Biocognitive Rehabilitation of Down Syndrome

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Abstract: Important progresses in understanding the biology of Down syndrome open new perspectives for cognitive rehabilitation of persons with this genetic condition. Research developments toward specifying a field of cognitive pharmacology for persons with intellectual disability appear promising. The availability of animal models of trisomy 21 allows for the testing of various molecules with the power of modulating the activity of particular genes involved in the causation of Down syndrome. *In vitro* experiments using induced pluripotent cells offer reasonable hope for removing or silencing overexpressed genes or even an entire chromosome 21. At the same time, cognitive intervention with children with Down syndrome is gaining in efficiency. The article reviews these developments. It is argued that combining biological and neurocognitive rehabilitation will boost the cognitive abilities of persons with Down syndrome to a large extent.

Keywords: Down syndrome, cognitive intervention, pharmacology, epigenetic therapy.

Down syndrome (DS) is a common disorder (about one case every 700 live births) with enormous personal, medical and social costs, caused by trisomy for chromosome 21. It is also the leading genetic cause of intellectual disabilities. The millions of people with DS across the world also face particular health issues, including congenital heart defects, haematopoietic disorders, earlier aging, as well as an augmented probability of early-onset Alzheimer's disease [1].

As a result of advanced medical care, raising children at home and better education, the life expectancy in DS has increased dramatically over the last 50 years. It is now estimated to nearing 60 years in average value, compared to 12 years in 1946 [2]. Although it could be argued that persons with DS are better off nowadays than in the past, much remains to be done at various levels in order to favor better development, school education, professional training and social inclusion.

The most compelling problems in DS are cognitive ones. Curiously, despite being virtually general in the condition, they do not seem to be unavoidable. Rare cases of quasi-normal language abilities and close to low-average intellectual functioning have been reported [3]. As discussed in Rondal [4], this indicates that the cognitive limitations usually observed in DS are not intrinsically tied to the genetic condition itself. They seem to stem in major ways from a series of interactions between epigenetic, developmental, environmental, and educational variables.

From such indications, it becomes easier to understand that cognitive aspects of DS might be as modifiable as physiological or medical aspects given appropriate rehabilitation strategies. Current research developments in pharmacology as well as regarding modulation of gene expression through the use of specific products, associated with more systematic cognitive intervention in memory and language, in particular, appear promising. The article summarizes the major data to date in these fields.

COGNITIVE PHARMACOTHERAPY

Neurobiological considerations in the study of cognition often emphasize synaptic neurotransmission. Signaling networks enable neurons to encode long-term changes in response to patterned information [5]. One of the neurological consequences of trisomy 21 is a reduction in synaptic density and spine dysgenesis that affects intellectual functioning [6]. Until recently, efficacious cognitive enhancing drugs simply did not exist. Anecdotal reports of benefits stemming from the administration of certain nutritional supplements (vitamins, metabolic precursors, and hormones) have been published. Most of these compounds were proposed without known mechanism of action. Their efficiency is all the most questionable [7].

Compelling evidence implicates the cholinergic system (i.e., acetylcholine –synthesizing neurons located in the basal forebrain) in learning, memory, and the control of attention through cortical activation [8]. Although the integrity of cholinergic function has not been ascertained in children with DS, by middle age cholinergic neurons in midbrain and brainstem nuclei show evidence of atrophy [9].

Four acetylcholinesterase enzyme inhibitors (tacrine, donezepil, rivastigmine, and galantamine) have been approved by the American Food and Drug

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E-ISSN: 2310-8231/14

Administration for the treatment of cognitive deficits in Alzheimer's disease (AD) [10]. They reduce the degradation of acetylcholine, therefore increasing synaptic availability for augmenting cholinergic signaling. A few studies regarding use of donezepil and rivastigmine in aged persons with DS have been published that are difficult to interpret given their small sample sizes, and thus an increased risk of confounding treatment-induced and residual interindividual variability. In a larger sample study (123 subjects with DS, 18-35 years) and better controlled double blind, placebo-controlled), Kishnani *et al*. - summarized in [10] - reported significant improvement on the Vineland Adaptive Behavior Scales (VABS) in donezepil-treated subjects. On the Rivermead Behavioral Memory Test for Children and on the Clinical Evaluation of Language Fondamentals (CELF-P), a positive trend was reported for the donezepil-treated subject which was not significantly different between experimental and placebo groups. The subjects received placebo or donezepil at 5mg for 6 weeks and 10 mg for the remaining 6 weeks. Donezepil-treated subjects reported abdominal pain nausea, vomiting, and insomnia at twice the rate of the placebo group. Most adverse effects were mild and transient. However, two subjects receiving donezepil experience hypertension and were withdrawn from the study.

Kishnani *et al*. [11] have reported a study using donezepil in 129 children 10-17 years, in a double-blind, placebo-controlled study. The subjects received either placebo or donezepil at 2.5mg starting dose, increased in 2.5mg increment every 14 days to 10mg. Several cognitive measures including the Test of Verbal Expression and Reasoning (TOVER) showed improvement in both groups with no between group differences. The most common adverse effects in the treatment group were transient diarrhea and vomiting.

No controlled study has been reported to date for tacrine and galantamine, to the best of my knowledge. The effect of rivastigmine has been examined in 11children and adolescents with DS in a 16-week study by Heller *et al*., summarized in [10]. Dosage was 1,5mg and then 3mg of a liquid formulation of rivastigmine in the first eight weeks and 4,5mg dosage in the second eight weeks. Significant improvements were observed in adaptive functioning on the VABS composite and on the Communication and Daily Living Skills domains. Also significant language effects were noted both on the TOVER and the CELF-P. Subjects showed improved attention on the Leiter-R Attention Sustained tests A and B as well as significant gains on two memory measures emphasizing language: Narrative Memory and Immediate Memory for Names. Cholinergic enhancement induced transient vomiting, diarrhea, stomach ache and insomnia in 4 subjects, either during the first or the last weeks of treatment (thus at the 4,5mg dosage).

The primary excitatory neurotransmitter in the brain is the amino acid glutamate produced by pyramidal neurons in layers III-V of the neocortex. Glutamate is utilized by over 50% of brain synapses [12]. In theory, potentiating glutamate signaling could improve synaptic transmission and stabilize neuronal networks. However, controlled studies with the drug piracetam in children with DS over large periods of time at doses around 100mg/kg per day, have failed to demonstrate any benefit in the treated group regarding learning, memory, and attention measures. Only, spatial working memory showed a trend toward improvement in treated subjects after 48 weeks. Irritability and sleep problems, probably due to overstimulation of glutamate receptors in the brain, were observed at 100mg/kg per day, receded when the dose was lowered to 65mg/kg per day, but appeared again when the dosage was increased [10].

Gamma-aminobutyric acid (GABA) functions as the primary inhibitory neurotransmitter in the cerebral cortex and is utilized by as many as 30 or 40% of cortical synapses [13]. Too little inhibitory modulation of the brain parts that underlie cognitive functions may be responsible for the difficulties observed in children with DS. Currently, however, despite the existence of a number of drugs designed to modulate GABA functions, no controlled study has been published. A similar situation prevails for the possible beneficial effects on the cortical functions depending on the prefrontal brain (particularly, attention, working memory and impulsivity) of administering dopamine and noradrenaline (norepinephrine) enhancing agents at the right moment and dosage in the brain development of children with DS.

Animal models of trisomy 21 have been made available in recent years. Mouse orthologs of HSA21 genes (the critical zone for the etiology of DS in humans) are located on chromosomes 16, 17, and 10 (in quantitative order). Trisomic mice (*Musmusculus*) Ts65Dn, Ts1Cje, Ts1RhR, and tgYACDy2k1a are currently produced. The region present in three copies is syntenic to 85 human genes in Ts65Dn mice. These mice present some features of DS: craniofacial

abnormalities, developmental delay, and impaired performance in learning tests. High resolution magnetic resonance imagery (MRI) and histological analyses reveal a volumetric reduction of the cerebellum.

These models are particularly useful for studying and experimenting on brain development, preclinical screening of pharmacological products that could prove efficacious in dealing with the effect of trisomy 21 in humans [14], and (as we shall see) in the context of genetic therapies in Down syndrome. It must be kept in mind, however, that pertaining to cognitive functions in particular, trisomy 21 in humans is incommensurably more complex than in mice models. It follows that clinical research at the human level will always be necessary.

In *conclusion*, pharmacological agents targeting a number of neurotransmitters hold promise for improving brain maturation in children with DS at least to a certain extent. Many questions remain without answer. Safety and longer-term residual adverse effects are a great concern. Developmental timing is of utmost importance. One aims at enhancing cognitive development without disrupting the subtle equilibrium of ontogeny. Critical or sensitive periods of development are the ones to be targeted in priority. The major caveat in this respect is that for most cognitive functions the developmental calendar is not known with sufficient precision and individual variability may be substantial including in people with Down syndrome.

As advocated also further in this paper, it is not likely that biologically based treatments will eliminate the need for neuropsychological rehabilitation and educational care (hence the title of this article). A rational objective should be to combine biological and behavioral strategies, translating advances in neuropharmacology and cognitive neurosciences into safe and efficient therapeutic strategies for children with DS; see also the discussion [15] under the label of *hybrid therapeutic strategies* in DS.

EPIGENETIC THERAPIES

Advances in molecular genetics in the latter decades have rendered possible envisaging realistic gene-based and chromosome-based corrective strategies. Li *et al*. [16] have reported a successful *in vitro* attempt to transform trisomic pluripotent stem cells obtained from the skin of persons with DS into disomic cells. Pluripotent cells can be obtained through genetic manipulations (consisting in adding several specific genes) in reprogramming human adult cells [17]. Li *et al*. [16] introduced a fusion transgene carried by an adenovirus at the locus APP (amyloid preprotein) of chromosome 21. The result was the elimination or in some cases the silencing of the additional chromosome 21 in the treated cells. It was observed that the derived disomic cells proliferate more rapidly *in vitro* than their trisomic counterparts, determining a positive selection in the solutions.

Jiang *et al*. [18] used another strategy with the same objective of silencing the third chromosome in trisomic cells also *in vitro*. The technique takes advantage of a common genetic phenomenon, i.e., the silencing of the second X chromosome in women following fecundation (in order to avoid genic over dosage given that the X chromosome carries many more genes than the tinier Y one in males). The silencing occurs through the activation of a gene, named XIST, located on the X chromosome. This gene is particular in the sense that it does not code for a specific protein but rather for an important quantity of noncoding ARN (ribonucleic acid) which wraps the chromosome and inactivates it through the methylation of its ADN (desoxyribonucleic acid, the chemical substance of the chromosome). Jiang *et al*. [18] used pluripotent cells obtained in reprogramming trisomic skin cells from a male person with DS *in vitro*. They inserted an XIST gene at the locus 21q22 of the gene DYRKYA on one of the three chromosomes 21 which caused the silencing of that chromosome in more than 85% of the cells. The resulting disomic cells showed an augmented differentiation and proliferation capacity as was also observed in Li *et al*.'s experiment. No alteration of the other chromosomes was observed in the cells that were treated.

These experiments open important therapeutic perspectives in Down syndrome. A number of additional investigations (beyond mere replications) must be carried out before it could be thought to proceed towards clinical applications at the human level. The safety of the procedure must be established *in vivo.* One will keep in mind that the natural silencing of one of the two X chromosomes in women is never complete. Some genes are usually left active, apparently on a random basis. Therefore it is not sure that artificially silencing one additional chromosome 21 will be complete either.

The restitution of a normal genotype or close to still appears to be a task of an exceptional technical

complexity. However, some of the first major steps towards potential development of chromosome therapy are being surmounted.

Ethical problems are in store too. Other chromosome disorders, such as Edward syndrome (trisomy 18) and Patau syndrome (trisomy 13), are possible target for similar treatments. But to prevent trisomy, the genome editing would have to be performed on a fetus, or better an embryo in the womb, and the sooner in cell differentiation the better. That is far beyond what is possible, or allowed, today. Besides, this technology implies that a very early prenatal diagnosis of trisomy can be performed. With the new "Prenatest" (legally authorized in a growing number of countries), a highly reliable (99%) diagnosis of trisomy 21 can be made as soon as the tenth week of pregnancy. That is still relatively late in the perspective of genome editing.

Targeting individual gene expression may be at hand in the near future. The general research strategy is as follows. The gene must be localized on chromosome 21, HSA region. Genes located outside this area on chromosome 21may also be involved in DS phenotypes but probably to a lesser extent. Observations from persons with partial trisomy 21 suggest that a region of about 2.5Mb (megabases) located between the genes CBR and ERG, if triplicated, is associated with numerous features of DS, physical as well as cognitive [14]. These genes when triplicated should theoretically show dosage effects that increase expression by 50% at the RNA (ribonucleic acid, carrying the genetic information from the DNA - desoxyribonucleic acid – from the cell nucleus onto the cell cytoplasm whereby protein synthesis is achieved) and protein level. These effects, either individually gene by gene or possibly additively, will result in perturbations of the cellular processes in which the genes are involved, which, in turn, will determine the neurodevelopmental abnormalities characteristic of DS. But matters may be more complex. Transcriptome analyses of mouse models show that most of the genes when triplicated are 1, 5 overexpressed. However, some genes are expressed more than 1, 5-fold while others - about 50% - do not exhibit changes in expression or sometimes decrease their expressivity [19].

Several genes on HSA21 are being targeted in ongoing experimental and clinical research. For example, the Lejeune Foundation in Paris, has deposited a patent for a molecule with an inhibitory action on the gene CBS which codes for the enzyme cystathionine beta-synthase, an enzyme overexpressed in persons with DS in several neural structures, among which the cerebellum and the hippocampus.

Bain *et al*. [20] have shown *in vitro* that the expression of the gene DYRK1A is inhibited by epigallocatechingallate (EGCG), a natural molecule that is the main component of the polyphenols from green tea. DYRK1A expression is elevated in the brain of individuals with DS. The corresponding enzyme is thought to be involved in the control of neurogenesis. Guedj *et al*. [21] and also Delabar [14] have demonstrated that chronic administration of EGCG reduces the level of active DYRK1A in transgenic mice with a corrective effect on brain alterations. Comparing treated and non-treated mice with three copies of DYRK1A, it could be shown that EGCG improves cognitive performance.

EGCG is currently being tested on groups of adolescents and young adults with DS in several university research centers in France and at the Center for Genetic Studies in Barcelona, Spain [22]. Beginning results are promising. Of course, one will have to wait several more months for the complete results to be fully analyzed.

These indications are consistent with the hypothesis of a central role for DYRK1A in central nervous system development and functioning. They suggest potential clinical benefits from the administration of DYRK1A inhibitors. Other genes on chromosome 21 and their overexpressed products in DS are currently in the experimental pipeline. Clinical applications are likely in the immediate future.

Other epigenetic strategies are being also considered even if they have not yet been translated into clinical essays at the human level [23,24]. RNA and the gene products, i.e., the proteins or their catalytic counterparts the enzymes, are possible targets for corrective interventions in DS. Any overproduction of DNA causes a corresponding increase in messenger RNA. It seems possible to utilize some "little" RNA (for example, RNAsi- si for silence) in such a way as to inactivate any gene in the genome. Alternatively, one could directly target the protein coded by an overexpressed gene in order to decrease the amount produced.

In *conclusion*, a number of epigenetic and genetic strategies are currently in the research pipeline for

correcting at least some of the most pernicious phenotypic effects of aneuploidies such as Down syndrome. It is likely that in a matter of a few years one will reach a stage at which clinically sound interventions will be performed with controlled safety risks. They will result in improving the phenotype of DS to a significant extent.

COGNITIVE INTERVENTION

Performing early and continued cognitive intervention, regarding particularly language, memory, and computational abilities, will always be necessary in Down syndrome and other congenital syndromes of intellectual disability. Deciding that given the new biological therapeutic perspectives cognitive intervention should be reduced, left aside or even discouraged, would be a grave error. To put it simply, biological therapies will soon be in a position to improve the brain and the physical aspects of people with the condition. In Western countries, medical supervision and specialized health programs have already succeeded in improving or even eliminating a number of physical shortcomings and difficulties in the life of people with DS.

However, as good as it could be, correcting negative brain and body characteristics and imparting lasting behavioral systems for learning, memorizing, and communicating are different things, albeit connected ones. Rather than possibly arguing about prioritizing some rehabilitation avenues rather than others, whether biological or behavioral, the more compelling task will be how to combine rationally based therapies and interventions so as to insure greater benefits for the persons with DS [15].

What about the present state of cognitive intervention in DS?

Language rehabilitation is carried out in many centers at least in Western and in some developing countries. Young children are being proposed various activities under the supervision of trained professionals sometimes with the help of responsive parents [25]. Early language stimulation and prelinguistic training are recommended. Rehabilitation work is conducted on various language components depending on the age and the child's developmental pace; from articulation and speech to textual organization, passing through vocabulary development and morphosyntactic training. Augmentative communication (e.g., manual signing, graphic symbols) may be proposed for those children demonstrating particular difficulties with speech production and in order to boost early vocabulary development. Several chapters in the opus edited by Rondal and Buckley [26] expose and discuss the knowledge base and the intervention technologies available in these domains. Early exposure to written language is advisable for it is also of help in promoting oral language. Kumin [27] has documented a number of practical tasks that can be used by professionals and parents in order to promote various aspects of speech and language in children with DS.

When correctly applied by trained professionals and sufficiently intensive, these programs are efficient in promoting speech and language development in most Down syndrome children and adolescents. The objective is to have these programs made available to all families with children with DS. This means training more professionals than what is actually the case and providing adequate financial resources to the centers in charge of this type of remediation.

Perhaps less well known is the training of memory in persons with DS.

Human memory is a complex system with several components. Short-term memory (STM) should be distinguished from longer-term memory (LTM). The former comes in two main registers, auditory-vocal (AV) and visual-spatial (VS). Four major long-term memory stores can be identified: perceptive, episodic, semantic, and procedural. It is possible to distinguish further between explicit and implicit memorizing.

People with DS have reduced memory abilities. Their weakness is usually more marked in STM than in LTM and in AV than in VS memory. Visual processes in DS are usually better preserved than auditory ones [28].

A number of research studies have been conducted in recent years on STM in DS either within or without the theoretical framework of working memory (WM) as defined by the British psychologist Alan Baddeley [29]. STM span in numbers or nonsense words does not change much between 8 and 38 years and may contain between 2.5 and 3.6 items with standards deviations around .60 [30,31,3].

Three major elements in the functioning of WM are lacking in persons with DS. Memory span is reduced as indicated; phonological strategies needed to keep the entering information alive in the short-term store are lacking or underdeveloped; and the clustering

(chunking) processes that can be utilized for organizing the information in the STM store remain primitive. In general, persons with DS make little to no use of inner speech or private external speech to assist cognitive operations.

Intervention techniques have been tested to contrasts these deficiencies at least to a certain extent [32]. Positive results have been reported in research works conducted with children and adolescents with SD. The training sessions lasted from 15 to 30 minutes a week for 6 to 8 weeks. The techniques were based on open cumulative recall. The learner is invited to repeat one by one the words (mono-, bi-, or trisyllabic) proposed by the clinician recapitulating from the beginning of the series each time a new item is added to the list. For example, starting a series with the word *cat*, the second word in the list being *ball*, correct repetition will be *cat-ball* in the order; the third item being *dog*, correct repetition is *cat-ball-dog*, and so on until reaching the end of six-word series. Gains up to two or three points in STM scales (that go from 1 to 8 or 9 points) have been confirmed. The effects of training persist without relearning over at least 8 months. However, controls at three-year intervals fail to confirm the stability of the benefits suggesting a need for periodical retraining.

Visuo-spatial short-term memory is also amenable to a similar improvement through the use of corresponding intervention techniques.

There is little doubt that a more intensive and prolonged training could warrant even better results. Using the computer in order to systematize the training operations would certainly be welcome. Also, more attention should be devoted to encouraging the use of private speech (external or better internal) in plausible attempts to keep memory traces alive and the case being refresh them, as is the case spontaneously in TD people beyond 6 or 7 years of age.

Even less popular are the attempts at boosting mathematical abilities in people with DS. There is no question that such abilities are among the most useful in ordinary life (e.g., dealing with money). Until recently, however, little attention has been devoted to these cognitive aspects and even fewer intervention proposals have been tested.

A look at the specialized literature reveals how little is known for sure regarding the development of mathematical abilities, particularly regarding the basic arithmetical operations [33,34]. A short list of likely determinants has been identified mostly through the analysis of cases of dyscalculia, but how exactly they act either individually or collectively to constrain computational development is not clear at this stage. General cognitive functions such as attention and short-term memory are involved. So is also the case of language and visual-spatial abilities. Both probably play a role in the semantic representation and coding of quantities as well as in the associated processes.

Little is now on the specific difficulties of persons with DS in computational cognition. Few systematic studies have been conducted. Counting, enumerating, and understanding the correspondence principle at the basis of the system of cardinal numbers can be acquired by these persons. Approximate judgments of quantity (many versus few) and so-called subitizing (speedy and correct estimate of small sets: up to 3 or 4 objects no matter of spatial display) seem to be preserved. But their development is delayed [35]. These basic abilities are considered innately given in human beings and perhaps supplying the foundation for additional quantitative development. Progress in computing is slow. In eight-year olds with DS, the numerical chain may still be unstable and correct counting and enumerating may not go beyond 10.

The most difficult aspects concern the logical and the arithmetical operations as well as the computations in base 10. Simple additions and subtractions can be learned with time and difficulties but they remain weak in many adolescents and adults with DS. Multiplication and divisions are most often hopeless. Reading Arabic numbers or writing them under dictation (transcoding) is always difficult and error prone [36].

Clearly, computational cognition raises a particular challenge to education and intervention in Down syndrome. Several pedagogical tools have been proposed but systematic evaluation is mostly missing. The Numicon system (http://www.numicon.co.uk) has been tested with children with DS [37,38]. This multi-sensory tool allows children to physically combine patterned shapes and rods representing numbers in order to make their calculation concrete and organized spatially. As said, visual-spatial cognition is usually more efficient in people with DS. A series of broad learning stages can be defined and gradually implemented (ordering the shapes, number names, ordering shapes and number names together, relating numbers to each other, adding and subtracting, money and simple measuring). Children with DS following the

Numicon approach are reported to exhibit more progress than other children with Ds not using the system, although important individual differences are registered.

Other systems, exploiting similar learning principles have been proposed but not systematically tested so far with persons with DS; for instance the Stern teaching material (Stern Structural Arithmetic: http://www;sternmath.com), and the more demanding Kumon method of teaching mathematics (http://www.kumon.co.uk). For more detail and anecdotal reports of mathematical progresses and relative proficiency in children with DS, see several articles in the issue 1, volume 12 of *Down Syndrome Research and Practice*, July 2007.

Curiously, in the literature that I have reviewed for this article, there is no mentioning of the possible use of the pocket calculator in persons with Ds in order to circumvent at least partially their computational difficulties. Understanding the base relationships in the number system is notoriously difficult for persons with DS (base 10 in our systems notwithstanding the French excursions in base 20 – e.g., *soixante-dix, quatre-vingt-dix*; and the Belgian *quatre-vingt*, which certainly do not simplify the computational learning of younger children whether TD or with DS). Using a pocket calculator transforms base operations into sequential ones which are easier to teach and to use. This would supply the persons with a severe intellectual disability with a learnable, portable, discrete, and useful tool for simple computational tasks.

CONCLUSION

The field of developmental intellectual disabilities, and particularly Down syndrome, is changing, even if there is still a lot to do in research and social matters in order, in particular, to contrast the unjustified discrimination that these people have been and are still experimenting in many countries in the world.

New pharmacological products are in the research and the clinical pipeline. They should supply efficient ways to boost and sustain cognitive development and functioning in the condition. Realistic perspectives of epigenetic and genetic interventions now exist. In a few years' time they will give birth to powerful therapeutic strategies to improve the very existence of persons with DS to levels unthinkable even just a few years ago.

At the same time, behavioral interventions, cognitive and otherwise, are gaining in efficiency.

As suggested and justified in this paper, a multidisciplinary biocognitive intervention strategy holds the best possibilities for rehabilitating people with DS. The general objective should be, out of a sense of distributive equality, to make these progresses and new opportunities available to every child and family in need.

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Received on 05-03-2014 Accepted on 13-12-2014 Published on 18-12-2014

DOI: http://dx.doi.org/10.12970/2310-8231.2014.02.03.5