he retired from public performance.

In 1981 Gould released a new recording of Bach's Goldberg Variations, a work with which Glenn was still closely identified. Compared with the highly energetic 1955 recording, this second one was careful, sage, and more introspective with slower tempi. This interpretation, marking the completion of an ideal circle in Gould's life, sounds almost like this enigmatic genius's musical farewell. Indeed, on September 17, 1982, just days before his 50th birthday, Gould suffered a massive stroke. He did not come out of his coma and died on October 4. Gould's eccentric attitudes and behaviors have led his biographer and friend Peter Ostwald (23) to speculate about the possibility that he was affected by AS (24). Asperger's syndrome is characterized by difficulty with reciprocal social interactions, a narrow range of interests and insistence on set routines, with no general delay in cognitive development and occasionally giftedness in some particular field of expression, such as music (7). Unfortunately, no diagnosis of AS was possible in Gould's lifetime because he died before the syndrome was first included in the DSM. However, Glenn Gould's eccentricities, such as his humming and rocking, his ritual of soaking his hands and arms in hot water before each concert, his isolation and difficulties in social interaction, and his exceptional musical ability, seem reminiscent of characteristics typically found in people with AS. In particular, his conducting hand movement and his tendency to bring his face down very close to the keyboard and then rock his body in a circular motion may be likened to stereotyped and repetitive movements. Other traits indicative of Gould's insistence on *sameness*, as reported by his biographers, were his insistence on controlling his playing environment and the fact that he would only give concerts sitting on a folding chair his father had made.

Moreover, as in people with autism, he frequently hummed along while he played; he claimed he could not stop this habit, because it was unconscious, and it increased proportionately with the inability of the piano to produce the music he had in mind.

Additionally, the ability and desire to memorize, typically described by Gould's biographers (22,23), is common among subjects with AS. Gould also showed an extreme aversion to being touched and was hypersensitive to the environment. Such hypersensitivity, which could explain Gould's penchant for wearing heavy coats and scarves, even in the summer, is not uncommon in AS.

Another important point was his difficulty in forming social relationships. Already rather solitary as a little boy, as an adult he never married and apparently never formed normal relationships with other adults. In later life he refused to talk to almost anyone in person, relying on the telephone and letters for communication. Finally, exceptional musical talent is frequently associated with AS. Gould's eccentric behavior and difficulty in social situations are well docu-

mented in numerous videos, which, if considered from a psychiatric point of view, prompt interesting reflections. Relevant clips can be found at the website of the Canadian CBC digital archives ([http://archives.cbc.ca/arts\\_entertainment/music/topics/320/](http://archives.cbc.ca/arts_entertainment/music/topics/320/)).

However, in the absence of a definite, post-mortem clinical diagnosis, these considerations can only suggest that Gould was affected by a high-functioning form of autism (23). Despite his abnormalities in relationships, Gould did gather a group of friends who described him not only as eccentric but also as kind, funny, charming, warm and loyal. He is especially remembered by his friends for his special and particular humanity – a “variation on the theme” of autism. A fascinating example of this unusual and peculiar form of humanity is available online in the clip “Gould performs for blind kids at Vancouver International Festival” ([http://archives.cbc.ca/arts\\_entertainment/music/topics/320/](http://archives.cbc.ca/arts_entertainment/music/topics/320/)).

### What is altered in the autistic brain?

#### *Microcircuit alterations: excess synaptic excitation and minicolumnopathy*

*In vitro* investigations and molecular genetics have uncovered specific cellular abnormalities related to the manifestation of autism in humans and animal models. Mutations in laboratory animals match those observed in certain autistic syndromes of genetic origin. These include the *shank* deletion (25) on chromosome 22q13 (Phelan-McDermid syndrome) and the *IB2* deletion, which occurs on the same telomere (26 and Giza J, Prestori F, Urbanski MJ et al. Behavioral and neuronal abnormalities in mice lacking the autism-linked gene islet Brain-2. Submitted). Other interesting mutations involve the *neuroligin/neurexin* complex, or 22q7 deletion syndrome (27). In all cases, the common theme seems to be exaggerated activation of certain receptor subtypes at glutamatergic synapses, providing the molecular substrate for local hyperexcitability. These abnormalities could produce a pervasive alteration of neural processing, which, interacting with environmental and developmental factors, contributes to the complexity of the disorder and results in different phenotypes (28). Accordingly, autism is a wide *spectrum* of clinical conditions and may be considered a peculiar form of cerebral organization that, in terms of behaviors, skills and cognitive capacities, has various expressions.

In autism, circuit mechanisms in the cerebral cortex underlying local hyperactivity have been described by Casanova (29), who defines autism as a minicolumnopathy. Interestingly, minicolumnar abnormalities have been shown in talented healthy scientists (30). Minicolumns, which are the basic functional units of the brain (31), are more numerous and narrower than normal in the frontal cortex of autistic and Asperger people (29). Narrow minicolumns seem to be most prominent in the peripheral neuropil compartment, a space rich in unmyelinated projections of some interneurons. These alterations could be linked to a deficit of lateral inhibition in autism (32). Normally, an activated minicolumn presents a central area of excitation limited by a peripheral area of lateral inhibition, which creates a typical Mexican-hat profile of excitation/inhibition. In autism, the

pathological minicolumns with lateral inhibition deficit show a large excitation area which is not limited and tends to activate an entire module, resulting in a stovepipe hat profile (32).

#### *Long-range circuit alterations: the cerebro-cerebellar connection*

A consequence of this local overactivation is the generation of patterns of weak long-range connectivity (Fig. 1, Box. 1). Particularly implicated in deficits of long-range connectivity is the cerebellum, which is strongly involved not only in sensorimotor processing, but also in emotion and cognition (33,34). In autism, the cerebellum has been shown to present hypoplasia of the vermis and hemispheres and reduced numbers of Purkinje cells (35). Notably, the reduction in Purkinje cells may have the effect of disinhibiting the deep cerebellar nuclei, producing abnormally strong local connectivity associated with weak connectivity along the cerebello-thalamo-cortical circuit (28). This altered connectivity may be related to the abnormal overgrowth observed in prefrontal lobes (PFLs), to which the cerebellar hemispheres are closely linked (36). This overgrowth is especially evident in the dorsolateral convexity, suggesting that the most affected cortical areas are, precisely, the broadly projecting, phylogenetically and ontogenetically late-developing regions (37).

Another region strongly implicated in the savant phenomenon is the left anterior temporal lobe (LATL), which seems to be low-functioning in autistic savants (19). The LATL, producing top-down inhibition on raw and low-level information processing, is crucial for semantic processing and conceptual knowledge: normally, the conceptual networks implicating the LATL tend to inhibit networks concerned with details (38). However, when the LATL is damaged or less functioning, conscious access to literal details and particulars is facilitated. This phenomenon may contribute to the peculiar autistic cognitive style, mainly characterized by weak CC, and may lead to savant skills. Accordingly, savant skills may be induced artificially in healthy subjects through 15 minutes' repetitive transcranial magnetic stimulation (rTMS) over their LATL (19). In this sense, savant abilities seem to be facilitated by privileged access to raw, less processed sensory information, that is normally regulated by top-down inhibition.

Sometimes the interactions between functional abnormalities, environment, and cognitive and developmental compensatory processes may, as in the case of low-functioning autistics, result in severe dysfunctions, including disruptive behavior and severe learning disabilities. In other cases the complex interactions may have a relatively positive effect on cognition and behavior, at the same time reducing the primary core dysfunctions of autism. This is the case of AS and high-functioning autism, where the local networks, hyperfunctioning and isolated, may acquire novel functional properties leading to the formation of enhanced functions (39).

#### *Rhythm, music and the autistic brain*

Rhythm, fundamental for creating the explicit architecture of time, also allows musical elements to emerge in meaningful patterns (2). As in the case of a piece of music, rhythm is also crucial in organizing and coordinating

global brain functioning: rhythmicity favors the learning, development and performance of motor and cognitive functions (40). Rhythm formation is a complex activity involving the integration of sensory perception and motor entrainment into cognitive operations and motor transformations (40). An important brain structure, mediating the different aspects of rhythm formation, is the cerebellum, which may be regarded as the timekeeper of the whole brain (5). Accordingly, lesions of the cerebellum produce ataxia and a cognitive affective syndrome (cerebellar cognitive affective syndrome) that reflects dysfunctions in rhythmicity and synchronization not just of movements (dysmetria) but also of thoughts (dysmetria of thought) and emotions. Therefore, as well as being a pathology of connectivity, autism also seems to be a pathology of central rhythms: the cerebellum may be critically involved in both pathogenetic mechanisms. Surprisingly, autistic subjects at both ends of the spectrum, i.e. low- and high-functioning subjects, show a particular interest in music, sometimes accompanied by enhanced pitch memory and discrimination and surprising musical abilities. Despite their interpersonal difficulties, they are sensitive to the affective aspects of music (41, 42) and have been found to display a similar taste in music to healthy subjects (43). Moreover, music produces cognitive and affective improvements in autistic people and may be useful in therapeutic contexts (13,14, 15). The link between music and autism remains both mysterious and fascinating. It has been suggested that music could be processed by cerebral mechanisms that do not seem to be damaged by the autistic pathology (44), but our considerations on brain rhythms and organization seem to open up another, attractive possibility: music might restore to the autistic brain the natural rhythmicity that was altered by the pathology. In other words, music, as an external source of rhythm, may produce synchronization and organization within the abnormal circuits in the autistic brain, partially compensating for the dysmetria of thoughts and emotions and promoting neuronal plasticity.

#### *Implications for functional testing*

Whereas animal models could help to further understanding of the molecular basis of autism and the anomalies in short-range connectivity that are associated with it, a careful investigation of long-range connectivity in humans is required to address implications at the system level. We have maintained that autism involves alterations in functional connectivity between the prefrontal lobe (PFL), inferior parietal lobe (IPL), left anterior temporal lobe (LATL) and cerebellum, and it is conceivable that the functional relationships between these areas in relations to stimuli, tests and therapies might be able to shed light on the mechanisms of autism.

Whereas local circuit hyperfunctioning finds correlates at cellular level, investigation of the complex interactions between large brain areas (Fig. 1) would require a combination of neuropsychological testing, clinical neurophysiology and functional imaging (Fig. 1, Box 1). Allen and Courchesne (45) examined cerebellar functional activation during attention and motor tasks, and found both greater cerebellar motor activation and smaller cerebellar attentional activation in autistic patients. In another fMRI study, Gomot et al. (46) investigated attention switching in children with autism and demonstrated ab-

normalities in cingulate gyrus, temporo-parietal and frontal regions, areas typically related to the cerebellum. More recently, an fMRI study investigating visual attention demonstrated atypical fronto-cerebellar activation not only in autistic subjects but also in their siblings (47). In addition, Lee and colleagues (48) have described abnormal nicotinic receptor composition in the cerebella of autistic individuals, which is of great interest given the role of the nicotinic receptor in attention (49). A further fMRI analysis of the correlations between these areas – including the PFL, IPL, LATL and cerebellum – would be needed to clarify this aspect. Moreover, interference with circuit functioning at critical points – including the PFL, IPL, LATL and cerebellum – through high frequency rTMS (19) may prove useful to transiently alter signal processing in the normal and autistic brain.

We have suggested that autism might involve alterations in the coherence of central rhythms, and analysis of the coherence of cortico-cerebellar activity could be performed using magnetoencephalography (MEG) and by combining EEG and fMRI to reveal network entrainment under musical stimulation.

#### **Concluding remarks**

The evidence outlined in this paper suggests that autism may involve alterations in fundamental brain processes (including short and long-range circuit organization and possibly activity synchronization and binding), affecting the internal representation of the world and its coherence, leading in turn to abnormal novelty detection, learning and attention switching. The disorders in language and social interaction observed in autism (with the rigid insistence on sameness, the isolation, and the communication impairment) would be the negative consequences of this at the higher behavioral level. However, these same alterations, as well as causing deficits and disability, could promote the generation of an intense world of emotions, interests, abilities and capacities, which are often unexpected and sometimes exceptional (50).

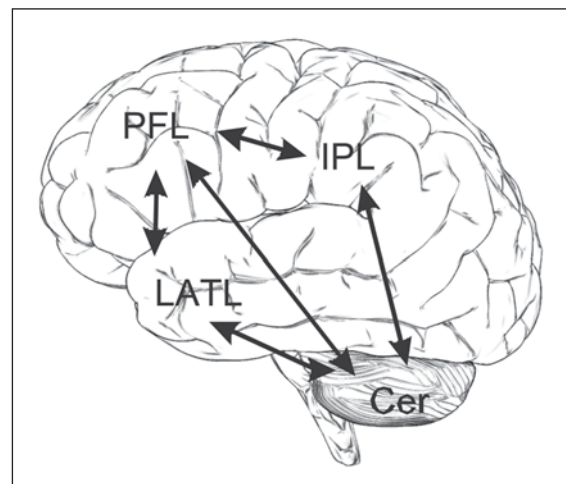


Figure 1 - Altered functional connectivity between the prefrontal lobe (PFL), inferior parietal lobe (IPL), left anterior temporal lobe (LATL) and cerebellum is considered to be at the basis of the autistic pathology.

## The cerebello-cortical loop: behavior, cognition and emotion and potential implications in autism

Besides its involvement in motor learning, the cerebellum is strongly implicated in cognition, attention, emotions and behavior (34,51,52). Different parts of the cerebellum contribute to distinct aspects of motor and cognitive performance. The spinocerebellum, including the vermis and the intermediate part of hemispheres, is involved in movement execution including feedback adjustments; it receives somatosensory, labyrinthine, visual and auditory input (53,54). Conversely, the cerebro-cerebellum, represented by the lateral part of the cerebellar hemispheres, plays an important role in preparation, initiation and timing of motor acts via the dentate nuclei; its principal inputs arise from the premotor and posterior parietal cortex (55). Additionally, there is a suggestion of an anterior-sensorimotor versus a posterior-cognitive dichotomy within the cerebellum (40, 47).

In particular, association and paralimbic cortical regions send feed-forward projections through the basal nuclei to the cerebellum and receive feedback projections from the cerebellum (6,34). The association cortex includes the prefrontal, posterior parietal, dorsal parastriate and superior temporal regions, whereas the paralimbic areas involve the posterior parahippocampal cortex, the cingulate gyrus and the anterior insular cortex (34,56). The corticopontine connections are funneled through the cerebrocerebellar circuit and converge in a precise topographic order on the pons (56).

Physiological and anatomical investigations show that the association and limbic areas are connected with the posterior lobe of the cerebellum, in particular crus I and II (55). From the cerebellar cortex, information is transmitted through the cerebellar corticonuclear microcomplex

to the deep cerebellar nuclei and from here to the thalamus and back to the cerebral cortex (52). In particular, the fastigial, interpositus and dentate nuclei of the cerebellum send efferent projections to the thalamic nuclei, in particular the ventrolateral, centrolateral, paracentral, centromedian, parafascicular and medio dorsal nuclei, which are connected with the association cortices (34). Within this cerebello-cortical loop, the cerebellum could organize and modulate behaviors, cognition and emotions in the same way as it organizes and modulates motor coordination and control. Accordingly, cerebellar alterations affecting the cerebello-cortical loop may lead not only to motor abnormalities but also to behavioral, cognitive and affective alterations, which may be manifested as severe psychiatric and developmental disorders (4,34). The cerebellum is fundamental for contextualizing specific stimuli and coordinating their spatio-temporal evolution, generating coherent ensemble activities (6). Therefore, dysfunction of the cerebellar circuit and of information reentry toward the frontal and parietal cortex may contribute to preventing the formation of coherent and contextualized behaviors (4). Additionally, the cerebellum is critical for revealing differences (either error or novelty) between predictions elaborated by the cortex and the reality conveyed by experience through the senses and motor interactions (4,6). Thus, dysfunction of the cortico-cerebellar circuits may prevent the detection of novelty and impair attention switching, explaining the indifference or even the aversion of autistic patients for certain environmental changes (46). A side effect may also be that of reinforcing perseverations and the attachment to familiar objects and situations (46).

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