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DSQ

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DSQ

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The aim of the Down Syndrome Quarterly (DSQ) is to provide easy access to research papers and evaluated results for clinicians, professionals, and families. The journal will have a broad focus and cover a wide range of topics relating to Down syndrome. It will include relevant research abstracts, commentaries relating to practice, peer reviewed research papers, literature reviews, and regional reports. It will include reports and international work, especially encouraging submissions from developing countries. There will be the opportunity to exchange ideas, and discussion papers on key issues will be included.

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Inside this Issue

I am doubly honoured to have also been asked to contribute the editorial as a guest to this Volume 12, Issue 1 of Down Syndrome Quarterly. Indeed as a non scientist I am humbled when I read the abstracts of the papers that are included.

One of the papers has been submitted by an award winner of the 2nd Annual Josephine Mills Research Awards in 2009 as follows.

Dr. Yoshio Okada for: Excellence in MEG Research in Developmental Neuroscience Award.

The second paper is by Dr. David E. Most and Dr. Deborah Fidler.

The papers have potential practical outcomes which is excellent for people with Down syndrome and their families. If I may, I should like to put forward a thought that was raised at a recent meeting of researchers into intellectual disability in general, the majority of whom were working in the field of Down syndrome. The comment made noted that researchers are mainly focused on their research projects, collecting data, getting the work published and then seeking funding for the next initiative. Unfortunately this is the nature of the academic world. As such, most do not have the time to properly disseminate the information gathered or promote the practical outcomes of their work. At the meeting this seemed plausible, but in light of the papers published in this issue of DSQ I am wondering whether this is correct. Perhaps this has been discussed before and may not be an issue but I would welcome reader's thoughts.

Sincerely,
Patrick Clarke
President, Down Syndrome International

Human brain development research: Helping children maximize their potentials

Yoshio Okada
Children's Hospital Boston, &
Harvard Medical School, Boston, MA

Please address correspondence to:
Yoshio Okada
Children's Hospital Boston, &
Harvard Medical School, Boston, MA
Phone: (781) 216-1143 Fax: (617) 730-4671

Abstract
This article reviews studies of development of neuronal functions in the human brain in utero and after birth, based on two noninvasive techniques called magnetoencephalography (MEG) and electroencephalography (EEG). MEG measures the magnetic field outside the head, whereas EEG measures the electrical potential on the scalp, both produced by electrical currents in active neurons. Although we are beginning to understand the structural and functional development of the human brain, we still know very little about its electrophysiological activity, which provides a view of brain functions during the development with a millisecond resolution. Recent advances in MEG instrumentation have made it possible to measure neuronal activity of the fetal brain in utero. It is now possible to measure not only ongoing activity of the brain at rest, but also the brain activity evoked by external auditory and visual stimulations, from outside the womb. We are also beginning to learn the maturation of the sensory cortices after birth and to define the extent of cognitive abilities in newborns and older infants. Our study based on a novel pediatric MEG system is beginning to show the utility of MEG for clinical studies of infants and children. We have obtained evidence for profound capabilities of the human brain to reorganize itself after an injury. We may have also identified biomarkers of epileptogenesis and autism spectrum disorder. These clinical studies indicate that a more sophisticated pediatric MEG system we are planning to construct today may be useful for helping children with Down syndrome (DS), specifically for understanding the physiological basis of DS and also for devising methods for individualized, neuroscience-based early education of children with DS for maximizing their individual potentials.

1. Introduction

This article is based on a talk I was to give at the dinner on March 26, 2009, as a recipient of this year's Josphine Mills Research Award. Even though I had planned this talk, I ended up not giving it. Instead I simply expressed from my heart the breadth and depth of dedication I felt during my visit with those who had been long involved in helping people with DS at Down Syndrome Research Foundation started by late Josephine Mills.

I received my award for the development of an instrument called babySQUID and applications of this instrument for brain development research. The babySQUID is a prototype pediatric MEG system optimized for baby studies. Prior to inventing the babySQUID, I often sat with my wife over dinner who had been working at Carrie Tingly Children's Hospital in Albuquerque, NM, and listened to her stories of children who had been affected by cerebral palsy (CP). She as a nutritionist had been helping these children with severe forms of CP to eat and drink or, in more severe cases, to provide the necessary nutrition through total parenteral feeding. She talked about love and appreciation in the eyes of these patients toward their parents and siblings, and dedication and reciprocal love of the parents and siblings. As I listened to her stories, I often felt the desire to be able to help children with various disorders, using my knowledge and expertise.

During those days, I had been carrying out research to understand brain functions using MEG and EEG. MEG measures the magnetic field just above the scalp, whereas EEG measures the electrical potential on the scalp, both produced by neuronal activity in the brain. These methods are completely passive and hence safe. They simply measure the signals produced by the brain without applying any energy to the brain. These are the only techniques available today that are capable of measuring signals directly related to electrophysiological activity of the brain with a millisecond time resolution. I had been studying how these signals are produced in the brain of the juvenile swine, so that I could help interpret MEG and EEG signals from our own brain. In this animal model, I was able to measure MEG signals associated with the cortical activity produced by external stimulations during each epoch of activity without averaging responses. Since the thicknesses of the scalp and skull in the neonatal and juvenile swine were comparable to those of human newborns and infants, I realized that it should be possible with MEG to measure cortical activity in real time without response averaging from human babies if we had an MEG instrument similar to the one I had been using for the swine research (Okada et al. 1994).

The confluence of the stories from my wife and my insight based on my own research led to the design of the babySQUID prototype in 1994 for early diagnosis of brain disorders. It uses the very sensitive magnetic field detectors

called superconducting quantum interference devices (SQUIDs), which had been used for MEG instrumentation for already many years. But, it took 10 years to convince a manufacturer to build it, to find the necessary funds and to actually complete the system. I was able to convince Tristan Technologies, inc., San Diego, CA, to manufacture the instrument for me and obtained the funds from the National Institutes of Health. In 2006, we installed the system in Mind Research Network, a non-profit research institute in Albuquerque, NM, and started to evaluate the usefulness of the babySQUID, which was designed as a prototype to obtain the proof-of-concept that a babySQUID-like MEG system is useful for human brain development research.

In this review I will cover the use of MEG in different laboratories for studying the brain activity in human fetuses in utero and the use of MEG and EEG by many laboratories including my own for studying brain functions in newborns, infants and children. I will then describe the design of a second-generation babySQUID, motivated by our experience with the prototype, which I believe will be truly useful for helping babies and children with various disorders. I will end this contribution by describing how MEG could help understand the physiological basis of DS and how it could be used as a tool for designing and monitoring individualized early education to help children with DS.

2. Fetal studies

We know that our brain undergoes a complex and yet specific sequence of development in utero. Yet we know very little about the electrophysiology of the fetal brain since it has been only during the last 10 years that we have a technique capable of reliably measuring the electrical activity of the neurons completely non-invasively from outside the mother's abdomen. As mentioned above, MEG and EEG are the only techniques that are presently capable of non-invasively measuring the electrophysiological signals from the human brain. However, EEG is not suited for measuring fetal brain activity. EEG electrodes can be attached to the scalp of the fetus in utero, but it is invasive and is rarely used except in urgent clinical cases. Fetal EEG can be non-invasively measured in principle on the abdominal surface of the mother, but the method is very rarely used. Extrapolating from a study comparing electrocardiograms (ECGs) and magnetocardiograms (MCGs) (Wakai et al. 2000), the difficulty of measuring fetal EEG is the vernix caseosa, a thin fatty layer that surrounds the fetus' body to protect the skin from the aqueous medium of the womb. The vernix is approximately 100 times less conductive than the underlying tissue and aqueous media in the womb and thus acts as an electrical insulator, especially during 28 to 34 weeks of gestational age. The vernix significantly reduces and distorts ECG signals, whereas MCG signals do not appear to be distorted (Wakai et al 2000). The lack of distortion for magnetic field is most likely due to the thinness of the vernix since the attenuation by a poorly conducting medium is determined in part by its thickness (Huang et al., 1990). Thus, MEG is the only non-invasive technique suitable for measuring the electrical activity of the brain of the fetus in utero.

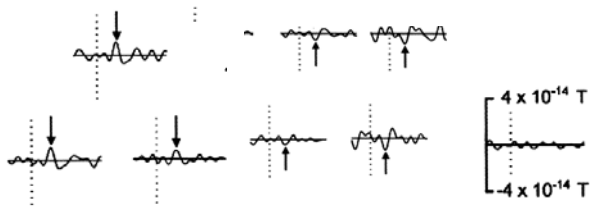

Fig. 1 Averaged auditory evoked fetal MEG with polarity reversal over two sides of the auditory cortex recorded from a 36-5/7 week GA fetus in utero. Recording Duration 1.0s. MEG amplitude full scale = +/- 40 fT. Bandwidth of data: 2 to 10 Hz. (Adapted from Fig. 1 of Lengle et al. 2001).

The initial report of evoked fetal MEG appeared in 1985 (Blum et al., 1985). The results had been, however, questioned for many years due to poor quality of the signals reported. More reliable reports of fetal MEG elicited by auditory stimuli started to appear in the mid-1990's from the group of Ronald Wakai at University of Wisconsin (Wakai et al., 1996; Lengle et al., 2001; Chen et al., 2006). In the study by Lengle et al. (2001) involving 16 healthy fetuses, auditory evoked MEG signals were recorded from fetuses as young as 29 weeks of gestational age (GA). The recordings were done with a 37-channel MEG system originally made for adults. Although the system was not optimal, it was possible to measure reliable signals as shown in Fig. 1, which displays an example of clearly recorded auditory evoked fetal MEG from a 36-5/7 GA fetus. The averaged response is based on a train of 1.5 kHz 50 ms tone bursts presented several hundred times at a mean presentation rate of 1.25 s. Soon, other groups have started to reproduce similar results. A group at Friedrich-Schiller University in Jena, Germany, was able to record auditory evoked MEG signals from the fetuses as young as 27 weeks GA, using a standard adult 31-channel MEG system, although the signal quality was low (Schleussner et al., 2001, 2004)

These pioneering studies motivated the development of a specialized MEG instrument optimized for fetal studies. The Canadian Thin Film (CTF), inc., in Vancouver, Canada, developed a fetal MCG/MEG system called S.A.R.A. (Squid Array for Reproductive Assessment) shown in Fig. 2. There are 151 sensors in liquid helium inside a fiber glass cryogenic probe. Figure 2b shows an exposed view of the sensor array. The mother sits on a chair with her abdomen against the sensor array (Fig. 2a). This system has been installed at the University of Arkansas and has been used for research in perinatology under the direction of Dr. Curtis Lowery. The second system is now installed in University of Tübingen and is used for MCG and MEG research under the direction of Hubert Preissl. Using the SARA, the Arkansas group has been able to obtain not only auditory, but also visual evoked MEG signals from fetuses as young as 27 weeks GA (Eswaran et al., 2002; Preissl et al., 2004; Eswaran et al., 2005; Sheridan et al., 2008).

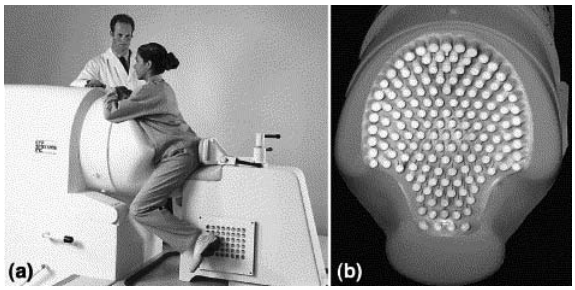

Fig. 2 Fetal MEG system (SARA) manufactured by the Canadian Thin Film, inc. (a) Pregnant mother sits against the sensor array (b) shaped to fit over the abdomen. Sound or light is delivered to the fetus by having a speaker or light emitter applied to the abdomen.

Two groups have shown that the human fetuses are capable of discriminating sounds. In a study using an adult MCG system, Huotilainen and her colleagues (Huotilainen et al., 2005) reported the magnetic mismatch negativity (MMN) in fetuses between 35 and 40 weeks GA. When a human subject is presented with a sequence of frequent and infrequent sounds, the subject shows differential responses to the standard and rare stimuli. The difference is called MMN (for review see Näätänen et al., 2007). It is believed that the MMN reflects the ability of the person to discriminate two types of sound. It is a well-established type of EEG response in adults, children and even in newborns. These investigators used the magnetic analog of MMN to show that the fetuses are capable of discriminating a standard and a target sound. The standard consisted of three harmonics at 500, 1000 and 1500 Hz with 3 and 6 dB attenuations for the second and third harmonics, respectively. The infrequent target sound consisted of 750, 1500 and 2250 Hz with the same amplitude attenuation pattern as the standard. The standard and target were presented with frequencies of 80-20%. Draganova et al. (2005) showed magnetic MMN to sounds using the SARA system.

Although it appears that evoked responses can be detected reliably from fetuses as young as 27 weeks GA, their quality is still relatively poor. Spontaneous brain activity, on the other hand, can be measured quite clearly with the SARA system. Eswaran et al. (2007) measured the so-called "tracè discontinue" from fetuses as young as 29 week GA as reported in Fig. 3. They also found other types of spontaneous activity well known from EEG studies of prematurely born babies (e.g. tracè alternant and delta brush).

The high quality of these spontaneous signals indicates that fetal MEG could be useful for both clinical and basic research. As EEG is used for staging brain development in neonates, MEG could be used for staging the brain development in fetuses in utero.

Recent studies of EEG in prematurely born babies also suggest that the corresponding MEG signals may be useful for studying the development of the γ-aminobutyric acid type A (GABAA) receptor system in humans in utero (Vanhatalo et al. 2005). These investigators have shown that the low-frequency component of spontaneous EEG below 1 Hz decreases rapidly during several weeks before 40 weeks GA and that this decrease is correlated with an increase in expression of a potassium-chloride co-transporter called KCC2. KCC2 controls the extrusion of intracellular chloride for maintaining the equilibrium potential for GABA receptors at a hyperpolarized level in mature brains. The opening of GABAA receptors is depolarizing when excess chloride ion can not be extruded due to inactive KCC2 and thus the GABA channel is effectively excitatory in the developing brain and switches to being inhibitory after KCC2 becomes functional. It may be possible to study this type of developmental changes in neurotransmitter systems based on spontaneous MEG signals since they can be clearly measured.

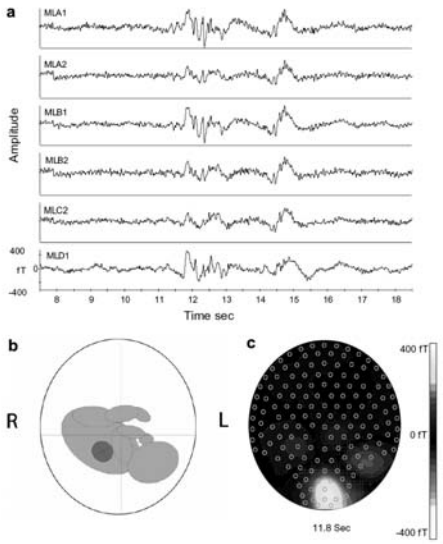

Fig. 3 Spontaneous brain activity called "trace discontinue" recorded from a 29 week GA fetus. (Eswaran et al. 2007).

3. Neonatal studies

The brain development in newborns and infants has been studied with both MEG and EEG. To limit the scope of this review, we will focus on MEG studies with some highlights from EEG studies. The spontaneous activity of the brain seen with MEG is similar to that seen with EEG in newborns (Pihko et al., 2004; Haddad et al., 2006).

According to Lutter et al. (2006), the MEG sleep pattern of newborns matures into an infantile form already by 48 weeks GA, before the evoked auditory magnetic field (AEF) starts showing maturational changes around 48 weeks GA. Figure 4 shows the transformation of the U-shaped initial response in newborns to a W-shaped initial cortical response around 52 weeks GA. They suggested that the brain may need to achieve a certain level of overall maturity manifested in the spontaneous activity, before the cortex enters a phase of significant functional development reflected in the evoked auditory response. This hypothesis seems to merit further testing.

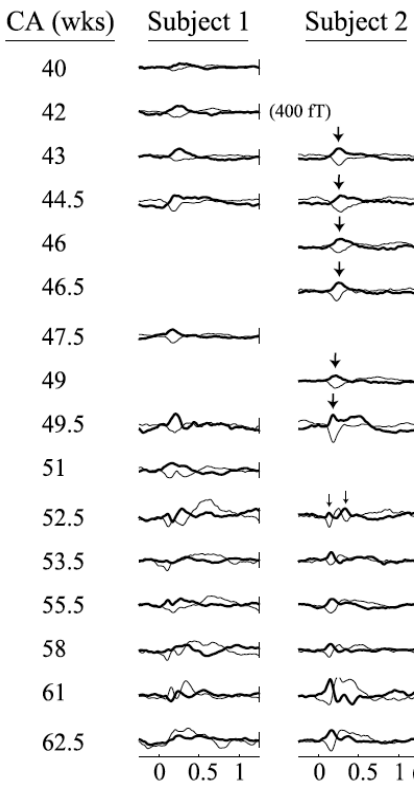

Fig. 4 A longitudinal measurement of evoked AEF in two subjects produced by a train of 1.5 kHz 100 ms tone bursts at 70 dB SPL with a mean interstimulus interval of 3s. (Adapted from Fig. 4 of Lutter et al. , 2006).

The somatosensory system also shows a rapid development of cortical processing during the first year of life. The initial cortical response in the evoked somatosensory magnetic field (SEF) elicited by tactile stimulation (Fig. 5) is U-shaped as in AEF (Pihko et al., 2004, Nevalainen et al., 2008; Pihko et al., in press). Around 6 months of age, the waveform becomes W-shaped (Fig. 5). It is not clear, however, whether the waveform change occurs earlier, say by around 52 weeks GA as in the case of AEF.

In addition to sensory responses, MEG can be used to study cortical areas involved in language reception and production. One study has measured activity in the Broca's area in newborns and 6- and 12-month old infants during presentations of different auditory stimuli including pure tones, harmonic chords and speech syllables (Imada et al., 2006). The activation of Broca's area increased with age.

EEG is also a useful tool to study sensation, perception and cognition in newborns, infants and children. Here I mention just a few of quite fascinating cognitive studies using the MMN paradigm. Some studies have revealed a rather amazing ability of newborns to discriminate or segregate complex streams of sounds. One study showed that newborns can segregate concurrent streams of sounds, one stream consisting of frequent and infrequent sounds presented at 1813 Hz and another stream between 250 and 300 Hz (Winkler et al., 2003). Newborns can discriminate the frequent and rare sounds in the first stream, even in the presence of the second. Another showed that sleeping

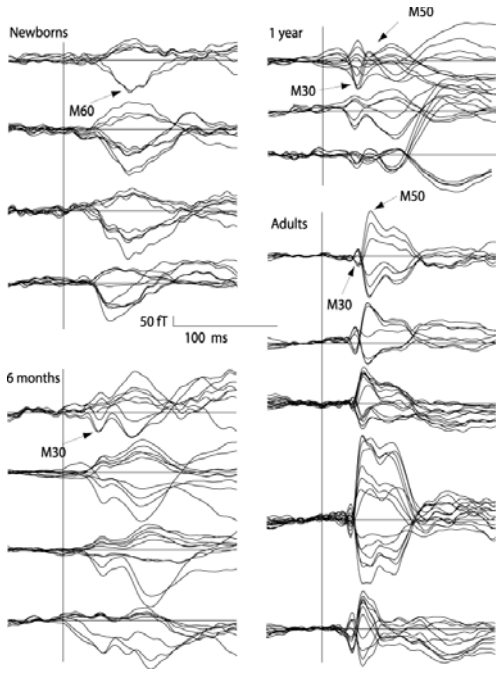

Fig. 5 Maturation of the SEF elicited by tactile stimulation in 4 newborns (quiet sleep) and 4 older infants and 4 adults (all in slow wave sleep). (From Pihko et al. in press). Traces from different sensors.

healthy newborns are capable of discriminating two sets of sound, defined by orthogonal conjunctions of frequency, intensity and duration, constructed in such a way that prevented identification of the sounds by simple stimulus features (Ruusivirta et al., 2004). Another study showed that newborns are capable of learning to discriminate phonemes in sleep (Cheour et al., 2002). Newborns could not discriminate phonemes /y/ and /y/i/ when they were presented in a stream of sounds in a MMN task. They, however, showed MMN responses the morning after they were presented with the same stream of sound for several hours while asleep at night. Comparable newborns did not show discriminative behavior when they were presented with no training stimuli or control training stimuli consisting of a stream of /a/ and /e/.

Fig. 6 BabySQUIDprototype, a pediatric MEG system optimized for babies. The 76 MEG sensors are 6 mm below the head rest. (Adapted from Okada et al. 2006).

4. Development of a pediatric MEG system

The above studies of newborns, infants and older children have been carried out using MEG systems designed for adults or fetuses. Although they have already provided some useful information, the results are limited due to the fact that the data were obtained with MEG systems that are suboptimal for pediatric studies. Conventional MEG systems do not take advantage of the special features of the head of infants. Since the scalp and skull of infants are thin (only 2-3 mm together at birth) and these structures are in general transparent to MEG signals (Okada et al. 1999), the cortical activity can be measured just above the brain as if the brain was exposed, if there was an MEG system with sensors only a few millimeters above the scalp. At such a short distance, the cortical activity can be resolved with a fine resolution. However, the adult MEG systems can not measure MEG signals at less than approximately 20 mm from the scalp. Nor do they have a sensor density that is high enough to take advantage of the high spatial resolution possible in infant studies. The babySQUID was designed to improve these deficiencies of adult MEG systems by using a design that made it possible to measure the MEG signals at a distance of 6 mm with a sensor density of ~1 cm instead of 3-4 cm between channels (Okada et al., 2006). Even with a relatively high noise level (17 fT/√Hz), we have shown that it is possible to detect evoked somatic responses to gentle tactile stimuli (indentation of the skin of a finger) with a 50 Hz bandwidth after averaging as few as 4 responses. The spontaneous activity exhibits rapid changes over the scalp across the channel spacing of 12-14 mm, indicating that this level of channel density is necessary to capture the spatial information of MEG signals from infants.

5. Studies of CNS pathophysiology with the babySQUID

We have been evaluating the usefulness of the babySQUID prototype for clinical research in three areas – CP, epilepsy and autism spectrum disorder (ASD).

5.1 Cerebral palsy

In a preliminary study we have obtained evidence of brain reorganization in children with CP due to unilateral brain injury (Okada et al., unpublished). We studied five CP patients between 7 and 13 yrs of age and five age matched healthy controls. In this study, tactile stimulation was applied to two lateral edges of the lips, and both left and right thumb, index, little finger and big toe. The SEF was measured over the somatosensory cortex in the affected hemisphere, then over the so-called unaffected hemisphere, for both the contra- and ipsilateral stimulations. The SEF waveforms in some patients showed what appears to be an intrahemispheric reorganization in the affected hemisphere (Fig. 7). In this 9-year old patient, the "unaffected" right cortex showed a robust contralateral response to left index finger stimulation. In the "affected" left hemisphere, the contralateral response was weak, but there was a clear unusual ipsilateral response. There was also some evidence for interhemispheric plasticity, that is reorganization in the hemisphere opposite to the affected right hemisphere (Fig. 8). In this hemisphere there was a strong ipsilateral

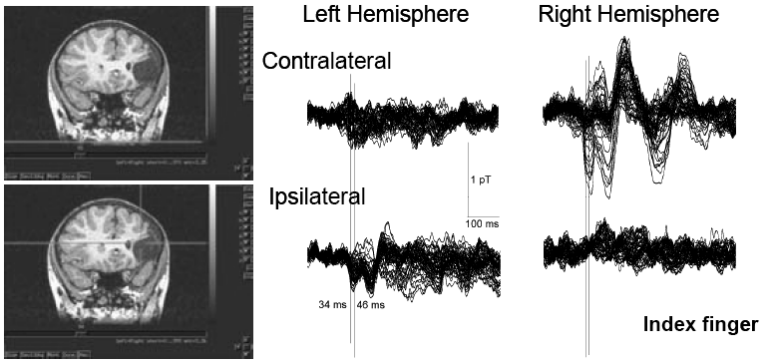

Fig. 7 Coronal MRI of a 9-year old patient with a congenital unilateral malformation in the sensorimotor area of the left cortex. Evidence for intrahemispheric reorganization in the the "affected" hemisphere.

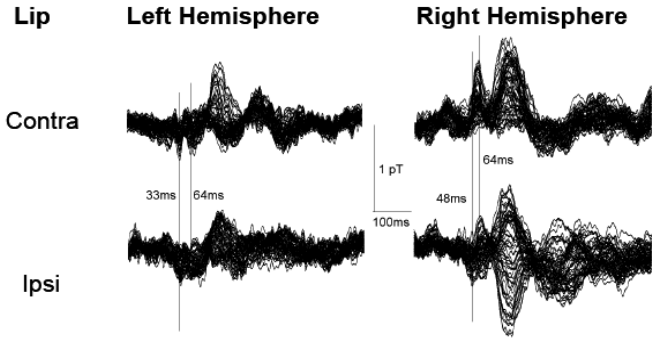

Fig. 8 Example of interhemispheric reorganization in the the "unaffected" hemisphere. The unaffected right hemisphere showed an unusual ipsilateral response to lip stimulation with latencies comparable to those in the contralateral response. (Okada et al. unpublished).

response to stimulation of the right side of the lip, which is again unusual in the normal population, even though young children tend to show ipsilateral responses. This type of profound plasticity points out perhaps a general concept that our brain reorganizes itself after some brain injury or any type of disorder, using all the functional regions of the brain to maximize its functions.

5.2 Epilepsy

In a preliminary study of epilepsy we found an interesting high frequency oscillation (HFO) between 80 and 200 Hz that was superimposed on some, but not on all interictal spikes, in 2/7 children with possible events in two other patients. Figure 9 shows an example of the HFO seen in a 16-month old infant. The interictal spike was localized in the cortex. This result is interesting because it is thought that the HFO could be the analog of the so-called fast ripple observed in adults with mesial temporal lobe epilepsy and in rat models of epilepsy (Bragin et al. 1999a, b, 2002). Fast ripple is seen only in those regions of the brain that produce seizure. Therefore, it is considered as a biomarker of epileptogenesis. The HFO found in our study in the infants could be a potential biomarker of epileptogenesis in the

pediatric population, even though the frequency is lower than the 250-500 Hz range for fast ripple. It is very possible that the frequency of HFO increases with age.

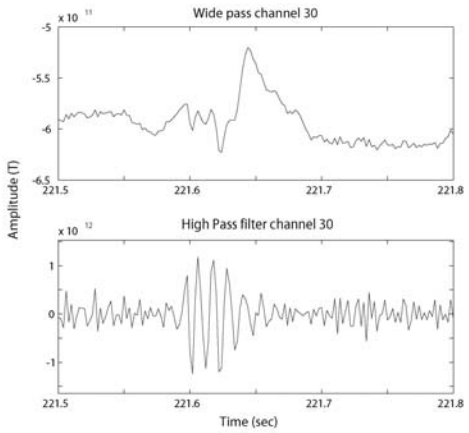

Fig. 9 A high frequency oscillation between 80-200 Hz superimposed on an interictal spike in a 16-month old infant with neocortical epilepsy. (Stephen et al. Unpublished)

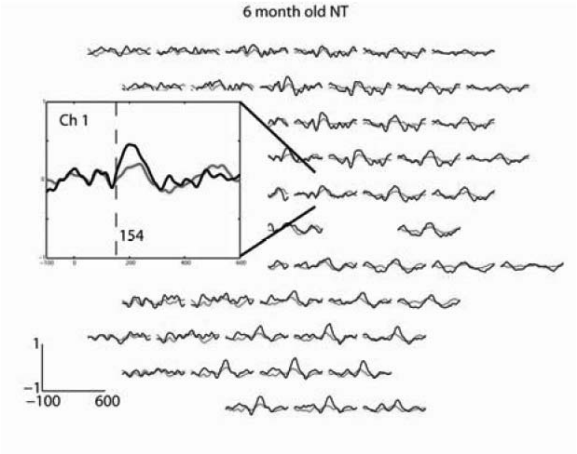

Fig. 10 Somatic-auditory cross-modal sensory integration response. The MEG response to the simultaneous presentation of auditory (A) and somatic (S) stimuli is larger than the sum of the responses to the separate presentations of A and S starting 154 ms after the stimulus presentation (Stephen et al. to be submitted)

5.3 Autism spectrum disorder (ASD)

Julia Stephen in our group obtained evidence using the babySQUID showing that children with ASD may have abnormally slow long-range functional connectivity. We came to this conclusion based on results from a cross-modal sensory integration task in which each child was presented with a train of somatic (S) stimulation alone (tapping of the skin of the index finger), with a train of auditory (A) stimulation alone (tone burst presentations) or with a simultaneous presentation of S and A. Dr. Stephen measured the responses over the somatic and auditory areas of one hemisphere for the three conditions in neurotypically developing children (NT) between 6 and 36 months of age and 36 month old children with ASD. She found that the linear sum of the responses to separate presentations of A and S (A+S) is smaller than the response to the simultaneous presentations of A and S (AS). Figure 10 shows an example of the larger AS response compared to the A+S response in a neurotypical 6 month old infant. The latency at which the AS response became stronger than the A+S response (154 ms in this case) was taken as the time when cross-modal sensory integration started. She found that this latency decreased with age between 6 and 36 month olds. More interestingly, she found that this latency is longer for the 3-year old ASD patients compared to the neurotypically developing 3 year olds. We interpret this slower latency as reflecting a slower speed of long-range corticocortical integration between the somatic and auditory cortices. This finding may be generally applicable to the entire brain, in showing that long-range functional corticocortical connectivity is slower generally in this population. This concept merits further testing.

6. Future directions for pediatric MEG research

These studies of healthy children and children with CNS pathophysiology demonstrate the exciting opportunities for future applications of MEG in the research on human brain development. We believe the most important initial step is to develop MEG systems that are optimized for pediatric studies. This step is critical for rapidly advancing our understanding of human brain development. We believe based on our experience with the babySQUID prototype that we are in a position to develop a second-generation babySQUID with exciting capabilities. In fact we have designed such a system - a whole-head pediatric MEG system. Based on our theoretical calculations and the data from the prototype, we believe this new instrument should be capable of simultaneously measuring cortical activity from all around the head with an unprecedented level of sensitivity that enables us to detect cortical activity without averaging as the response occurs in real time. It should also provide an unprecedented level of spatial resolution necessary for identifying active cortical tissues and estimating the causal relationship among the active areas. These predicted capabilities of the babySQUID II will provide an enormous opportunity for advancing our understanding of the electrophysiology of the developing brain.

7. Relevance of MEG for Down Syndrome

How can MEG be useful for children with DS? Of course this is the question readers would be asking. As I evaluate DS, I can suggest two areas in which MEG may be helpful. One is understanding the physiological basis of DS and the second, which builds on the first, is early preschool education from birth to 5 years old.

7.1 Understanding the physiological basis of Down Syndrome using MEG

There are anatomical and physiological bases for abnormalities in brain functions of children with DS. MRI studies have shown reduced volume of the frontal cortex, hippocampus and cerebellum in adults with DS (Pearlson et al., 1998; Aylward et al., 1999). The reduced regional brain volume appears to be caused by disruption of neurogenesis and apoptosis (Roper et al., 2006; Guidi et al., 2008). These developmental abnormalities may be due to the 1.5 fold increase in the genes present in the human chromosome 21. A recent study has identified two genes (dual-specificity tyrosine-(Y)-phosphorylation regulated kinase 1A (DYRK1A) and Down Syndrome critical region gene 1 (DSCR1)) that control the function of a transcription factor called nuclear factor of activated T cells (NFAT) (Arron et al., 2006). DYRK1A and DSCR1 cooperatively destabilizes a regulator circuit, leading to reduced NFATc activity and consequent reduction in neurogenesis. Spontaneous activity is believed to be important in neural development; it seems to have a functional role in controlling the development of the brain by increasing NFATc and thereby promoting neurogenesis. The moderate abundance of DYRK1A and DSCR1 suppresses the transnucleation of NFATc induced by spontaneous activity and thus reduces neurogenesis.

These results suggest that the development of local cortical circuit and brain connectivity may be affected in children with DS, especially in brain networks that include the frontal lobe, hippocampus and cerebellum. MEG can be used in a number of ways to test for function of each brain area of interest and evaluate their functional connectivity in newborns and infants. One is to use a generalized paradigm similar to the multisensory integration paradigm mentioned above for autism and measure functional connectivity between the auditory, visual and somatosensory cortices. This approach may be useful for characterizing the suspected slow speed of connectivity in children with DS as found in children with ASD. There is some evidence that children with DS may show this type of abnormality since poor functional connectivity may be the basis for the high level of concordance between DS and ASD (7% - Kent et al., 1999).

Another method is to present a task that requires the involvement of two or more cortical areas for successful execution. For example, one could study the speed of communication between Wernicke's area involved in receptive speech and Broca's area involved in expressive speech by presenting a word either visually or auditorily and asking the individual to repeat the word or to name another word related to the first in some ways, say semantically. Such a task is known to activate the visual, motor and Broca's areas (Salmelin et al., 1994). MEG can be used to measure the timing of activation in the Wernicke's and Broca's area to see if this is abnormal in children with DS since they commonly have difficulties in expressive speech. Another example is the use of tapping task (Gross et al., 2002). The tester can ask an individual to tap the finger at a certain rate. This is known to activate a brain circuit that involves the premotor and primary cortex, thalamus and cerebellum. Such a task could be used to determine the speed of communication among these areas using the methods such as Granger Causality analysis. Children with DS are known to have difficulties with motor control, thus they will most likely show abnormality in the timing of activation in this circuit. Short-term memory and decision tasks such as a delayed match or nonmatch to sample task or two-alternative forced choice tasks can be used to probe the activity of the prefrontal lobe, anterior cingulate area and hippocampus.

The babySQUID II will be quite helpful for carryout out this type of research because of its high sensitivity and spatial resolution. We predict that it will be possible to obtain high resolution brain connectivity maps from children with and without DS to identify the specific physiological functions affected by DS. This specific information should be useful for helping to construct new individualized protocols for early education of children with DS.

7.2 Early preschool education

Early education seems to be the key for helping individuals with DS to maximize their potentials and become well integrated into the society. Despite the known chromosomal differences and anatomical and physiological abnormalities in children with DS, these individuals are indistinguishable in many aspects at birth (Fidler & Nadel, 2007). The gap between this population and neurotypically developing infants in sensory, motor and cognitive abilities becomes increasingly clear during the infancy and preschool periods. Therefore, if we were to provide normal inclusive education to these children, it is important to minimize this gap during the preschool years. Fortunately, the developing brain is endowed with an enormous capacity to take advantage of learning to reorganize its structure in order to maximize its functions, as we saw in the case of cerebral palsy.

To help these children the most straight-forward approach seems to be to assess the sensory, motor, speech and cognitive functions of each child and to enhance their abilities in those areas that are deficient by providing individualized instructions, repeating the assessment and training on a periodic basis to move toward the path of optimized education. However, this approach is commonly based on intuition of the teachers about the best method for teaching the children. Instead of relying on intuition, one could construct a neuroscience-informed teaching strategy using neuroimaging tools such as MRI and MEG. The use of such tools is quite burdensome to any child and is expensive for the society to absorb the cost. Therefore, it is important that these tools do provide significant improvements in early education. I suggest that we could make differences in their lives using MEG, by viewing this as one of the tools along with other tools like functional MRI to construct teaching strategies that are optimized for each child. This could be achieved by identifying specific brain areas and cortico-cortical connections that are affected in children with DS for carrying out basic components of daily tasks such as motor coordination, speech reception and expression, explicit vs implicit learning, auditory vs visual memory, etc. As mentioned above, we can use MEG in many different ways to identify the cortical areas and functional connectivity affected in children with DS. This type of information can serve as a basis for devising new instructional strategies

to help improve the achievement level of each individual, so that the child will be ready as much as possible for integrated inclusive education. For example, we might find that the speed of communication between the auditory and Broca's area is poor compared to the speed between the visual area and Broca's. We can then construct a remedial program to improve the connectivity in the former pathway and monitor the improvement not only behaviorally, but also physiologically. Similar analysis can be carried out to assess the functions of the auditory area, Wernicke's and Broca's area, prefrontal lobe, hippocampus and cerebellum.

The research is hard and slow, but I believe there are many exciting ways to help children with DS maximize their potentials if we as a community give a concerted dedicated effort to help these children.

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Acknowledgements and notes

*Y. Okada at the time of this writing is Professor and Director of Biomedical Research and Integrative NeuroImaging (BRaIN Imaging) Center at the University of New Mexico, Albuquerque, NM. He has now joined the faculty of Harvard Medical school with a joint appointment at the Mind Research Network, Albuquerque, NM.

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Growth Trajectories of Word Identification and Applied Problem Solving in Students with Down Syndrome

David E. Most, PhD
School of Education
Colorado State University, Fort Collins, CO

Deborah J. Fidler, PhD
Human Development and Family Studies,
Colorado State University

Please address correspondence to:
David E. Most, PhD
School of Education
Colorado State University, Fort Collins, CO
Phone: (970) 491-6464
email: david.most@colostate.edu

research

Abstract

In this brief report, we examine the academic growth trajectories of students with Down syndrome in two areas: word identification and applied problem solving. Data from the Special Education Elementary Longitudinal Study (SEELS) database are analyzed. Students were assessed at three timepoints using two subtests from the Woodcock-Johnson III (Applied Problems and Letter-Word Identification). Relative to typical norms, deficits in Letter-Word identification were moderate in the primary grades, while deficits in Applied Problems were more pronounced. By late adolescence, average performance in Letter-Word Identification skills reached the average performance of a typical 7.5 year old child, while proficiency in Applied Problems was below an average 6 year old. Implications for research in Down syndrome are discussed.

Characterizing developmental trajectories in the context of academic skills may be useful for informing educational planning and instructional approach in Down syndrome and other developmental disorders. If longitudinal analyses demonstrate that a certain academic domain develops more slowly than others on average, it may be possible for educational planning to monitor and potentially address that area in a targeted way. Timely implementation of strategies to improve performance in an area of emerging vulnerability could prevent dissociations from becoming more pronounced. Such an 'anticipatory guidance' approach (Fidler, Philofsky & Hepburn, 2007) is only possible with an understanding of the trajectories of development in areas of academic relevance. Turner and Alborz (2002), in their longitudinal study of students with Down syndrome in the United Kingdom, also note that such studies make it possible to develop more accurate expectations for achievement in this population and address the "persistence of misconceptions regarding the educability" (p. 564) of individuals with Down syndrome.

Individuals with Down syndrome show a specific pattern of strengths and weaknesses in cross-sectional studies of various areas of development. Some aspects of this phenotypic profile, such as strengths in visual processing and deficits in verbal/auditory processing (Byrne, Buckley, Hesketh & Chapman, 1998; Jarrold, Baddeley & Hewes, 1999; Klein & Mervis, 1999; Laws, 1998), have a direct influence on academic performance. Because of the complex relationship between these areas of information processing and reading development, the issue of literacy skills in Down syndrome has been the focus of more investigation than most other areas of academic achievement in this population.

Among the most notable findings in cross-sectional studies of reading performance in children with Down syndrome is that word identification skills have been shown to be an area of distinct relative strength (Boudreau, 2002; Byrne et al., 1995; Fidler, Most & Guiberson, 2005). Fidler et al. (2005) found that strengths in visual processing contribute to component skills of reading, such as word identification and the development of sight vocabulary. There is also evidence that children with Down syndrome do recruit their verbal/phonological processing skills when identifying words, despite the weakness observed in this area of information processing (Cupples & Iacono, 2000; Fidler, Most & Guiberson, 2005). Though word identification has been shown to be an area of relative strength for individuals with Down syndrome, other areas of reading, such as reading comprehension and non-word reading (reading of nonsense words), have been shown to be more impaired (Byrne et al., 1995; Cupples & Iacono, 2000; Kay-Raining Bird et al., 2000; Verucci, Menghini & Vicari, 2006). In one longitudinal study conducted to date, Kay-Raining Bird et al (2000) followed 12 students with Down syndrome over a span of 4.5 years and found that the relative strength in word identification in individuals with Down syndrome became more pronounced relative to other aspects of literacy as children grew older.

Aside from literacy skills, there is also some evidence that children with Down syndrome show specific difficulty with various aspects of mathematics. For example, one study showed that middle-childhood aged students with Down syndrome have difficulty counting past eleven or greater (Irwin, 1989). Students with Down syndrome may need specific instructional techniques to target important skills such as 'counting on' (Irwin, 1991) and counting coins (Stith & Fishbein, 1996). Understanding additional aspects of this profile is important because numeracy skills, or the use of mathematics in daily living, are critical to the development of life skills and independence within the community (Faragher & Brown, 2005). Using a case study approach, Faragher

and Brown (2005) found that skills such as measurement of weight, division of food items, and addition and subtraction of money for budgeting money contributed to important outcomes such as self-image, choices, and personal control in adults with Down syndrome.

Because performance in Down syndrome in the area of mathematical skills is so poorly characterized—even cross-sectionally—identifying the developmental trajectory in these skill areas will contribute to our understanding of the larger profile of academic performance in Down syndrome beyond reading skills, and perhaps will motivate further research into this area. The one longitudinal study of academic achievement in Down syndrome does not involve analyses that characterize or model individual trajectories of growth (Turner & Alborz, 2002). Thus, it is difficult to learn much about individual growth and development based on the analyses reported in the study.

In this brief report, we examined the performance of school-aged children with Down syndrome on the Direct Assessment component of the Special Education Elementary Longitudinal Study (SEELS). In particular, we examined performance in two areas of interest—word identification skills and mathematical problem solving—as measured by two subtests of the Woodcock-Johnson III (Woodcock et al., 2001). We examined change in these areas of academic achievement over time in children aged seven to seventeen with Down syndrome and compare these performances to typical norms. Trajectories of development are modeled using the methods of individual growth modeling (Singer & Willett, 2003). Individual growth modeling yields estimates of mean individual academic achievement trajectories, which are informative about both the level and rates of change in achievement over time, as well as the extent of between-person variability in trajectories.

Database and Selection of Students

Individual student-level data were obtained from the Special Education Elementary Longitudinal Study (SEELS), a large-scale study of school-age students funded by the Office of Special Education Programs in the U.S. Department of Education. The SEELS data provide trend information on a nationally representative sample of students with disabilities who were between the ages of 6 and 13 in 1999. Measures of students' educational, social, vocational, and personal characteristics were documented over time in three waves covering a four or five year period of time. Information about each student was gathered from parents, teachers, principals, school records, and students themselves. The longitudinal character of these data is of particular interest here, as they permit an examination of student development.

Academic skills of interest were measured in the Direct Assessment (DA) component of SEELS. The DA is composed of various measures, each of which is a shortened section of a common assessment used in education. Details regarding all aspects of the SEELS, including study design, can be found at http://www.seels.net/. While the goal of SEELS was to collect assessment information on every student in the study, a screening process was used at each wave to determine whether the student had sufficient ability to participate. If the student was able to cooperate with an assessor and read words from a words list or identify letters, then the student was deemed eligible for DA. Students not eligible for DA in any given wave were eligible for an Alternate Assessment (AA). The AA, which was completed by the student's teacher, is a rating scale of student's abilities to perform a variety of tasks related to independent behavior. As students could be assessed up to three times during the SEELS, it was possible for a student's eligibility for DA to vary by wave within the SEELS data.

The DA and AA only refer to 13 federal disability categories, and, therefore, it is not possible to determine if a student has Down syndrome from the assessment data alone. In order to select the subset of students in the SEELS with Down syndrome, it was necessary to refer to the family-reported disability/problem information provided by parents in the Parent Interview (PI) component of the SEELS data. A consequence of this feature of the data is that the students with Down syndrome who were assessed but whose parents did not complete the PI could not be selected for inclusion in the study. Further, while the goal of the SEELS study was to obtain a nationally representative sample of students with disabilities, participation rates by selected parents or students in any particular component (e.g., PI, DA or AA) of the study was around 70 percent. Approximately one third of the students identified with Down syndrome, for unknown reasons, did not participate in any student assessment portion of the SEELS. Thus, assuming that participation rates for students with Down syndrome and their parents were similar to those for all those selected to participate in the SEELS, it is likely that assessment data are available for less than 50 percent of the students with Down syndrome in the SEELS data set. Despite this limitation, the SEELS data offer a unique opportunity to examine change over time in a national sample of students with Down syndrome who have received special education services.

The total SEELS sample of 11,512 students was constructed using a complex two-stage selection of local education agencies and students within local education agencies by federal disability category (Appendix A reference). Using the PI data, it was possible to identify 140 students with Down syndrome. Of the 140 students with a family-reported disability/problem of Down syndrome, 96 received the DA, the AA, or both the DA and AA on at least one occasion over the course of the SEELS. Academic achievement data were collected using the DA on at least one measurement occasion for 58 of the 96 students with Down syndrome. Forty four students received only the DA and 14 received both the DA and the AA at least one time across the three waves of assessment. The remaining 38 were deemed eligible for only the AA and thus were not included in the analyses. As the interest here is on changes in academic achievement, the focus is on the 58 students who were assessed via DA at least one time.

While 58 students with Down syndrome were assessed via DA in at least one wave of the study, not all students were assessed in all three waves. Forty students were assessed in the first wave, 45 students were assessed in the second

wave, and 43 students were assessed in the third wave of data collection. Across all occasions of assessment, 96% of students received letter-word identification score and 86% of students received an applied problems score. An important feature of using growth modeling to study change over time is that balanced longitudinal data (i.e., an equal number of waves for each individual) are not required to estimate growth trajectories (Singer & Willett, 2003).

Measures

A student who participated in the SEELS Direct Assessment at any of the three timepoints completed the Research Edition of the Woodcock-Johnson III Psychoeducational Battery (Woodcock et al., 2001). The Woodcock-Johnson is a widely used measure in American educational settings to assess academic performance and cognitive/neuropsychological functioning. There are 27 subtests in the Woodcock-Johnson. However, in the SEELS study, only four subtests were administered. In this study, we report data from the two achievement areas of interest: Letter-Word Identification (reading/decoding) and Applied Problems (mathematical skills).

The Letter-Word Identification subtest includes 40 items that assess an individual's ability to name individual letters and identify single words. Initial items involve identifying letters in print and in cursive. As items become more difficult, the assessment involves identifying high frequency sight words (e.g. cat, see, said) and then lower frequency, more difficult words to decode and identify (e.g. significance, trivialities, facetious). The Applied Problems subtest is a 31-item measure that assesses the use of quantitative reasoning in problem solving contexts. Items can include picture representations or text. More basic items include "Show me 2 fingers" or "How many cows are there in this picture?" Intermediate items include addition and subtraction (e.g. "If you take away two cans, how many would be left?"). Difficult items involve more advanced mathematical skills (e.g. "A yardstick has been divided into 4 equal parts. How long is each part?"). While the Applied Problems domain involves the use of quantitative reasoning in order to solve problems, it does not isolate other specific skill areas such as calculation. In addition, there is an important language confound with this measure. A correct answer includes the use of receptive language skills in order to interpret the orally presented question, as well as expressive language skills in order to answer properly. These confounds will be addressed further in the discussion section.

Analytic Approach

The primary analytic goal of this study was to examine patterns of growth over time in academic achievement in students with Down syndrome as measured by the Woodcock-Johnson subtests. Following other studies (e.g., Jordan et al., 2002), the methods of growth modeling were used to estimate average rates of change, also called growth rates or slopes, for both domains. For all growth model analyses, W scores, which are Rasch-scaled scores from the Woodcock-Johnson, were used. The W scale is centered on a value of 500, which corresponds to the average performance of a typical child at age 10 (Jaffe, 2009). A W score has equal interval properties and a constant metric. These properties make the study of change over time in W scores appropriate via the methods of growth modeling (Francis et al., 1996; Jordan et al., 2002, Singer & Willett, 2003). As time is measured by the age of a child in years, a growth rate can be interpreted as change in W score per year over the duration of the study.

A trajectory of growth in achievement is characterized by the level of achievement, in addition to the rate of change over time. As age seven was the earliest age at which students with Down syndrome were assessed, the time variable corresponding to the age of the student was centered at seven years in order to facilitate a substantively meaningful interpretation of the intercept in a growth model as initial status. In other words, the initial status is the level of achievement at seven years of age. For both academic skill domains, an overall mean initial status and growth rate were estimated by fitting a model in which each domain was modeled as a linear function of age. As a maximum of three waves of data are available for each student, a linear functional form was used to capture individual trajectories of change.

Growth models were not estimated for the typically developing children. However, the nature of growth over time can be approximated from the 2001 cross-sectional norms for the Woodcock-Johnson. As McGrew and Evans (2002) note, the cross-sectional data strictly yield the average performance by age rather than individual growth. For the purposes of comparing the children with Down syndrome to the typically developing children, the mean initial status in the children with Down syndrome was compared to the average performance at age seven for the typically developing children. Similar comparisons can be made at other ages of interest. Further, differences in average performance between ages in typical children were used to approximate average rates of change, which were compared to the mean growth rates derived from the models for children with Down syndrome.

Results

Growth models were estimated for the Letter-Word Identification and Applied Problems subtests for the children with Down syndrome. For each domain, a mean initial status (i.e., proficiency at age seven) and a mean growth rate (in the metric of points per year) were estimated. Comparable values for typically developing children were obtained from the 2001 Woodcock-Johnson norm data.

The estimated average proficiency in Letter-Word Identification at age 7 for the children with Down syndrome was approximately 375. The median performance at age 7 for the typically developing children was approximately 418. According to Jaffe (2009), a difference of this magnitude could be characterized as moderate delay relative to typically developing children. For the children with Down syndrome, the mean rate of change in Letter-Word Identification scores was 7.0 points per year. This translates to an approximate

70 point average increase over the 10-year period from ages 7 to 17, which is the full range of ages of students in the SEELS database. The average performance for typically developing children increased approximately 130 points over this same age range. In other words, the rate of increase in Letter-Word Identification skills for the children with Down syndrome was slightly less than half of that for typically developing children. As a consequence, the gap in proficiency by age 17 was approximately 100 points, which corresponds to a delay that would be considered severe. The mean level of proficiency for 17-year old individuals with Down syndrome was approximately equivalent to the mean for typically developing 7.5 year old children.

The estimated average proficiency in Applied Problems at age 7 for the children with Down syndrome was 386. The median performance at age 7 for the typically developing children was approximately 455. The magnitude of this difference, which is approximately 1.6 times as large as that for Letter-Word Identification at age 7, could be characterized as constituting a severe delay (Jaffe, 2009), relative to typically developing children in terms of development. For the children with Down syndrome, the mean rate of change in Applied Problems scores was 4.3 points per year. This translates to an approximate 43 point average increase over the 10-year period from ages 7 to 17, which is the full range of ages of the students in the SEELS database. The average performance for the typically developing children increased approximately 87 points over this same age range. In other words, as with Letter-Word identification, the rate of increase in Applied Problem skills for the children with Down syndrome was approximately half of that for typically developing children. And, the gap in proficiency by age 17 was approximately 100 points. In the case of Applied Problem skills, by age 17, the mean level of proficiency for the children with Down syndrome was lower than the mean for typically developing six year old children.

Discussion

As one of the few longitudinal studies involving a national sample of children with Down syndrome in the United States, this brief report offers new information regarding trajectories of academic achievement in this population. Delays in word identification relative to typical norms were somewhat milder in the primary grades in this sample, while deficits in applied problems were more pronounced. By late adolescence, mean performance on the word identification task reached the average performance of a typical 7.5 year old child, while average performance on the applied problems task was below the level of an average 6 year old. Thus, while both areas, over time, show increasingly pronounced impairment relative to typical norms, the relative severity of the impairment seems to vary across domain and age.

There are several implications for these findings for educators and practitioners working with individuals with Down syndrome. First, a longitudinal approach makes it possible to identify that the early performance on word identification tasks in younger, elementary school-aged children with Down syndrome is only moderately delayed relative to typical peers. While empirical studies are necessary in order to assess the validity of effective targeted approaches, understanding this trajectory raises questions regarding whether it may be possible to "capitalize" on that momentum in early word identification competence. In addition, these findings suggest that even from the earliest ages, rudimentary applied problem solving skills in young children with Down syndrome are a pronounced area of weakness relative to typical peers. Based on these findings, it may be the case that a more pronounced impairment in applied problem solving should be targeted more aggressively in the early years, before this area becomes an even more pronounced weakness in the Down syndrome academic profile.

Findings from this study also raise questions regarding whether the increasing disparity between word identification skills in children with Down syndrome and typical peers is a function of expression of the syndrome's genetic underpinnings, or whether this is an artifact of environment, or an interaction between the two. From a methodological perspective, findings from this study suggest that the severity of impairment of academic skill proficiency across domains in Down syndrome—and perhaps other disorders as well—may depend on the ages of students under consideration. If a domain of development becomes more impaired with age, then accurately characterizing the nature of such differences requires the collection of longitudinal data and using appropriate methods for analyzing longitudinal data. In other words, assumptions that age matters and that interest extends beyond the study of difference at a single age would lead to a shift in focus from a study of difference to a study of development or change.

There are several limitations to this brief report that should be considered. First, as discussed above, some children were unable to complete the direct assessment aspect of the SEELS study, and therefore their performances were not included in the longitudinal analyses described in this brief report. This limits the utility of the findings reported this brief report, as we are only able to make conclusions about growth and performance in a subset of children with Down syndrome who were able to respond to the demands of the direct assessment procedures. In light of this issue, future studies should be focused on replications of the findings of this brief report, if possible, with a sample that includes a fuller range of functioning levels in students with Down syndrome. A second limitation of this brief report relates to the methodology for identifying those children in the SEELS study who had a diagnosis of Down syndrome. As mentioned in the Methods section, the only method available for confirming a diagnosis of Down syndrome was through parent report. Because not every parent participated in the SEELS study, there may have been some students with Down syndrome in the larger SEELS sample that were not included in our analyses.

As the data only included performances of children with Down syndrome, and none of the other groups of individuals with intellectual disabilities were examined, any conclusions are limited with regard to the specificity of the findings to children with Down syndrome. It is possible that the growth trajectories reported in this study are common to children with intellectual disability in general, and not a unique

aspect of the genetic underpinnings associated with Down syndrome. Additionally, the Applied Problems domain assessed in this study is not a comprehensive measure of mathematical skills, rather it is a narrow measure of the use of quantitative reasoning skills to solve applied problems. Therefore, broader conclusions regarding calculation and other relevant mathematical skills should not be drawn from this study. The Applied Problems domain is also confounded by language skills, as both receptive and expressive language skills are involved in the process of correctly answering each item. Thus, the results of this study should be interpreted with an additional note of caution. Future studies should examine the degree to which language performance in Down syndrome correlates with or serves as a confound for performance on this domain.

Despite these limitations, the findings described in this brief report provide a longitudinal view on academic achievement growth trajectories in children and adolescents with Down syndrome. Studies of growth and development over time allow for a deeper understanding of both the trajectories of development associated with a genetic disorder and the potential targets of educational intervention.

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DSQ 2010 Selected Citations

Fallyn Leibovitch
McGill University

Conducting Research with Individuals with Down Syndrome

Griffith, Gemma M.; Hastings, Richard P.; Nash, Susie; Hill, Christopher

Using Matched Groups to Explore Child Behavior Problems and Maternal Well-Being in Children with Down Syndrome and Autism

Journal of Autism and Developmental Disorders, May 2010, Volume 40(5), 610-619

Abstract

Mothers of children with Down syndrome, autism, and mixed etiology intellectual disabilities, matched on child age, gender, and communication skills (n = 19 in each group) completed measures of their child's adaptive and problem behaviors, their own parenting stress, and positive perceptions of their child. Children with autism were rated as having more problem behaviors and lower levels of social competence than children with Down syndrome and mixed etiology intellectual disabilities. Mothers of children with autism scored lower on positive perceptions of their child, and higher on stress than the other two groups. After selecting closely matched groups, we found several group differences in child behavior but little evidence of group differences in maternal outcomes.

Cebula, K. R.; Moore, D. G.; Wishart, J. G.

Social Cognition in Children with Down Syndrome: Challenges to Research and Theory Building

Journal of Intellectual Disability Research, February 2010, Volume 54(2), 113-134

Abstract

Characterising how socio-cognitive abilities develop has been crucial to understanding the wider development of typically developing children. It is equally central to understanding developmental pathways in children with intellectual disabilities such as Down's syndrome. While the process of acquisition of socio-cognitive abilities in typical development and in autism has received considerable attention, socio-cognitive development in Down's syndrome has received far less scrutiny. Initial work in the 1970s and 1980s provided important insights into the emergence of socio-cognitive abilities in the children's early years, and recently there has been a marked revival of interest in this area, with research focusing both on a broader range of abilities and on a wider age range. This annotation reviews some of these more recent findings, identifies outstanding gaps in current understanding, and stresses the importance of the development of theory in advancing research and knowledge in this field. Barriers to theory building are discussed and the potential utility of adopting a transactional approach to theory building illustrated with reference to a model of early socio-cognitive development in Down's syndrome. The need for a more extensive model of social cognition is emphasised, as is the need for larger-scale, finer-grained, longitudinal work which recognises the within-individual and within-group variability which characterises this population. The value of drawing on new technologies and of adapting innovative research paradigms from other areas of typical and atypical child psychology is also highlighted.

Alzheimer's and/or Dementia in Individuals with Down Syndrome

Prasher, V. P.; Airuehia, E.; Carey, M.

The First Confirmed Case of Down Syndrome with Dementia with Lewy Bodies

Journal of Applied Research in Intellectual Disabilities, May 2010, Volume 23(3), 296-300

Abstract

Dementia with Lewy bodies (DLB) is the second commonest cause of dementia in the general population. Several researches have established an association between Down syndrome (DS) and Alzheimer's disease. Very few studies have however showed such an association between dementia with Lewy bodies and Down syndrome. The occurrence of DLB in persons with DS is widely unrecognized. We report the first case of a person who fulfils the operational criteria for DLB and was also found to have Lewy bodies on neuropathological examination. It is important to make an early and accurate diagnosis as patients with DLB may respond differently than Alzheimer's dementia patients to certain behavioural and medical treatments.

Adams, Dawn; Oliver, C.

The Relationship between Acquired Impairments of Executive Function and Behaviour Change in Adults with Down Syndrome

Journal of Intellectual Disability Research, May 2010, Volume 54(5), 393-405

Abstract

Background: The latter stages of dementia in individuals with Down syndrome are well documented; however, earlier cognitive and behavioural changes have only recently been described. Holland et al. suggested such early signs of dementia in this population are behavioural and are similar to those seen in frontotemporal dementia, but there is, as yet, no evidence to determine whether such behavioural changes are associated with a declines in specific cognitive functions, including those associated with the frontal lobes. Methods: A longitudinal design of three time points across 16 months was used across 30 adults with Down syndrome aged 30 years and over. Measures of cognition (Neuropsychological Assessment of Dementia in Individuals with Intellectual Disabilities), receptive language (British Picture Vocabulary Scales), adaptive behaviour (Vineland Adaptive Behavior Scales), behavioural excesses and behavioural deficits (Assessment

for Adults with Developmental Disabilities) and measures of executive functioning were completed at each time point. Using a data-driven method, cognitive deterioration was determined using the Reliable Change Index on performance on the Neuropsychological Assessment of Dementia in Individuals with Intellectual Disabilities across the duration of the study. Performance on the remaining measures were then compared between those with (n = 10) and those without (n = 20) cognitive deterioration. Results: Only individuals with cognitive deterioration showed decreases on measures of executive function and significant changes in behaviour across the duration of the study, which was not solely due to declines in memory. There were no changes between the groups on levels of adaptive behaviour. Conclusions: Even in the early stages of cognitive deterioration, specific behavioural changes can be identified that are not present in those without cognitive deterioration. The differing effects of cognitive deterioration on behavioural excesses and deficits are discussed in relation to potentially differing underlying neuropathological causes.

Ball, S. L.; Holland, A. J.; Watson, P. C.; Huppert, F. A.
Theoretical Exploration of the Neural Bases of Behavioural Disinhibition, Apathy and Executive Dysfunction in Preclinical Alzheimer's Disease in People with Down's Syndrome: Potential Involvement of Multiple Frontal-Subcortical Neuronal Circuits
Journal of Intellectual Disability Research, April 2010, Volume 54(4), 320-336

Abstract
Background: Recent research has suggested a specific impairment in frontal-lobe functioning in the preclinical stages of Alzheimer's disease (AD) in people with Down's syndrome (DS), characterised by prominent changes in personality or behaviour. The aim of the current paper is to explore whether particular kinds of change (namely executive dysfunction (EDF), disinhibition and apathy), associated in the literature with disruption of different underlying frontal-subcortical circuits, are a) more or less frequently reported than others and b) related to poor performance on tasks involving different cognitive processes. Method: Seventy-eight participants (mean age 47 years, range 36-72) with DS and mild to moderate intellectual disability (based on ICD-10 criteria), without a diagnosis of dementia of Alzheimer's type (DAT) or other psychiatric disorders, were selected from a larger sample of older adults with DS (n = 122). Dementia diagnosis was based on the CAMDEX informant interview, conducted with each participant's main carer. Informant-reported changes in personality/behaviour and memory were recorded. Participants were scored based on symptoms falling into three behavioural domains and completed five executive function (EF) tasks, six memory tasks (two of which also had a strong executive component) and the BPVS (as a measure of general intellectual ability). Multiple regression analyses were conducted to determine the degree to which the behavioural variables of "EDF", "disinhibition" and "apathy", along with informant-reported memory decline and antidepressant medication use, predicted performance on the cognitive tasks (whilst controlling for the effects of age and general intellectual ability). Results: Strikingly, disinhibited behaviour was reported for 95.7% of participants with one or more behavioural change (n = 47) compared to 57.4% with reported apathy and 36.2% with reported EDF. "Disinhibition" score significantly predicted performance on three EF tasks (designed to measure planning, response inhibition and working memory) and an object memory task, (also thought to place high demands on working memory), while "apathy" score significantly predicted performance on two different tasks, those measuring spatial reversal and prospective memory (p less than 0.05). Informant reported memory decline was associated only with performance on a delayed recall task while antidepressant medication use was associated with better performance on a working memory task (p less than 0.05). Conclusion: Observed dissociation between performance on cognitive tasks associated with reported apathy and disinhibition is in keeping with proposed differences underlying neural circuitry and supports the involvement of multiple frontal-subcortical circuits in the early stages of DAT in DS. However, the prominence of disinhibition in the behavioural profile (which more closely resembles that of disinhibited subtype of DFT than that of AD in the general population) leads us to postulate that the serotonergically mediated orbitofrontal circuit may be disproportionately affected. A speculative theory is developed regarding the biological basis for observed changes and discussion is focused on how this understanding may aid us in the development of treatments directly targeting underlying abnormalities.

Down Syndrome and Health

Jones, Jill; Hathaway, Dorothy; Gilhooley, Mary; Leech, Amanda; MacLeod, Susan
Down Syndrome Health Screening--The Fife Model
British Journal of Learning Disabilities, March 2010, Volume 38(1), 5-9

Abstract
People with Down syndrome have a greater risk of developing a range of health problems, including cardiac problems, thyroid disorders, sensory impairments, reduced muscle tone (hypotonia) and Alzheimer's disease. Despite this increased risk, regular screening is not typically offered to individuals with Down syndrome. A multidisciplinary health screening clinic was set up by a Community Learning Disability Team in Fife to offer regular health screening to people with Down syndrome. The format of the clinic, outcomes after 18 months and future service developments are discussed.

Pysden, Karen; Fallon, Penny; Moorthy, Bhagavatheswaran; Ganesan, Vijeya
Presumed Perinatal Stroke in a Child with Down Syndrome and Moyamoya Disease
Developmental Medicine & Child Neurology, February, 2010, Volume 52(2), 212-214

Abstract
Moyamoya disease describes a cerebral arteriopathy characterized by stenosis or occlusion of the terminal internal carotid and/or the proximal middle cerebral arteries. We report a female child with trisomy 21 and bilateral moyamoya disease who presented, unusually, with a presumed perinatal cerebral infarct. The clinical, radiological, and angiographic features of moyamoya disease in children with Down syndrome are similar to those with other aetiologies or idiopathic cases. Early

recognition is important as moyamoya disease presenting in childhood is associated with a high rate of recurrent stroke and there is evidence that surgical revascularization can prevent further events. An important practical lesson arising from this case is that although the evaluation of children with presumed perinatal stroke tends to be limited relative to the evaluation of arterial ischaemic stroke in older children, this may need to be more comprehensive in infants at high risk of arteriopathy. The parents of the child gave informed consent to the publication of this report.

Memory, Learning and Academics in Individuals with Down Syndrome

Mosse, E. K.; Jarrold, C.
Searching for the Hebb Effect in down Syndrome: Evidence for a Dissociation between Verbal Short-Term Memory and Domain-General Learning of Serial Order
Journal of Intellectual Disability Research, April 2010, Volume 54(4) 295-307

Abstract
Background: The Hebb effect is a form of repetition-driven long-term learning that is thought to provide an analogue for the processes involved in new word learning. Other evidence suggests that verbal short-term memory also constrains now vocabulary acquisition, but if the Hebb effect is independent of short-term memory, then it may be possible to demonstrate its preservation in a sample of individuals with Down syndrome, who typically show a verbal short-term memory deficit alongside surprising relative strengths in vocabulary. Methods: In two experiments, individuals both with and without Down syndrome (matched for receptive vocabulary) completed immediate serial recall tasks incorporating a Hebb repetition paradigm in either verbal or visuospatial conditions. Results: Both groups demonstrated equivalent benefit from Hebb repetition, despite individuals with Down syndrome showing significantly lower verbal short-term memory spans. The resultant Hebb effect was equivalent across verbal and visuospatial domains. Conclusions: These studies suggest that the Hebb effect is essentially preserved within Down syndrome, implying that explicit verbal short-term memory is dissociable from potentially more implicit Hebb learning. The relative strength in receptive vocabulary observed in Down syndrome may therefore be supported by largely intact long-term as opposed to short-term serial order learning. This in turn may have implications for teaching methods and interventions that present new phonological material to individuals with Down syndrome.

Martinez, Elisabetta Monari; Pellegrini, Katia
Algebra and Problem-Solving in Down Syndrome: A Study with 15 Teenagers
European Journal of Special Needs Education, February 2010, Volume 25(1) 13-29

Abstract
There is a common opinion that mathematics is difficult for persons with Down syndrome, because of a weakness in numeracy and in abstract thinking. Since 1996, some single case studies have suggested that new opportunities in mathematics are possible for these students: some of them learned algebra and also learned to use equations in problem-solving. Here an educational study with 15 teenagers with Down syndrome is presented: fractions, percentages, first-degree equations and problem-solving with equations were taught and learning was monitored. The students' performances during the course and in a final test were compared: the students seemed to have learned the new programme and to remember it one month later. They seemed to perform better with equations and problem-solving with equations than with other more conventional topics. There were no significant differences in the performance of different gender groups.

Miscellaneous

Lanfranchi, S.; Jerman, O.; Dal Pont, E.; Alberti, A.; Vianello, R.
Executive Function in Adolescents with Down Syndrome
Journal of Intellectual Disability Research, April 2010, Volume 54(4), 308-319

Abstract
Background: The present work is aimed at analysing executive function (EF) in adolescents with Down Syndrome (DS). So far, EF has been analysed mainly in adults with DS, showing a pattern of impairment. However, less is known about children and adolescents with this syndrome. Studying adolescents with DS might help us better understand whether performances on EF tasks of individuals with DS are determined by age or by Alzheimer disease, as some studies suggest, or whether their performances are directly related to DS cognitive profile. Method: A battery of EF tasks assessing set shifting, planning/problem-solving, working memory, inhibition/perseveration and fluency, as well as a tasks assessing sustained attention has been administered to a group of 15 adolescents with DS and 15 typically developing children matched for mental age. All EF tasks were selected from previous studies with individuals with intellectual disabilities or from developmental literature and are thought to be useful for the samples considered. Results: The present results revealed that the group of individuals with DS performed at a significantly lower level on tasks assessing set shifting, planning/problem-solving, working memory and inhibition/perseveration, but not on the tasks assessing fluency. In addition, individuals with DS demonstrated a greater number of errors and less strategy use for the sustained attention task. Conclusions: The results suggest a broad impairment in EF in adolescents with DS, and are consistent with several similar studies conducted with adults with DS. We assume that EF deficit is a characteristic of DS.

Rihtman, Tanya; Tekuzener, Esti; Parush, Shula; Tenenbaum, Alex; Bachrach, Steven J.; Ornoy, Asher
Are the Cognitive Functions of Children with Down Syndrome Related to Their Participation?
Developmental Medicine & Child Neurology, January 2010, Volume 52(1), 72-78

Abstract
Aim: There is a lack of investigation into the functional developmental profile of children with Down syndrome. On the basis of current international health paradigms, the purpose of this study was to assess the developmental profile of these children. Method: Sixty children (33 males,

27 females) with Down syndrome (age range 6-16y; mean age 9y 3mo, SD 28.8mo), who had received standard, holistic, early intervention, were assessed. Of these, 42 (70%) had congenital anomalies, 12 had severe congenital heart defects. Participants were assessed on measures of cognitive function (Beery-Buktenica Developmental Test of Visual-Motor Integration; Stanford-Binet Intelligence Scale) and participation (Vineland Adaptive Behaviour Scales). Results: No difference was found on any measure on the basis of severity of congenital anomaly. Results showed improvements in age-related body function and correlations between specific body functions and participation. No decline in IQ was found with age, and significant correlations between IQ and all other measures were noted. Although sex differences were found in the body functions of short-term memory and motor function, no difference in measures of activity performance and participation was found. Interpretation: Our findings emphasize the need for paediatric Down syndrome intervention to encourage improved body functions while emphasizing the acquisition of functional skills that enable enhanced participation in age-appropriate activities.

Lloyd, Meghann; Burghardt, Amy; Ulrich, Dale A.; Angulo-Barroso, Rosa

Physical Activity and Walking Onset in Infants with Down Syndrome

Adapted Physical Activity Quarterly, January 2010, Volume 27(1), 1-16

Abstract

Infants with Down syndrome (DS) are described as being less active and they also experience significant delays in motor development. It is hypothesized that early infant physical activity may be influential for the acquisition of independent walking. Physical activity was monitored longitudinally in 30 infants with DS starting at an average age of 10 months participating in a treadmill training intervention. Actiwatches were placed on infants' trunk and right ankle for a 24-hr period, every other month until walking onset. Data were analyzed to separate sedentary-to-light activity (low-act) and moderate-to-vigorous activity (high-act). Results showed that more leg high-act at an average age of 12 and 14 months is related to earlier onset of walking. It is recommended that early leg activity should be promoted in infants with DS.

Parenting

Dabrowska, A.; Pisula, E.

Parenting Stress and Coping Styles in Mothers and Fathers of Pre-School Children with Autism and Down Syndrome

Journal of Intellectual Disability Research, March 2010, Volume 54(3), 266-280

Abstract

Background: The study examined the profile of stress in mothers and fathers of preschool children with autism, Down syndrome and typically developing children. A further aim was to assess the association between parenting stress and coping style. Methods: A total of 162 parents were examined using Holroyd's 66-item short form of Questionnaire of Resources and Stress for Families with Chronically Ill or Handicapped Members and the Coping Inventory for Stressful Situations by Endler and Parker. Results and Conclusions: The results indicated a higher level of stress in parents of children with autism. Additionally, an interaction effect was revealed between child diagnostic group and parent's gender for two scales of parenting stress: dependency and management and limits of family opportunities. Mothers of children with autism scored higher than fathers in parental stress; no such differences were found in the group of parents of children with Down syndrome and typically developing children. It was also found that parents of children with autism differed from parents of typically developing children in social diversion coping. Emotion-oriented coping was the predictor for parental stress in the samples of parents of children with autism and Down syndrome, and task-oriented coping was the predictor of parental stress in the sample of parents of typically developing children. The results strongly supported earlier findings on parenting stress in parents of children with autism. They also shed interesting light on the relationship between coping styles and parental stress.

DSI PRESIDENT'S REPORT - 2009

It is indeed an honour that I write this piece as newly elected President of Down Syndrome International. The annual general meeting took place on the 18th August 2009 and preceded the 10th World Down Syndrome congress in Dublin City University, Dublin.

I list below the Executive and Board members who were elected for the coming term of office. Pat Clarke, President. Ireland; Penny Robertson, Immediate Past President, Indonesia; Vanessa dos Santos, Vice President and 11th World DS Congress Chair, South Africa; Bridget Snedden, Secretary, New Zealand; Dawn McKenna, Treasurer, Canada; Paul Zanon, Company Secretary, United Kingdom.

The board members are, Prof. Roy Brown, Canada; Carol Boys, United Kingdom; Dr Jacob Burack, Canada; Grete Falt-Hansen, Norway; Marja Hodes, Holland; Dr. Eiichi Momotani, Japan; David Patterson, United States; Dr. Rehka Ramachandran, India; Claudia Ritzel, Colombia; Dr Balbir Singh, Singapore; Kirsten van Burm Singapore; Prof. Daniel Weeks, Canada.

I wish to thank Penny Robertson for her stewardship and for assuming the role of President on the passing of our esteemed colleague Mrs Jo Mills. As a board we have a lot to live up to in order to do justice to the long years of service Jo gave to DS International. " Ar dheis De go Rabh a anaim May she be at God's right hand."

The AGM decided to make a number of special achievement awards to those elected to the new DS Special advisory Board. The following people are now the members of this advisory board:- Prof. Juan Perera, Spain; Prof. Sylvia Escamilla, Mexico; Prof. Cliff Cunningham, United Kingdom; Prof. Janet Carr, United Kingdom; and Prof Sigfreud Peuschel, United States.

The 10th World Down Syndrome Congress was preceded by the 1st International Synod of people with Down syndrome. This powerful event was opened by the Lord Mayor of Dublin with the Presidents of DS International and DS Ireland also speaking. The President of Ireland, Mrs Mary McAleese, sent a video message of welcome as she was not in a position to attend. The participants were addressed by Ms Mairead McGuinness a member of the European Parliament and David Hingsburger from Canada who spoke about citizenship and living in and being part of the community. Twenty countries were represented at the Synod with 120 delegates taking part. The participants were so energised by the event that they did not wish to finish at the end of the day and quite a number continued their discussions in an adjacent room until it was time to attend the state reception and presentation of the DS International awards.

The 10th World Congress opened the following day with record numbers attending and with a record number of plenary speakers, oral and poster presentations. There was also a full programme for people with Down syndrome of all ages with record numbers participating. The congress opened with a number of speeches, presentations and a video welcome from the President of Ireland Mrs. Mary McAleese. The opening ceremony was concluded by a vigorous dance performance by the Counterbalance Dance group which received a standing ovation from the delegates.

The world congress is a very pleasant memory at this stage and it is now time for DS International to begin its ambitious work programme for the future. Its five year plan is published in detail on our new website. I recommend that you visit it, but I list the main objectives here:

Objective 1. Organise a World Congress every three years.

Objective 2. Establish an international scientific committee to support the World Congress.

Objective 3. Develop outreach programs to bring expertise to countries that need our support.

Objective 4. Establish a website and email distribution list promoting international discussion and collaboration.

Objective 5. Promote World Down Syndrome Day on the 21st March each year.

Objective 6. Actively solicit funds to fulfil the objectives and other specific projects.

DS International also needs to be involved in promoting the United Nations Convention on the Rights of People with Disabilities (UNCRPD) if it is to be a truly international organisation representing people with Down syndrome. We will be drafting position papers on the various articles of the convention. DS International through the world congresses and World DS Day successfully promotes research and practical strategies in the fields of education, health, independence and quality of life. However these strategies are of little relevance where access to education and health care are denied and where our people are destined to live their lives in segregated residential centres. DS International must take its place with other Disabled Peoples Organisations in fighting discrimination everywhere in the world. Being involved in promoting the UNCRPD is essential and timely.

Pat Clarke,

President,
Down Syndrome International
November 2009

Submitting a Paper to Down Syndrome Quarterly

DSQ will publish papers that advance the understanding of Down syndrome in all areas of science, education, health care and practice. Articles must be comprehensible to a broad audience, including researchers, practitioners, and families of children with Down syndrome.

Three categories will be considered for publication:

1. **Research**
   Articles reporting original clinical, educational, psychological, or basic science findings and contributing to the international literature in their respective disciplines. Manuscripts should contain a clearly written abstract, including background, methods, results and interpretation (summarized in tabular format where possible), and discussion concerning application of the findings as they apply to Down syndrome. Suggested length is 2500 words, excluding the abstract, figures, tables, and references.

2. **Practice**
   Articles directed at practicing clinicians and educators. These may include case reports on teachings, brief educational reviews of a focused problem, or short descriptions of innovative programs and preliminary findings. Suggested length is 2500 words.

3. **Review**
   a. Scholarly evidence-based reviews of topics relevant to practice. Systematic reviews should attempt to answer a focused question. Suggested length is 2500 words, excluding abstract, tables, figures and references.

   b. Narrative reviews provide readers with a synthesis of the existing literature in a particular field and are prepared by experts with a comprehensive understanding of the research area. Authors should discuss the application of existing evidence to practice. Suggested length is 3000 words, excluding abstracts, tables, figures and references.

Manuscripts should be prepared either according to the standards set out by the International Committee of Medical Journal Editors (ICMJE), found in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication, or according to the format specified in the Publication Manual of the American Psychological Association (APA) (5th Ed. 2001). All information regarding ethical considerations and manuscript preparation and submission can be found at the ICMJE website: http://www.icmje.org/ or at the APA website: http://www.apa.org/.

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Down Syndrome Research Foundation
+1 604 444 3773
info@dsrf.org