



# Neurophysiological and cognitive effects of Transcranial Direct Current Stimulation in three girls with Rett Syndrome with chronic language impairments

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## ABSTRACT

**Background:** this study was based on both neurophysiological decelerated activity and communication deficits in Rett Syndrome (RTT).

**Aims:** the aim was to examine the neurophysiological and cognitive effects of Transcranial Direct Current Stimulation (tDCS) in three girls with RTT with chronic language impairments.

**Methods and procedures:** we proposed an integrated intervention: tDCS and cognitive empowerment applied to language in order to enhance speech production (new functional sounds and new words). Because maximal gains usually are achieved when tDCS is coupled with behavioral training, we applied tDCS stimulation on Broca's area together with linguistic training.

**Outcomes and results:** the results indicated a general enhancement in language abilities (an increase in the number of vowel/consonant sounds and words and the production and comprehension through discrimination), motor coordination (functional movements), and neurophysiological parameters (an increase in the frequency and power of alpha, beta and theta bands).

**Conclusion and implications:** we assume that tDCS stimulation combined with the cognitive empowerment applied to language can significantly influence a chronic impairment even in genetic syndromes. Our results provide data that support the role of tDCS in fostering brain plasticity and in particular in empowering speech production and comprehension in girls with RTT.

## What this paper adds?

The essential contribution of the study is the demonstration that tDCS stimulation combined with the cognitive empowerment applied to language can significantly influence a chronic impairment even in genetic syndromes. That is, the present study provides evidence that tDCS combined with cognitive empowerment can improve language abilities and motor coordination and foster brain plasticity in girls with RTT. Hence, this study supports the role of tDCS stimulation as a new methodology in the rehabilitation of RTT.

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## 1. Introduction

Rett syndrome (RTT) is a rare, neurodevelopmental genetic disorder that contributes significantly to severe intellectual disability mostly in females worldwide (Bergström-Isacson, Lagerkvist, Holck, & Gold, 2014) although males have been reported (Budden, Dorsey, & Steiner, 2005; Villard, Cardoso, & Chelly, 2000). It is associated with mutations in *MECP2*, a gene located on the long arm of the X chromosome (Xq28) (Amir & Zoghbi, 2000; Sirianni, Naidu, Pereira, Pillotto, & Hoffman, 1998). The severity of impairments depends on not only on genotype but on the extent of X inactivation. *MECP2* encodes the transcriptional repressor methyl-CpG-binding protein 2, a protein involved in the synaptic development and function (Kaufmann, Johnston, & Blue, 2005). Recently it has been discovered that variants which were previously called “congenital” or “early onset epilepsy” are caused by different mutations. It is established that the “congenital” variant, also called the “Hanefeld variant”, is caused by the mutation, *FOXG1*, while the variant with early onset of epilepsy is connected to mutation *CDKL5*, however, *CDKL5* disorder seems to be an independent clinical entity from Rett syndrome although they may be related (Ariani et al., 2008; Evans et al., 2005; Pini et al., 2012; Rajaei et al., 2011).

The course of the disorders may be divided into four characteristic stages. After an apparent normal development during infancy, the girls with RTT go through a period of developmental regression (Fabio, Antonietti, Marchetti, & Castelli, 2009). Once developmental regression begins, the individuals with Rett syndrome usually progress through four stages, early onset deceleration stage, rapid destructive stage, pseudostationary stage, and motor deterioration stage. After the regression most children are unable to walk, talk, or use their hands for functional activities, but there is considerable variability in this regression, mainly determined by genotype (Fabio et al., 2014; Sigafoos et al., 2009). It has become apparent that the phenotypic range of this disorder is much wider than previously thought. Some individuals may have a milder phenotype and retain the ability to walk or speak and others have an earlier onset with more severe features. Those females who have some but not all of the necessary criteria have been categorized as atypical or as one of six variant forms (Hagberg & Witt-Engerström, 1986).

The core of clinical manifestations includes severe linguistic and motor impairments. As for communication abilities, genotype is one of the most important predictors of level of communication. A recent study of Urbanowicz, Downs, Girdler, Ciccone, and Leonard (2015) investigated the relationships between *MECP2* mutation type and speech-language abilities in girls with RTT and reported that girls vary in their use of speech and language, based on their age and severity of regression. These variations are partly explained by genotype. More precisely, the majority of the sample (89%, 685/766) acquired speech-language abilities in the form of babble or words at some point in time. Of those who acquired babble or words, 85% (581/685) experienced a regression in these abilities. Those with a p. Arg133Cys mutation were most likely to use one or more words, prior to (RRR = 3.45; 95% CI 1.15–10.41) and after (RRR = 5.99; 95% CI 2.00–17.92), speech-language regression.

Moreover, Woodyatt and Ozanne (1992) reported that most of the patients with RTT are at a pre-intentional level of development with only a few girls able to signal intentions. Budden, Meek, Henighan (1990) assessed a group of 20 girls with RTT using the *Sequenced Inventory of Communication Development* (1975), and compared the communication abilities of their participants to the stage of their disorder. By then stages II and III of the disorder, communication skills had regressed to the 8–12 month level with no further regression noted as in stage IV Hagberg & Witt-Engerström (1986).

Even if there are variants of RTT called preserved speech or Zappella variants, most individuals with RTT have no speech (Bates, Benigni, Bretherton, Camaioni, & Volterra, 1977). The individual's level of language before regression varies; however, after regression there is seldom speech production, but comprehensive abilities are maintained and may improve (Dahlgren Sandberg, Ehlers, Hagberg, & Gillberg, 2000; Lavås, Slotte, Jochym-Nygren, van Doorn, & Engerström Witt, 2006; Woodyatt & Ozanne, 1997; Zappella, Meloni, Longo, Hayek, & Renieri, 2001).

On the other hand, Burford and Trevarthen (1997) suggested that girls with RTT present higher communication, attitudes, and that their positive orientation to the human face and eyes may facilitate learning. In fact, Fabio, Giannatiempo, Antonietti and Budden (2009) showed that some girls with RTT are often more visual, paying special attention to objects and people, tracking their movements and even showing preferences by means of ‘eye pointing’.

Several studies have recently focused on the relationship between attention, communication and neurophysiological factors and on the quantitative EEG analysis (QEEG) of the empowerment of cognitive processes (Vignoli et al., 2010). In the study of Gorbachevskaya, Bashina, Gratchev and Iznak (2001) QEEG revealed that girls with RTT were characterized by higher levels of theta activity and reduced levels of alpha and beta activity. Grachev (2001) showed that an increased frontal theta activity in girls with RTT was significant and positively related with earlier onset of the disease, reflecting more severe damage to the frontal lobes.

Currently the literature on cognitive rehabilitation and behavioral training in Rett is based on operant conditioning principles (Lovaas and Leaf, 1981; Smith, Klevstrand, & Lovaas, 1995) and includes intervention and implementation in communication (Sigafoos, Laurie, & Pennell, 1996; Watson, Umansky, Marcy, & Repacholi, 1996) which have been implemented in individuals with RTT. Other interventions have focused on the role of the environment and the caregiver (Burford and Trevarthen, 1997; Castelli et al., 2013; Evans & Meyer, 1999, 2001; Fabio et al., 2011; Koppenhaver, Erickson, Harris, McLellan, Skotko, & Newton, 2001; Ryan, McGregor, Akermanis, Southwell, Ramke, & Woodyatt, 2004; Tortora, 2001; Watson, Umansky, Marcy, & Repacholi, 1996) and on the use of special programmes and devices (Skoto, Koppenhaver, Erickson, 2004) including non-verbal training aimed at teaching basic and complex emotion recognition (Hetzroni, Rubin, & Konkol, 2002) in order to understand other people's behavior on the basis of mental reasoning (Antonietti, Castelli, Fabio, & Marchetti, 2008).

Recent investigations (Antonietti, Castelli, Fabio, & Marchetti, 2002; Fabio, Antonietti, et al., 2009; Fabio, Giannatiempo et al., 2009) in which patients with RTT received intensive cognitive rehabilitation using the assessment of non-verbal communication and language precursors showed that they can go beyond the stage of pre-intentional level of development and that it is possible to teach them to understand the issues of subjectivity, starting from simple nonepistemic mental states (emotions, desire-emotion) and

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