Prevention of schizophrenia deficits via non-invasive adolescent frontal cortex stimulation in rats

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Abstract
Schizophrenia is a severe neurodevelopmental psychiatric affliction manifested behaviorally at late adolescence/early adulthood. Current treatments comprise antipsychotics which act solely symptomatic, are limited in their effectiveness and often associated with side-effects. We here report that application of non-invasive transcranial direct current stimulation (tDCS) during adolescence, prior to schizophrenia-relevant behavioral manifestation, prevents the development of positive symptoms and related neurobiological alterations in the maternal immune stimulation (MIS) model of schizophrenia.

Introduction
Characterized by severe alterations in emotion, behavior, and cognition, schizophrenia constitutes one of the most devastating psychiatric afflictions [1] affecting approximately one percent of the population worldwide. Current treatment options include antipsychotic medications as first-line therapy [1]. Unfortunately, not only do these medications often introduce severe side-effects which might even worsen over time, but also a significant proportion of patients fails to respond or only partially responds to available pharmacotherapy [2], highlighting the need for improved treatment options. In this context, also preventive avenues capable of reducing or even completely abolishing the development of schizophrenia need consideration. The growing acceptance that schizophrenia constitutes a neurodevelopmental disorder, in which neuropathological processes gradually evolve over the developmental course and eventually result in behavioral manifestation in the form of psychosis outbreak [3], supports this approach. As for today, few randomized control trials sought to explore prevention options for individuals at high-risk to develop psychosis. Psychological, pharmacological, and nutritional prevention approaches were tested with generally positive outcomes suggesting that a preventive approach might be fruitful [4]; interestingly, results do not support the use of

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antipsychotic medications as a first-line preventive treatment [4]. When considering the potential side-effects of antipsychotics introduced at a highly sensitive period during adolescence during which emotional, social, and hormonal shifts take place, it becomes clear that other, less aggressive preventive avenues would be desirable.

Previously, using the neurodevelopmental maternal immune stimulation (MIS) model of schizophrenia, we demonstrated that continuous electrical stimulation delivered directly to the medial prefrontal cortex (mPFC) of young adolescent rats via invasive deep brain stimulation (DBS) prevented behavioral, brain structural, and neurobiological manifestation of schizophrenia [5]. These remarkable findings pointed to the pivotal role of the prefrontal cortex in the progression of schizophrenia and suggested it might serve as a viable locus for the implementation of preventive neuromodulation approaches/techniques. Obviously, due to its invasive nature, the application of DBS as a preventive measure in the clinical situation, prior to the development of psychosis, is not feasible. To this end, applying neuromodulation to individuals at high-risk of developing psychosis in an attempt to interfere with schizophrenia neuropathological processes would necessitate a non-invasive and safe technique. This prompted us to explore the preventive effects of transcranial direct current stimulation (tDCS) delivered to the PFC. tDCS modulates cortical excitability and neuroplastic processes in a polarity-dependent manner via weak electrical current application [6–9].

We hence subjected offspring of saline and MIS rats between postnatal day (PND) 35 to 47—a period equivalent to human early adolescence—twice a day to 20 min of tDCS delivered to the frontal cortex (FC). Rats from both groups were exposed to either anodal tDCS, cathodal tDCS or sham-stimulation and then left undisturbed until adulthood, i.e., PND 90, when behavioral and neurobiological testing took place (Fig. 1a).

Materials and methods

Computational finite element method (FEM) of young rat tDCS model and a predicted current density/field intensity of frontal cortex stimulation

FEM model analysis predicted a peak current density of 2.09 A/m² and peak field intensity of 4.17 V/m. As expected, average current density and average power dissipation (scaled to 50% of the peak) was higher under the electrode and its periphery. However, spreading was slightly more prominent in the caudal direction—towards the bregma than...
the rostral direction. Maximum average current density (scaled) and average power dissipation (scaled) at the frontal cortex region was ~1.34 A/m² and ~10.30 W/m³, respectively (Fig. 1b and Suppl. Fig. 1).

**Animals**

Rats were housed in a temperature and humidity controlled vivarium with a 12-h light–dark cycle with food and water ad libitum (unless otherwise stated). Experiments were performed according to the guidelines of the European Union Council Directive 2010/63/EU for care of laboratory animals and after approval by the local ethic committee (Regierungspräsidium Dresden, Germany).

**Experimental design**

Wistar rats (Harlan Laboratories) were mated and the first day after copulation was defined as day one of pregnancy. On gestation day 15, dams were given a single injection to the tail vein of either poly I:C (4 mg/kg; Sigma, Germany) dissolved in saline, or saline alone under isoflurane anesthesia [10, 11]. Altogether 12 Batches of saline and 11 Batches of poly I:C rats were generated with an average of 9.75 offspring of which 4.5 were males and an average of 10.72 offspring of which 4.4 were males, respectively. On postnatal day (PND) 21, pups were weaned and housed by sex and litter. On PND 33–34, poly I:C and saline male offspring were randomly divided into three stimulation groups (2 x 3 design): anodal tDCS (with the anode placed over the frontal cortex (FC)), cathodal tDCS (with the cathode placed over the FC) or sham-stimulation (i.e., sham electrode placed over FC) and then surgeries for tDCS electrodes placement were conducted (saline_sham: n = 15; saline_anodal: n = 14; saline_cathodal: n = 13; poly_sham: n = 14; poly_anodal: n = 12; poly_cathodal: n = 11). Anodal/cathodal/sham-stimulation began on PND 35 and was delivered twice a day for 20 min until PND 47. Behavioral and neurobiological analyses were conducted at PND > 90. Behavioral testing was done in the following order: pre-pulse inhibition, sucrose consumption test, social interaction, reversal learning, and amphetamine-induced hyperactivity. Experimenters were blind to the identity of animals when conducting experiments and analysis. Experiments and analyses were conducted by independent researchers.

**tDCS electrode-placement and current delivery**

On PND 33–34 rats received subcutaneous (s.c.) balanced anesthesia (fentanyl-dihydogencitrat 0.005 mg/kg, midazolamhydrochlorid 2.00 mg/kg, medetomidin 0.15 mg/kg) and were then placed in stereotactic frames. Skulls were carefully exposed at the frontal area and a round epicranial electrode holder was placed above the frontal cortices (at 3 mm anterior to Bregma, on the midline) and fixed using dental acrylic cement (Technovit® Heraeus-Kulzer, Hanau, Germany) and superglue. Upon completion, an antagonist cocktail was applied s.c. (naloxone (0.12 mg/kg, Inresa Arzneimittel, Germany), flumazenil (0.2 mg/kg, HEXAL Germany), and atipamezol (0.75 mg/kg, Elanco Animal Health, Germany)). For stimulation, an electrode (3.5 mm²) was connected into the electrode holder filled with 0.5 μl NaCl (0.9%) as conductive medium. Electrodes were connected via cables to an external computer-interfaced constant current generator (STG4008, MultiChannelSystems GmbH, Reutlingen, Germany). Anodal and cathodal stimulation were delivered at an intensity of 50 μA (Current density 14.3 A/m²) twice a day for 20 min in between PND 35 and PND 47. In order to avoid discomfort, stimulation begun and ended with current slowly ramping up and down, respectively, for 10 s. Stimulation continuity was monitored using an amperemeter. Both duration and current density were chosen to approximate parameters commonly used in human conditions proven to be below the threshold for inflammation and neurodegeneration (see refs. [12, 13]).

**Computational model and solution method**

Segmentation of an exemplary magnetic resonance imaging (MRI) scan of a template young rat head into nine tissue masks namely scalp, skull, cerebro-spinal fluid (csf), gray matter, white matter, cerebellum, hippocampus, thalamus, and air was performed using ScanIP software (Simpleware, Exeter, UK) to develop a high resolution (~0.1 mm) MRI derived FEM model. Conductivity values were assigned as, scalp: 0.465 S/m; skull: 0.01 S/m; csf: 1.65 S/m; air: 1x10–15; gray matter: 0.276 S/m; cerebellum: 0.276 S/m; hippocampus: 0.126 S/m; white matter: 0.126 S/m; thalamus: 0.276 S/m; electrodes: 5.99 x 107 S/m, saline 4 S/m, plastic cannula 1x10–15 S/m. All tissue values were based on prior literature [14, 15]. Computer aided design (CAD) models of epicranial electrode, plastic cannula, and glass isomer cement geometries with exact dimensions (from experiment) were first modeled in SolidWorks 2016 (Dassault Systemes Americas Corp., MA, USA), imported into the rat head model, and positioned based on the locations as in the experiment (Fig. 1b, c). The resulting volumetric meshes were later imported into COMSOL Multiphysics 5.1 (COMSOL Inc., MA, USA) to solve the model. The final FEM model was solved for greater than 5,950,000 tetrahedral elements. Electrical simulation was carried out using quasistatic approximation (Laplace equation, V(σ∇V) = 0), where V = potential and σ = conductivity) and the boundary conditions were applied as normal current density at the
exposed boundary of the gold electrode (anode = 50 μA) and ground at the exposed surface of the cathode (adhesive gel based electrode). Other remaining external surfaces of the model were electrically insulated. Predicted current density/field intensity plots and slices were generated, and the 50% of the peak values of average current density and average power dissipation at each slice from bregma to frontal cortex were reported.

**Behavior**

**Pre-pulse inhibition**

PPI is a cross-species phenomenon that measures sensorimotor gating. Reduced PPI reflects gating deficits seen in and relevant to schizophrenia [16]. PPI of the ASR was measured in a sound-attenuated chamber (Startle Response System, TSE, Bad Homburg, Germany) equipped with a wire mesh cage mounted on a transducer-platform and two loudspeakers [10, 17, 18]. Experiments consisted of a 5 min acclimatization phase and the test session. Throughout the experiment, background noise was set at 60 dB sound pressure level (SPL). During acclimatization, animals received five initial startle stimuli (100 dB SPL, white noise, 20 ms). The test session consisted of four different trial types delivered each ten times in a pseudorandom order with an inter-trial interval of 20 to 30 s: startle-pulse alone (100 dB SPL white noise, 20 ms) and three pre-pulses (81/73/69 dB, 20 ms) each followed by a startle-pulse with an inter-stimulus interval of 100 ms. PPI was calculated according to the formula $100 \times (\text{mean ASR of pulse-alone trials}) / (\text{mean ASR of PPI-trials}) - 100 \times (\text{average ASR of pulse-alone-trials})$. For analysis, the following responses were calculated and presented: acoustic startle response (ASR) alone, PPI for each of the pre-pulse intensities separately (81/73/69 dB, 20 ms) and an average PPI response over the three pre-pulse intensities (mean).

**Discrimination reversal (DR)**

DR is a cross-species phenomenon that reflects the ability of an organism to change its behavior in the face of changing contingencies. Abnormally rapid DR is relevant to the positive symptoms of schizophrenia as it indicates an excessive switching [19]. DR was assessed in a T-maze that had a hidden platform (15.5 x 15.5 cm) in one of the arms and was submerged in a swimming pool [5, 19]. On the first day (*position discrimination*) rats were trained to acquire left-right position discrimination with the platform consistently positioned in one of the arms. Rats were allowed to choose between arms. Once entered an arm, a door was lowered. If the correct arm was chosen, the rat was allowed to remain on the platform for 5 s, if the wrong one was chosen, the rat was confined to the arm for 5 s. Thereafter rats were taken to a holding cage for a 10 s inter-trial interval. Training continued until a criterion of five consecutive correct trials was reached. On the next day (reversal), rats were first retrained until the criterion of the position discrimination of the first day was reached, and then trained until reaching the criterion of the reversal of this discrimination, i.e., with the platform located in the opposite arm. The number of trials to reach the criterion was recorded in both stages.

**Sucrose consumption test (SCT)**

The SCT is based on the natural preference of rodents for a sweet solution over water, and decreased preference is considered to mimic anhedonia (decreased ability to experience pleasure/ reduced sensitivity to reward), a core affective state associated with negative symptoms of schizophrenia. 48 h prior to testing, animals were habituated to the individual testing cages and bottles (containing water). Twenty-four hours thereafter, animals were habituated to the sucrose solution (Nestlé, Milchmädchen gezuckerte Kondensmilch, (1:3)) for 30 min in their home cage and subsequently food restricted until time of testing (15 g food available per animal). On the day of testing, animals were placed in the individual cages with free access to the sucrose solution for 15 min. Bottles were weighed before and after testing. The amount of sucrose solution consumed over a period of 10 min after 21 h food restriction was normalized to the individual body weight [20, 21].

**Social interaction**

Social interaction deficits are considered to represent social withdrawal, a core feature of schizophrenia. Social interaction with an unfamiliar social partner was assessed in a dimly lit transparent box measuring 60 x 40 x 40 cm (l x w x h). Sessions were recorded using a video camera while the experimenter remained outside the test room during interactions. One day prior to testing rats were placed in the arena facing each other. Sessions lasted for 10 min. Social behavior was subsequently quantified offline by an experimenter blind to the experimental
condition. The frequency of the following social behaviors was quantified for the experimental rat [22]: Social exploration, divided in anogenital and non-anogenital investigation of the partner (sniffing or licking the anogenital or any part except for the anogenital area, respectively) and approaching the social partner throughout the test arena.

**Neurobiological assessments**

**Amphetamine-induced activity**

Increased locomotor response to amphetamine is considered to mimic the exacerbation of psychotic symptoms in response to amphetamine in schizophrenia [11]. Amphetamine-induced activity was measured in boxes measuring 60 x 40 x 40 cm³. Sessions were recorded using a video camera while the experimenter remained outside the test room during interactions. Analysis was done using EthoVision software. Tests begun with a habituation period to the box, after which rats were injected with amphetamine (Sigma, Germany; 1 mg/kg/mL), and activity was further recorded for 60 min Animals were tracked using EthoVision (Noldus). Distance moved in cm was recorded and analyzed over 10 min time bins.

**Preparation of brains for post mortem neurobiological assessments**

Rats were deeply anaesthetized with a single i.p. injection of pentobarbital (60 mg/kg) and perfused transcardially with cold 4% paraformaldehyde in 0.1 M phosphate buffer, pH 7.4. Brains were dissected from the skulls and postfixed in 10% buffered formalin for 72 h before being snap-frozen in methyl butane with liquid nitrogen between −60 °C and −80 °C and stored at −80 °C until sectioning. Brains were sectioned into 40 μm thick coronal slices. Every 3rd free-floating slice was rinsed several times in phosphate-buffered saline (PBS) and incubated with a polyclonal rabbit anti-parvalbumin antibody (Oncogene Research Products, San Diego, CA, USA, 1:500) in PBS with 0.3% Triton X-100 and 5% normal goat serum overnight at 4 °C as described earlier [24]. Sections were further washed in PBS and incubated overnight at 4 °C with a biotinylated secondary antibody (goat anti rabbit, Vector Laboratories, Burlingame, CA, USA, 1:1,000) and visualized by 3,3'-diaminobenzidine (DAB) after incubation with Vectastain Elite ABC HRP Kit (Vector Laboratories, Burlingame, CA, USA).

Parvalbumin-immunoreactive cells of the right medial prefrontal cortex (prelimbic and infralimbic cortices) between Bregma +3.2 to +2.7 (according to Paxinos and Watson [23] rat brain atlas) were quantified stereologically by a blinded investigator using a Leica DMRA microscope equipped with a Retiga-2000R Color camera and the Stereo Investigator System (MicroBrightField). To enumerate cells, the optical fractionator was used with the following sampling parameters: serial section interval = 3; section thickness = 40 μm; counting frame size = 250,000 μm²; the coefficient of error value (Gundersen, m = 1) reached by the counting was 0.046 ± 0.005.

**Statistical analysis**

Rats from both poly IC and saline dams were randomly assigned to treatments (anodal, cathodal, and sham), no more than 2–3 rats from the same litter were used for each experimental condition. PPI, SCT, SI, immunohistochemistry, and MRI data were analyzed using two-way analysis of variance (ANOVA; factors: phenotype, tDCS) followed by Holm-Sidak post hoc tests if applicable. DR and AIA were analyzed with three-way ANOVA (factors: phenotype,
tDCS, stage/time) followed by Tukey-HSD post hoc tests. Significance was set at $P < 0.05$.

## Results

### Computational finite element method (FEM) of young rat tDCS model and a predicted current density/field intensity of frontal cortex stimulation

FEM model analysis predicted a peak current density of 2.09 A/m$^2$ and peak field intensity of 4.17 V/m. As expected, average current density and average power dissipation (scaled to 50% of the peak) was higher under the electrode and its periphery. However, spreading was slightly more prominent in the caudal direction—towards the bregma than the rostral direction. Maximum average current density (scaled) and average power dissipation (scaled) at the frontal cortex region were ~1.34 A/m$^2$ and ~10.30 W/m$^3$, respectively (Fig. 1b and Suppl. Fig. 1).

### Schizophrenia-related behaviors and neuropathological manifestations prevented by adolescence tDCS

Pre-pulse inhibition (PPI) constitutes a cross-species behavioral phenomenon measuring sensorimotor gating. Reduced PPI is thought to reflect gating deficits observed in and relevant to schizophrenia [16]. As expected, adult offspring to MIS dams (poly_sham) exhibited reduced levels of PPI of an acoustic startle response (Fig. 2a) [5, 10]. Remarkably, adult offspring of MIS rats which received anodal tDCS during their adolescence period exhibited intact PPI (Fig. 2a), reaching inhibition levels comparable to those of control sham treated rats (saline_sham) (Fig. 2a). Interestingly, in offspring of saline rats, anodal tDCS during adolescence led to expression of PPI deficits in later adulthood (Fig. 2a). Two-way analysis of variance (factors: phenotype × tDCS) yielded a significant main effect for 81 db and significant interactions for all pre-pulse/pulse presentations (81/73/69 dB) and its mean (main effect

![Fig. 2](image)
phenotype: $F(1,68) = 5.48, P < 0.05$, interactions: $F(2,68) = 10.31, P < 0.001$; $F(2,68) = 9.59, P < 0.001$; $F(2,68) = 11.96, P < 0.001$; $F(2,68) = 14.53, P < 0.001$, respectively) and was followed by Holm-Sidak post hoc tests ($n$ saline: sham = 11, cathodal = 13, anodal = 14; $n$ poly: sham = 14, cathodal = 10, anodal = 12).

DR reflects the organism’s ability to change behavior in the face of altering contingencies. Also here, as expected, abnormalities in DR in the form of rapid reversal were observed in adult offspring to MIS dams (poly_sham) [5] (Fig. 2b), which is indicative of excessive switching behavior typical for positive symptoms of schizophrenia. We again found that anodal tDCS during adolescence was successful in preventing excessive switching behavior development in MIS offspring, whereas cathodal tDCS yielded no effect on DR performance (Fig. 2b). Three-way analysis of variance (factors: phenotype × tDCS × stage) yielded a significant effect for main factor stage ($F(1,61) = 87.93, P < 0.001$) and a significant stage × phenotype interaction ($F(1,61) = 5.56, P < 0.05$) and phenotype × tDCS × stage interactions ($F(2,61) = 5.04, P < 0.05$), followed by Tukey-HSD. ($n$ saline: sham = 14, cathodal = 11, anodal = 13; $n$ poly: sham = 10, cathodal = 8; anodal = 11).

Reduced PPI and rapid DR are thought to reflect positive symptoms of schizophrenia resulting from a hyperactive mesolimbic-dopamine system [19, 25]. Enhanced mesolimbic dopaminergic neurotransmission is generally characteristic of schizophrenia in the MIS offspring. Two-way analysis of variance (factors: phenotype × tDCS) yielded a significant effect for main factor phenotype ($F(1,71) = 3.93, P = 0.05$) but not for the factor tDCS and no significant interaction between the factors ($n$ saline: sham = 15, cathodal = 13; anodal = 13; $n$ poly: sham = 13, cathodal = 11; anodal = 12) (Fig. 3a).

Similarly, tDCS did not affect deficits in sociability in the MIS offspring as measured by the social interaction (SI) paradigm [22]. Reduced numbers of SI events, i.e., number of approaches to the partner and investigation of its non-anogenitals, were observed in adult poly I:C offspring (poly_sham), reflecting deficits in social behavior. Two-way analysis of variance (factors: phenotype × tDCS) yielded a significant main effect for treatment in the number of approaches ($F(2,65) = 5.24, P < 0.01$) and significant interactions ($F(2,65) = 4.25, P < 0.05$; $F(2,65) = 4.82, P < 0.05$, respectively) followed by Holm-Sidak post hoc tests ($n$ saline: sham = 14, cathodal = 12, anodal = 12; $n$ poly: sham = 13, cathodal = 9; anodal = 11). However, neither anodal nor cathodal tDCS affected deficits in SI in the MIS offspring (Fig. 3b).

Reduction in the number of parvalbumin-expressing cells was observed in the medial prefrontal cortex (prelimbic and infralimbic) of adult poly I:C offspring, reflecting deficits in fast-spiking GABAergic interneurons. Two-way analysis of variance (factors: phenotype × tDCS) yielded a significant effect for the main factor phenotype ($F(1,30) = 4.33, P < 0.05$) ($n$ saline: sham = 6, cathodal = 6, anodal = 6; $n$ poly: sham = 6, cathodal = 6, anodal = 6). Neither anodal nor cathodal tDCS were found to significantly affect reduced levels of parvalbumin-expressing GABAergic cells in the MIS offspring [28] (Fig. 3c).

**Discussion**

Here, we introduce a novel approach for the prevention of schizophrenia-development, i.e., the application of adolescence anodal tDCS.

We were able to show that applying anodal tDCS to the PFC during adolescence, prior to any overt schizophrenia-
related behavioral abnormalities, successfully prevented the manifestation of sensorimotor gating deficits and abnormal rapid reversal. Moreover, enhanced mesolimbic dopaminergic neurotransmission as indicated by abnormal AIA and the enlargement of lateral ventricles volumes were also prevented following focal non-invasive neuromodulation of the PFC.

For our study, we used the neurodevelopmental MIS rodent model of schizophrenia, in which a single injection of the synthetic analog of double-stranded RNA poly I:C during pregnancy elicits a virulent response via the activation of the transmembrane protein toll-like receptor 3 eventually results in neurodevelopmental pathologies in the offspring [29]. This model provides an excellent platform for the assessment of preventive strategies as—in line with the human condition—schizophrenia-relevant behavioral abnormalities first appear in adulthood, whereas brain structural and neurobiological adversities develop gradually and partially precede the occurrence of behavioral deficits [10, 30].

Given the high predictive, face and construct validity of the MIS model, the current study supports the notion that schizophrenia is a neurodevelopmental disorder entailing a critical period in brain-development during which imminent plastic changes may be modulated to affect later behavioral characteristics [3].

In fact, we here show that neuromodulation of the PFC during adolescence hindered the development of behavioral deficits related to the positive and cognitive symptoms. This is in line with previous studies [5] and suggests that during adolescence the prefrontal cortex plays a pivotal role in the development of delayed behavioral manifestation of schizophrenia. Further, the finding that neuromodulation of the PFC during adolescence prevented elevated amphetamine-induced activity suggests our intervention eventually led to normalization of the otherwise enhanced mesolimbic dopaminergic neurotransmission. This is in agreement with the demonstration that DBS to the mPFC affects and even balances subcortical neurochemical alterations [5]. Striatal dopaminergic overactivity has been associated with positive

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**Fig. 3** Schizophrenia-related parameters unaffected by adolescence tDCS. **a** Reduction in SC levels were observed in adult poly I:C offspring, reflecting a reduction in hedonic capacity (anhedonia); Adolescence tDCS yielded no effect on the development of SC. *(n saline: sham = 15, cathodal = 13; anodal = 12; n poly: sham = 13, cathodal = 11; anodal = 12). b** Reduced numbers of SI events, i.e., number of approaches to the partner and *investigation* of its non-anogenitals, were observed in adult poly I:C offspring (poly_sham), reflecting deficits in social behavior. *(n saline: sham = 14, cathodal = 12, anodal = 12; n poly: sham = 13, cathodal = 9; anodal = 11). c** Reduction in the number of parvalbumin-expressing cells was observed in the mediol prefrontal cortex (prelimbic and infralimbic) of adult poly I:C offspring, reflecting deficits in fast-spiking GABAergic interneurons. *(n saline: sham = 6, cathodal = 6, anodal = 6; n poly: sham = 6, cathodal = 6, anodal = 6). Left: bar plots show mean number of parvalbumin cells in the mPFC for each group; Right: representative images of parvalbumin cells in the mPFC for each group. Results are expressed as mean values ± s.e.m.; * = significant vs. respective saline group; # = significant vs. respective sham tDCS group
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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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References


