ORIGINAL ARTICLE

Down Syndrome: Neurophysiological Concepts

J of Neurophysiological Monitoring 2024; 2(3): 12-20 ISSN 2995-4886

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KEYWORDS: Down Syndrome; Intraoperative Monitoring; Coherence; Neurophysiology

CITE AS: Norton J, Haughain S, Almubarak S. Down Syndrome: Neurophysiological Concepts. J of Neurophysiological Monitoring 2024; 2(3): 12-20. doi: 10.5281/zenodo.13292884.

ARTICLE HISTORY:
Received: July 09, 2024
Accepted: August 04, 2024.
Available online.

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ABSTRACT

Introduction.
Down syndrome arises from a trisomy of chromosome 21. Neurophysiological aspects of Down syndrome have not been well studied. Subjects often have delayed motor milestones, an increased risk of epilepsy, and an early onset form of Alzheimer's disease.
Methods.
This report describes differences between Down syndrome individuals and neurologically normal control subjects using standard neurophysiological tests, such as motor and somatosensory evoked potentials and coherence between pairs of neurophysiological signals.
Results.
Subjects with Down Syndrome required a smaller voltage to elicit an equivalent motor evoked potential compared to control subjects (174V vs. 650V) and had larger cortical, but not spinal, somatosensory evoked potentials (52mV vs. 4.2mV). Both EEG-EEG and EMG-EMG coherence was higher in Down Syndrome than in control subjects.
Conclusions.
Because the sensory input to the nervous system is controlled between subjects, as evidenced by the consistent spinal amplitude, we believe that the increased amplitude results from supraspinal (thalamic or cortical) differences rather than spinal gating. We hypothesize that these findings represent a novel set of neurophysiological findings and may be due to an altered pattern of cortical excitability, possibly due to an increased presence of gap junctions in cortical cells.

INTRODUCTION

Down syndrome is an inherited genetic condition resulting from an individual inheriting three copies of chromosome 21, trisomy 21. First described in detail by Dr. John Down in 1862 and again in 1866, the genetic cause was identified in 1959 [1]. All sufferers have three copies of chromosome 21, but symptom presentation varies greatly, a characteristic known as mosaicism. Common features include a shorter-than-

average height and a lower-than-average IQ. Atlanto-occipital instability is seen in about 20% of individuals, and epilepsy is seen in 10% of children and up to 50% of adults [2-4]. Over 50% of individuals have vision and/or hearing issues, typically related to end-organ dysfunction rather than CNS disease. Congenital cardiac disease is common, occurring in up to 40% of children [2]. Many individuals develop early-onset Alzheimer's disease. Life expectancy is around 50-60 years. Children with Down syndrome tend to reach motor milestones later than typical children [5]. Scoliosis also occurs in these children [6,7].

Intraoperative spinal cord monitoring is commonly performed during surgical correction of scoliosis and atlanto-occipital instability [8,9]. This will include motor evoked potentials (MEPs) and somatosensory evoked potentials (SSEPs). Both the amplitude of the potential and the current/voltage to generate the potentials are recorded. The size of the potential SSEP reflects the number of cortical cells firing together with a similar orientation and, hence, a similar dipole. Since the skull is highly resistive, a thinned skull would have a larger potential, and a thicker skull would decrease amplitude. Similarly, a thinner skull would tend to reduce the stimulation amplitude required to elicit an MEP. There is no evidence of significantly thinner skulls in Down syndrome.

A method to assess connectivity between neurons or neuronal pathways is to examine the coherence between two signals [10,11]. Coherence can be measured from two electromyography (EMG) signals, electroencephalography (EEG) signals, or any combination of EEG and EMG signals [10]. Coherence is the frequency domain equivalent of cross-correlation and represents the shared drive between a pair of neural signals [12]. To examine connectivity between cortical regions, we measured coherence between electrodes on routine EEGs of patients with well-controlled epilepsy. We compared it with that of other individuals with well-controlled epilepsy. Connections between cortical motor regions and muscles were examined in otherwise healthy Down syndrome individuals and compared with healthy control data.

METHODS

We report observations from a series of seven individuals with Down syndrome who underwent spine deformity surgery with no signs of spinal cord compression or evidence of myelopathy. Additionally, we report EMG-EMG coherence of seven adults with Down syndrome and EEG-EEG coherence of three individuals with epilepsy who were undergoing routine EEG assessment. Local ethical approval was obtained from the University of Saskatchewan.

Evoked Potentials

Down Syndrome individuals undergoing spine deformity surgery with neuromonitoring were consecutively included. Our report includes data from our baseline pre-incision recordings to avoid surgical effects. We reported the amplitude of the cortical and spinal SSEP to median nerve stimulation, averaged across the

right and left sides. Stimulation amplitude was set to be twice the threshold to elicit a muscle twitch (9). The voltage required to elicit a motor reliably evoked potential in the upper limb (Abductor pollicis brevis) is reported. Electrodes were placed at C3' and C4' per our standard protocol [9,13]. Neurologically intact subjects, age, and height matched with adolescent idiopathic scoliosis patients were used as controls (n=7). All recordings were made under general anesthesia using an IV-based approach. Visual inspection of raw and spectral EEG signals was used to determine the depth of anesthesia during the surgical procedures. It was found to be similar between all cases.

Coherence

Non-ictal EEG was routinely recorded from awake (not sleep-deprived) subjects at rest. Data was recorded using XLTEK equipment, filtered at 0.5-50Hz, and amplified. EEG-EEG coherence between C3 and C4 was calculated offline using routines in MATLAB (The Mathworks, USA) based on the Neurospec2 software [14,15] between C3 and C4. EMG recordings were made from surface EMG electrodes placed over the belly of the muscle (first dorsal interosseous and flexor carpi radialis). Signals were amplified (1000x) and filtered (3Hz-3kHz, Neurolog, Digitimer, UK) and sampled on a PC (Spike2, Cambridge Electronic Design, UK) for offline analysis. Subjects performed an isometric contraction of both muscles by holding a tool. EMG-EMG coherence was calculated in the same manner. Each recording was 2 minutes in length in each case. Subjects with epilepsy undergoing EEG recording were used as controls for the EEG portion, and healthy control subjects were used for the EMG portion. The area under the curve and above the 95% confidence limit was measured to obtain the coherence values as described [11].

Statistical Analysis

The statistical analysis was performed in the MATLAB environment. Paired t-tests were used to compare the amplitude of the SSEP components, the stimulation currents, and the voltage required to elicit a threshold MEP. The coherence data was pooled across subjects [16] and compared between groups.

RESULTS

The threshold voltage for eliciting an MEP under anesthesia was significantly lower in Down syndrome subjects than in healthy control subjects (174 vs. 650V, $p<0.05$, paired t-test); Table 1 and the MEPs were similar between the two groups, Figure 1. There were no differences in the anesthetic regimen between the two groups. The stimulation current was set to twice the current required to elicit a thumb twitch. We matched the spinal SSEP amplitudes (3.2 vs 3.4 μV), indicating that the levels of nervous system stimulation were similar between the two groups. In contrast to the spinal SSEP amplitude, the cortical SSEP amplitude was much larger in Down syndrome individuals than in controls (52 vs. 4.2 μV, $p<0.05$, paired t-test).

Measure	Down Syndrome	Control
MEP Threshold (V) N=7	**174±21**	**650±32**
Cortical SSEP Amplitude (μV) N=7	**52±3**	**4.2±0.8**
Spinal SSEP Amplitude (μV) N=7	3.2±0.7	3.4±0.6
EEG Coherence (Hz) 1-4Hz N=3	**2.14**	**0.65**
EMG Coherence (Hz) 15-35Hz N=7	**1.466**	**0.1407**

Table 1. Summarizes our findings for individuals with Down Syndrome and control subjects. The threshold for eliciting an MEP is much lower in the Down syndrome subjects than in the control subjects. The cortical SSEP is significantly larger, while the spinally recorded evoked potential is similar in amplitude between the control and Down syndrome individuals. Both EEG and EMG coherence are significantly higher in Down Syndrome subjects than controls. Bold values indicate statistically significant differences ($p<0.05$, paired t-tests).

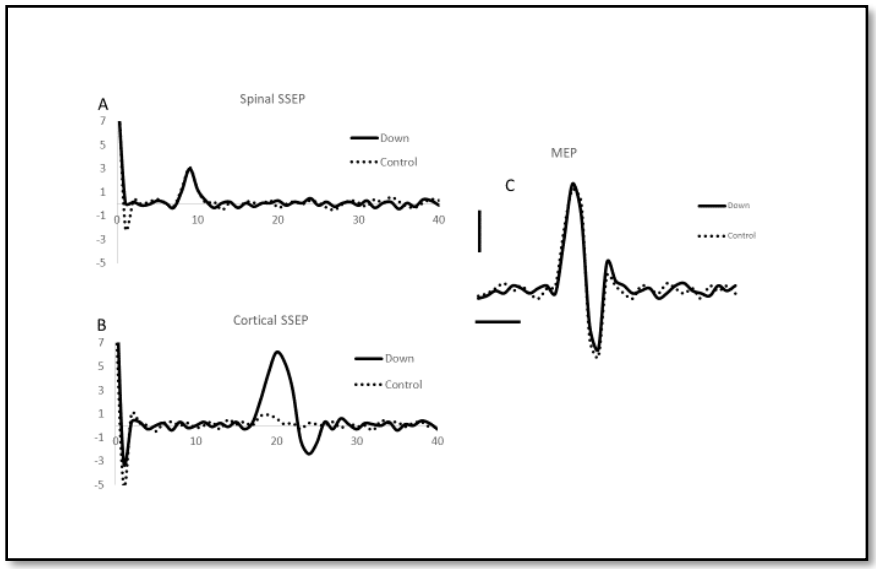

Figure 1. Typical evoked potentials from control and Down Syndrome subjects. 1A shows spinally recorded SSEP traces to left median nerve stimulation. 1B shows representative cortical SSEP traces to left median nerve stimulation. In 1A and 1B, the horizontal axis is time in milliseconds (ms) while the vertical is amplitude in mV. 1C shows representative MEPs from the abductor pollicis brevis at 'threshold' stimulation. Responses are robust and reproducible. The horizontal bar marks 20ms and vertical 30mV.

More coherence between cortical sites was observed during intra-ictal EEG in participants with Down syndrome than in other participants with epilepsy, but this was only observed in the lower frequency Delta band (1-4Hz) (2.14 vs. 0.65Hz, $p<0.05$, paired t-test). EMG-EMG coherence was measured in the seven participants with Down syndrome during isometric contractions of the upper limb and compared to neurologically intact participants. No differences were found in the lower frequencies, but the Beta band (15-35Hz), representing common cortical drive, was 10-fold higher in the participants with Down Syndrome (1.466 vs 0.1407 Hz, $p<0.05$, paired t-test), Figure 2.

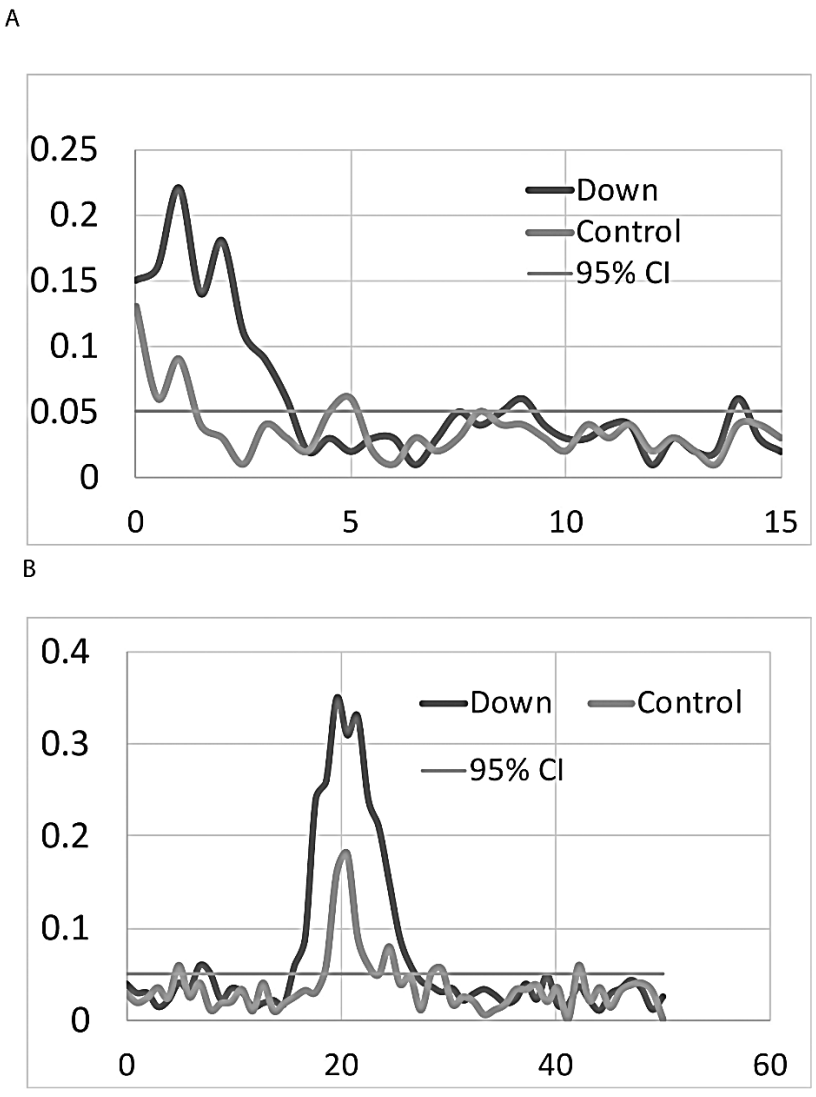

Figure 2. Coherence from A) EEG-EEG and B) EMG-EMG from control subjects (with epilepsy in A) and Down Syndrome individuals. Coherence above the 95% confidence limit is considered significant. EEG-EEG coherence shows a large low-frequency coherence in Down syndrome individuals who do not present in the control group. Similarly, in B) EMG-EMG coherence, although a peak is seen in the control subject, it is smaller than in the Down Syndrome individual.

DISCUSSION

We report differences in neurophysiology between individuals with Down Syndrome and control subjects, including evoked potentials under anesthesia and EMG-EMG and EEG-EEG coherence in awake subjects. The amplitude of the spinally recorded somatosensory evoked potentials was similar between the two groups, suggesting that any differences were in supraspinal sites rather than a result of spinal cord level gating. All the cortical amplitude measurements were significantly different between the two groups. The cortically recorded evoked potential is recorded from the scalp and is the summed result of potentials in many cells [17]. The potential amplitude depends on the number of cells firing synchronously and with the same dipole. Therefore, an increase in amplitude may reflect any of the following events: an increased number of cells firing, a change in the cortical structure that more uniformly aligns the dipoles, and reduced signal gating at the sub-cortical level.

The motor evoked potential is triggered by the electrical activation of pyramidal tract neurons [18]. The threshold for eliciting an MEP recorded in the muscle will depend on the number of pyramidal tract and spinal motor neurons activated. A depolarization in either cell type or a reduction in the tonic level of recurrent inhibition at the spinal level will lead to a reduced threshold in the MEP threshold. Based on the EEG, we assume that the level of consciousness is similar across all patients and is unlikely to alter the MEP amplitude. The latency is similar in all subjects, most likely that of a monosynaptic response. To our knowledge, there is no evidence of hyperexcitability in spinal motor neurons (heightened H-reflexes or F-waves).

Coherence measures the degree of similarity between two signals [19,20]. The EEG coherence between two distinct sites on the scalp may reflect electrical transmission between them. If multiple synapses are involved in the transmission pathway, then coherence is lost because of the variability in the timing of the synapses. Coherence and synchrony may represent similar processes, and previous reports have reported increased delta-band (1-4 Hz) synchrony in the EEGs of Down syndrome individuals [21] and using functional imaging data [22]. Our data support these findings of low-frequency, widespread coupling. Because epilepsy can alter brain structure and connectivity [23], Using epilepsy patients as the control group for the EEG-EEG coherence comparison reduced the risk that the changes we saw were due to epilepsy rather than Down Syndrome.

Coherence between two EMG signals in the beta-band (15-35Hz) is widely believed to represent common cortical input to the signals [10,11]. Our findings of increased inter-muscular coherence (EMG-EMG) in individuals with Down syndrome compared to healthy control subjects suggest that Down syndrome causes increased common cortical drive to the muscles. Common drive may result from increased cortical synchrony or increased connections at the spinal motoneuron level.

Several possible explanations for our findings exist, such as increased cortical excitation, increased cortical inhibition, decreased cortical inhibition, thalamic or cortical structural differences, and increased gap junctions in the cortical layers.

Increased cortical excitability may explain the neurophysiological findings we observed in this study and others previously reported. Increased excitability causes more cells to fire together and leads to both increased coherence and larger cortical potentials. Glutamate is the predominant excitatory neurotransmitter in the cortex, and there is limited evidence of glutamatergic abnormalities in Down syndrome.

Individuals with Down syndrome may have altered cortical inhibition, and both increased and decreased inhibition have been postulated to play a role in epilepsy [24,25]. Instinctively, a lack of inhibition is similar to an increase in excitation and, thus, is a possible cause of the findings we, and others, have described. Increased inhibition may increase the degree of synchronicity [25]. Synchronicity would explain most of our findings, especially our coherence findings. It is unclear why increased inhibition would result in a frequency differential effect on coherence from the increased inhibition [26]. Reduced inhibition in Down Syndrome has been shown using transcranial magnetic stimulation, which may partially explain our findings [24]. Removal of surround inhibition could lead to wider regions of the corticospinal tract being activated. Tonic inhibition, even under anesthesia, may hyper-polarize the cortical cells, and its absence in Down syndrome may bring the cells closer to the firing threshold, thus reducing the MEP threshold and increasing the SSEP amplitude. Short-interval cortical inhibition experiments might shed light on this mechanism [27].

Structural changes in the cortex or thalamus (or both) may also generate neurophysiological findings like those we observed, but we did not find advanced imaging studies in this population. In particular, if there is a more structured arrangement of the cortical cells such that the dipoles are similar, the cortical evoked potentials would be larger, and the threshold for eliciting an MEP may decrease. Gap junctions are physical connections between cells. They are prevalent in neonatal subjects and typically decrease with maturity [28]. Individuals with Down syndrome experience many differences in maturation [2]. Cells connected through a gap junction have a common membrane potential, and depolarization (including those above the firing threshold) will propagate between cells. This would increase the amount of apparent synchrony in the cortex. To date, we do not have evidence to support this theory or to suggest which of the processes described above may be responsible

ACKNOWLEDGMENTS

We are grateful to our subjects. We gratefully acknowledge the feedback and comments from Prof. Monica Gorassini, University of Alberta.

Funding Research funding was provided to SH (studentship) and JN (operating fund) through the College of Medicine, University of Saskatchewan.

Conflicts of interest/Competing interests: The authors declare no conflict of interest.

Aspects of this work were presented at the Canadian Congress of Neurological Sciences in June 2017 and the Annual Meeting of the American Clinical Neurophysiology Society in May 2018.

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