Improvement of social cognition in a Down’s syndrome patient after Bilateral PFC Deep HF-rTMS: A Clinical Case Report

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Case Report

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Abstract

Bilateral PFC Deep HF-rTMS protocol improved social cognition in a patient with Down's Syndrome (DS, also known as Trisomy 21). DS is a genetic disorder originating from the existence of all or part of the third copy of chromosome 21 and is usually associated with difficulties in motor development, expressive language, grammar, speech clarity, number skills, verbal short-term memory etc.

Introduction

Down's syndrome (DS, also known as Trisomy 21), is a chromosomyopathy caused by the existence of all or part of the third copy of chromosome 21. Patients diagnosed with DS face physical and cognitive challenges including physical growth delays, or mild to moderate intellectual disability (Schworer, Hoffman, & Esbensen, 2021). However, there is a belief that their social cognition is somehow not affected, but some do experience difficulties that tend to be significant in those areas (Pavlova et al., 2018). And their intelligence quotation declines as they get older (Roizen & Patterson, 2003). DS shows a deficit in some subcomponents of executive functions as well (Amadó, Serrat, & Vallès-Majoral, 2016).

Social cognition is important to have a fulfilling social and personal life. It is the set of abilities of cognitive nature used in social situations (Harvey & Penn, 2010). Research has indicated that children diagnosed with DS have difficulties in their theory of mind development (Binnie & Williams, 2002; Giaouri, Alevriadou, & Tsakiridou, 2010), showing false beliefs or the appearance of reality. They also show weaknesses in the affective aspect when interpreting facial expressions (Wishart, Cebula, Willis, & Pitcairn, 2007) and recognizing emotions (Kasari, Freeman, & Hughes, 2001; Kasari, Freeman, Mundy, & Sigman, 1995) including fear, anger, and surprise (Hippolyte, Barisnikov, & Van der Linden, 2008).

Concerning executive functions, research seems to point out that components such as inhibition or visual-spatial working memory (Costanzo et al., 2013; Lanfranchi, Baddeley, Gathercole, & Vianello, 2012) are more preserved, while working memory, verbal inhibition, or cognitive flexibility (Lanfranchi et al., 2012; Lee et al., 2011) are more affected.

In this regard, it is necessary to point out that in the last years, there has been an increase in the use of certain techniques to enhance cognitive functions, like non-invasive brain stimulation techniques (NIBS) (Serruya & Kahana, 2008). Which, until recently, is an area that has not been addressed before (Serruya & Kahana, 2008). Hence, these techniques are an advancement in cognitive neuroscience. It provides us with the ability to map causal links between cognition and its neural substrate. And among these techniques, transcranial magnetic stimulation (TMS) can modulate the cortical excitability in target regions and may enhance the cognitive functions that emerge from these regions (Luber and Lisanby, 2014).

Case Report
We present a 38-year-old DS female with DSM-IV TR diagnosis of unspecified psychotic disorder that reports to our unit to have suffered possible clinical regressions related to changes in medication.

She has a hip prosthesis, a congenital dislocation, and had been treated for hyperthyroidism. She had an active life, a good level of autonomy, a cheerful character, was very sociable, and observant of her environment. At the age of 21, she started working in a company with a good adaptation initially, but probably it was a source of stress for her. She began to appear more sluggish, with exacerbation of rituals (e.g., obsession with going to the toilet), less communicative, and apathetic. She was diagnosed with depression with psychotic symptoms since she was disconnected from her environment and commented on things that had not happened.

On psychopharmacological treatment since 2012, initially with sertraline 50 mg, which was changed to fluoxetine due to lack of response. She underwent a neuropsychological assessment in 2013 for suspected cognitive impairment, with an assessment as normal. Treatment with fluoxetine and aripiprazole was replaced by duloxetine (120 mg/day) and reboxetine (4 mg/day). She was very sedated with low doses of aripiprazole or amisulpride, and an attempt is made to withdraw it, but it is restarted because she showed again altered contents of thought.

At the end of 2013, treatment started with low doses of clomipramine, initially combined with lithium. When increasing clomipramine to 10 mg/day, she presented an evident psychomotor block, with explosive reaction when her will was opposed. She seemed more disconnected, with soliloquies. She did not keep the thread of the conversation, did not retain information, showed behavioural rigidity, had no initiative to relate, and did not maintain attention.

Explorations were repeated in mid-2014. There was a marked deterioration of frontal executive functions. Treatment with lamotrigine, low-dose ziprasidone, and fluoxetine was tried. And pimozide. The clinical manifestations persisted, and the response to pharmacological treatment was irregular. She continued to require supervision in daily activities.

In November 2019, she showed a good appearance and good emotional reactivity. The family expressed that she had difficulty expressing herself and tended to keep quiet. She started on Brintellix 10 mg in increasing doses. Objective changes remained minimal. As of 2022, the patient is currently taking Abilify 5 mg/day, Lorazepam 1 mg, Brintellix 15 mg, and Eutirox 75 mg.

During the visit to the clinic, in mid-2022, the family of the patient reported symptoms of anxiety related to certain obsessions, specific fears, a deficit in social cognition and relations to other people. And a variety of symptomatology, including negative psychotic and depressive symptomatology in specific moments. The patient also presented alterations in cognitive control.

We initially performed a brain mapping using a state-of-the-art multichannel EEG sensor (32 channels, Neuroelectrics) to decide if the patient could safely benefit from the Deep High Frequency-repetitive transcranial Magnetic stimulation (HF-rTMS) protocol treatment over the PFC, bilaterally, with preference
to the left hemisphere. Since the DS population has a higher prevalence of epileptic seizures compared to the general population (Altuna, Giménez, & Fortea, 2021; Kats, Roche, & Skotko, 2020; Rahman & Fatema, 2019) we needed to make sure the treatment would be safe for the patient.

The EEG confirmed that there was no risk of an epileptic seizure. The recording was performed at rest with eyes closed. The prior recording showed some diffuse slowing, the marked presence of low-frequency oscillations (mainly delta) in prefrontal areas, and a low level of faster frequency oscillations (alpha, beta, and gamma). The ratio between slow and fast waves was high in all analysed cortical regions. This pattern could be associated with impaired brain function. Hence, it could be explained by different factors. Research has shown that young DS patients can suffer from unexplained cognitive deterioration (Brunelin et al., 2022; Santoro et al., 2020), post-mortem studies indicate that most DS patients had by the age of 40 Alzheimer’s disease neuropathology (Brugge et al., 1994; Hithersay, Hamburg, Knight, & Strydom, 2017), or the cognitive phenotype in DS is defined by deterioration in verbal short-term memory, morphosyntax and explicit long-term memory (Lott & Dierssen, 2010).

The patient underwent a Deep HF-rTMS protocol treatment over the PFC, bilaterally, with preference to the left hemisphere. 21 sessions (5 sessions a week for 3 weeks, followed by 3 sessions a week for 2 weeks) (see Fig. 1). This protocol treatment was performed to enhance cognition. We used an H1 coil with a power of 120%MT and frequency of 18 Hz, focusing on the dorsolateral prefrontal cortex. Once the treatment was concluded, we did a posterior EEG mapping. Based on the EEG results obtained pre- and post-treatment, we did not observe significant differences regarding the activation patterns.

**Clinical Interview results: after treatment, 1 month after, and 2 months after**

After a clinical interview with the patient’s parents, changes in different areas are observed after the neuromodulation treatment. The patient improved in different aspects of cognitive control and social cognition. After the neuromodulation treatment, the patient is more motivated to do things, more communicative, more participative, and more aware of what is happening around her. Likewise, the patient does not shy away from physical contact and her relationship with other people has improved. The patient is more enthusiastic about herself (buying things, implementing activities, etc.). She tolerates dogs and children more. All these changes are noticed more markedly by people outside the family nucleus. On the other hand, the parents, and the caretaker report that the obsessions seemed to have increased and there is difficulty in the articulation of language.

*One month after the end of the treatment*, the patient shows a more elaborated speech. Furthermore, she better structures her thoughts. She can clearly ask for what she wants and deny what she does not want. She shows greater cognitive and behavioural flexibility. Furthermore, she does not behave in such a rigid way as previously reported. Likewise, she is more aware of things and shows more interest. Furthermore, she relates more markedly current aspects with memories. She shows more initiative for things and has increased her motivation for daily activities. She has strengthened her relationship with other people and
shows more empathy. With young children, she shows a lot of interest, which was not a common occurrence before the treatment. Although her speech is longer and more structured (especially in writing), the difficulty in language articulation remains.

Two months after the end of the treatment, the patient maintains the changes observed one month after the treatment. The patient can relate stimuli to each other and apply them in the appropriate context. She has a better understanding of things, relating events and situations better. She shows more initiative for things and has increased her motivation for activities, especially recreational ones. Not only that, but she has strengthened her relationship with other people and is more empathetic.

Discussion

After completing the treatment and conducting the clinical interview with the parents, HD-repetitive TMS on the prefrontal cortex for one patient with DS improved their social cognition. One of the main limitations that we have faced is the fact that we did not use a battery of questions to evaluate social cognition before and after treatment. We based the suggestion of the treatment as well as the results of the same on a clinical interview with the parents: before treatment, one week after the treatment was concluded, one month and two months after the end of treatment. However, since this protocol was mainly done as an experimental one, the process we followed was mainly that of cognitive psychological research. Additionally, clinical interviews have proven to be useful and effective to evaluate the treatment’s results (Swanson, Schwartz, Ginsburg, & Kossan, 1981).

A possible reason for the lack of differentiation between the pre-treatment and post-treatment EEG is that the post-treatment EEG took place 24h after the last TMS session. Hence, the changes in neural excitability could still be underway. Previous research has seen changes in the EEG in the case of epilepsy after treatment (5–20 min after rTMS treatment) and after a month (Starnes et al., 2022). In different studies, the post-treatment EEG (after 1 month) did not show significant effects for the rTMS treatment of depression (Spronk, Arns, Bootsma, Ruth, & Fitzgerald, 2008). Moreover, in the treatment of disorders of consciousness, no significant changes were seen in the EEG immediately after treatment or one week after rTMS treatment (He et al., 2018).

Conclusions

To conclude, for this case, we saw clear indicators reported to us by the family of an improvement in social cognition in a patient with DS. There is still a lack of research body that tackles the possible effects that NIBS can have on populations with developmental disorders. But considering the positive result achieved, non-invasive brain stimulation techniques could be a promising therapeutic tool to improve social cognition in patients with DS.

References


**Declarations**

All authors declare that they have no conflicts of interest.

**Figures**
Figure 1

**Procedure timeline.** Graphic representation of the treatment timeline.