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1. lékařská fakulta

Autoreferát disertační práce

Neuroanatomical aspects of non-motor effects of deep brain stimulation

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Disertační práce bude nejméně pět pracovních dnů před konáním obhajoby zveřejněna k nahlížení veřejnosti v tištěné podobě na Oddělení pro vědeckou činnost a zahraniční styky Děkanátu 1. lékařské fakulty.

SOUHRN:

Hluboká mozková stimulace subthalamického jádra (DBS STN) představuje standardní součást terapie středních stádií Parkinsonovy nemoci vedoucí k podstatnému zlepšení a stabilizaci hybnosti pacienta. Mezi nežádoucí účinky stimulace patří její vliv na afektivní a kognitivní funkce. Velmi častý je i nárůst tělesné hmotnosti. Mechanismus těchto změn není jasný, ale mohl by souviset s pozicí stimulujícího kontaktu v STN.

Cíle práce: Vzhledem k funkční organizaci subthalamického jádra, kde mediální část je zapojena k limbickému systému, střední část má vztah k asociačním strukturám a laterální část STN k motorickým oblastem mozku, bylo naším hlavním cílem zjistit, zda nárůst tělesné hmotnosti a změna funkce hypotalamicko-hypofyzární osy závisí na poloze stimulujícího kontaktu hluboké mozkové stimulace v tomto jádře. Naším vedlejším cílem bylo ověřit, zda změna funkce hypotalamicko-hypofyzární osy souvisí s pooperačním nárůstem hmotnosti a úzkostností.

Metodika: Studie 1- Hmotnost byla měřena v pravidelných intervalech u 20 pacientů s Parkinsonovou nemocí během 18-ti měsíců po operaci. Poloha stimulující elektrody byla hodnocena na základně vyšetření magnetickou rezonancí mozku (1.5T) s využitím T1 vážené sekvence. Studie 2- Plazmatický kortizol byl měřen u 20 pacientů ze studie 1, nedříve v den zahájení stimulace DBS STN, a poté za 1 a 17 měsíců. Úzkost a úzkostnost byla měřena pomocí dotazníků STAI (State-Trait Anxiety Inventory) 1 rok po operaci.

Výsledky: Studie 1- Zjistili jsme, že vzdálenost aktivního stimulujícího kontaktu od stěny III. mozkové komory signifikantně korelovala jak s nárůstem hmotnosti, tak se zlepšením motorického stavu pacientů měřeným na kontralaterální části těla pomocí UPDRS-III skóre. Studie 2- Po zahájení stimulace DBS-STN došlo k významnému poklesu kortizolu měřeného za 1 a 17 měsíců od operace. U pacientů s alespoň jedním kontaktem více mediálně byl pozorován podstatně větší pokles hladiny plazmatického kortizolu než u pacientů s oběma kontakty laterálně. Nadto, pooperačně stimulací indukovaná nižší hladina kortizolu byla spojena s větší úzkostností a větším nárůstem hmotnosti, což naznačuje možný vliv stimulace na oblast jádra zapojenou do limbického systému.

Závěr: Zjistili jsme, že mediální pozice aktivního kontaktu DBS STN je spojena s větším nárůstem hmotnosti, akcentací úzkostnosti a nižším ranním plazmatickým kortizolem, což naznačuje lokální vliv stimulace na limbické struktury**.**

SUMMERY:

Considering the functional organization within the subthalamic nucleus (STN); limbic, associative and sensorimotor regions residing in the medial, central and later STN respectively, we hypothesized that weight gain may be related to medial localization of stimulation, while motor improvement may be related to lateral localization of stimulation within the STN **(study 1).** We further hypothesized that stimulation close to the limbic and associative part of the STN may be associated with negative impact on limbic system leading to enhanced anxiety and changes in the hypothalamic-pituitary-adrenal axis (HPA)(**study 2).** Therefore, the primary aims our study were to assess changes in body weight **(study 1)** and the hypothalamic-pituitary-adrenal axis (HPA) **(study 2)** in relation to the position of the active stimulating contact within the nucleus. The secondary goals were to elucidate whether morning plasma cortisol changes after the initiation of stimulation are related to postoperative anxiety and weight gain. **Study 1.** Regular body-weight measurements were performed in 20 patients with advanced Parkinson's disease within a period of 18 months after implantation. T1-weighted (1.5T) magnetic resonance images were used to determine electrode position within the STN and the Unified Parkinson's disease rating scale (UPDRS-III) was used for motor assessment. We observed weight gain inversely related to the distance of contacts from the wall of the third ventricle, and patients with at least one contact located medially in the STN experienced significantly greater weight gain than those with both active contacts located laterally. On the contrary, motor improvement was related to the lateral part of the STN. **Study 2.** Plasma cortisol measurements were taken on the day of initiation of bilateral STN-DBS and then repeated after 1 and 17 months in twenty patients with advanced Parkinson's disease. After initiation of stimulation, cortisol levels significantly decreased and cortisol changes after 1 and 17 months strongly correlated with the position of active contact in subthalamic area. Patients with at least one contact localized more medially in the STN experienced a significantly greater decrease of cortisol than those with one or both active contacts localized more laterally**.** Furthermore, lower cortisol levels were strongly associated with higher trait anxiety and weight gain, suggesting a negative impact of STN-DBS on limbic system. Thus, medial position of the active contact is associated with weight gain, cortisol and anxiety changes, corresponding to manifestations of chronic stress and suggesting a regional effect of STN-DBS on adjacent limbic structures.

INTRODUCTION:

Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is currently recognized as a standard and highly effective method for the treatment of motor manifestations of advanced Parkinson disease (PD). Besides motor improvement, non-motor effects of STN-DBS have been reported, such as weight gain and various cognitive, emotional or motivational disturbances(Castrioto, Lhommee et al. 2014). These observations are consistent with research indicating that the STN serves as an important integrative structure for both motor and limbic processing(Baunez, Yelnik et al. 2011). Furthermore, the clinical effects of stimulation on motor symptoms have been shown to depend on the position of the active electrode within the STN in a manner that reflects the functional organization and connectivity of the STN(Hamel, Fietzek et al. 2003, Herzog, Fietzek et al. 2004). Extensive research in recent years has further revealed the very close clinical and neurobiological relationship among decision-making, body-weight regulation, the reward system and fear-stress circuits controlling the hypothalamic-pituitary-adrenal (HPA) axis (Berridge 2009, Dallman 2010). Therefore, we elected to investigate possible impact of STN-DBS on weight gain, anxiety and the endocrine system.

AIMS OF THE STUDY:

A. Considering the spatially distributed organization of the STN with limbic connectivity predominately in its medial part, and sensorimotor connectivity in its lateral part, the aim of the first study was to assess whether weight gain and motor improvement observed in PD patients treated by STN-DBS is dependent on the active electrode contact position in the STN, particularly with respect to the mediolateral direction.

B. As we previously observed a persisting decrease of morning cortisol plasma levels with the initiation of chronic stimulation (Novakova, Ruzicka et al. 2007, Ruzicka, Novakova et al. 2012), we further focused on the possible impact of STN-DBS on the endocrine system. Thus, the aim of the second study was to assess whether changes of plasma levels of morning cortisol depend on the position of the active electrode contact in the STN, which would corroborate the heterogeneity of this nucleus and confirm the impact of DBS on the HPA axis.

C. As STN-DBS may also influence the HP axis indirectly via the fear-stress circuits of the limbic system, the secondary aims were to elucidate whether morning plasma cortisol changes after initiation of stimulation are associated with postoperative anxiety and weight gain.

HYPOTHESIS:

1. We hypothesized that while weight gain would be associated with the medial contact site of STN stimulation, motor improvement would relate to stimulation in the lateral part of the STN.

2. We hypothesized the cortisol decrease would depend on the position of the stimulation contact in the medial (limbic) part of the STN.

3. We hypothesized that DBS-related cortisol decrease would be accompanied by an increase of anxiety and weight gain.

METHODS:

Study 1: Regular body weight measurements were made on the day of surgery and one, two, four, six, twelve and eighteen months after electrode implantation in 20 patients with advanced PD (6 women, 14 men; mean age 56.6±(SD)5.8 years; disease duration 13.2±4.5 years). Motor status was evaluated using the motor subscore of the Unified Parkinson's Disease Rating Scale (UPDRS-III). Magnetic resonance images were acquired at 1.5 T on a Siemens Avanto system (Siemens, Erlangen, Germany) in each patient approximately one year after DBS implantation. All four contacts (0,1,2,3) of the DBS electrode produced well-defined susceptibility artifacts on the T1-MPRAGE image in each patient. While the coordinates of contacts 0 and 3 were established directly from the center of the distal and proximal artifacts using MRIcro 1.40 software (www.cabiatl.com/mricro), the coordinates of contacts 1 and 2 were calculated. The x-coordinate of each contact was measured from the wall of the third ventricle, whereas the y- and z-coordinates were measured from the midcommisural point.

Study 2: The first plasma cortisol sample was taken in the morning on day of bilateral STN-DBS initiation (TIME 0). Further samples were taken at one month (TIME 1) and at 17 months (TIME 17) after STN-DBS initiation. Two neuropsychological tests were fully performed in a subgroup of 15 patients prior to implantation and more than one year following implantation (15.7 ± 2.6 months). The State-Trait Anxiety Inventory (STAI) was used to assess the severity of anxiety preoperatively and approximately one year after surgery. Body weight measurements were made on the day chronic STN-DBS (TIME 0) was initiated and longitudinally during each routine visit after 1, 3, 5, 11 a 17 months.

RESULTS:

Study 1: The maximum change in body weight in the eighteen-month period after implantation was on average +6.9kg±4.5kg (–0.3 to +18.3kg) and was strongly significant ($T=6.6$, $p<10^{-5}$) (Figure 1). In individual patients, the maximum weight gain correlated inversely along the x-axis with the distance of the active contact from the wall of the third ventricle in the left hemisphere ($r=-0.48$, $p<0.05$), right hemisphere ($r=-0.50$, $p<0.05$), and in pooled data ($r=-0.55$, $p<0.01$) if only more medial active contact regardless to hemisphere was considered (Figure 2). In addition, the hemi-body UPDRS-III subscores in sON condition inversely correlated with the distance of the contralateral active contact from the wall of the third ventricle in the mediolateral direction ($r=-0.42$, $p<0.01$). Patients with at least one active contact within 9.3 mm of the wall of the third ventricle demonstrated significantly greater weight gain (9.4±4.4 kg, N=11) than those patients with both contacts located more laterally from the wall (3.9±2.7 kg, N=9) (GLM, factor BORDER: $F=16.1$, $p<0.001$)

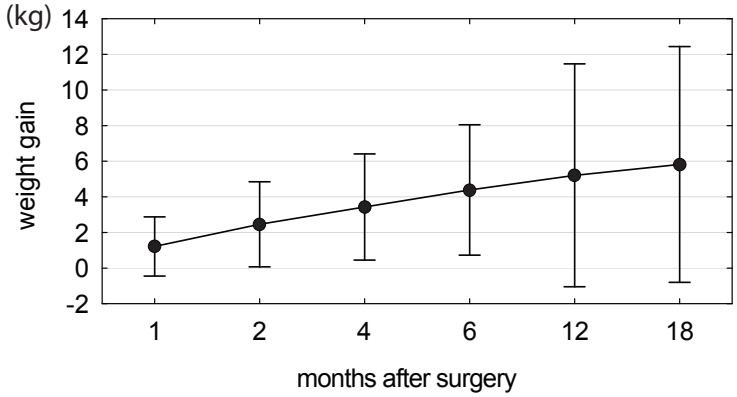

FIGURE 1

Mean changes in weight after implantation in 20 patients with Parkinson's disease. Body weight gradually increased during the study period. Weight gain represents the difference in weight (±SD) compared to the preoperative state.

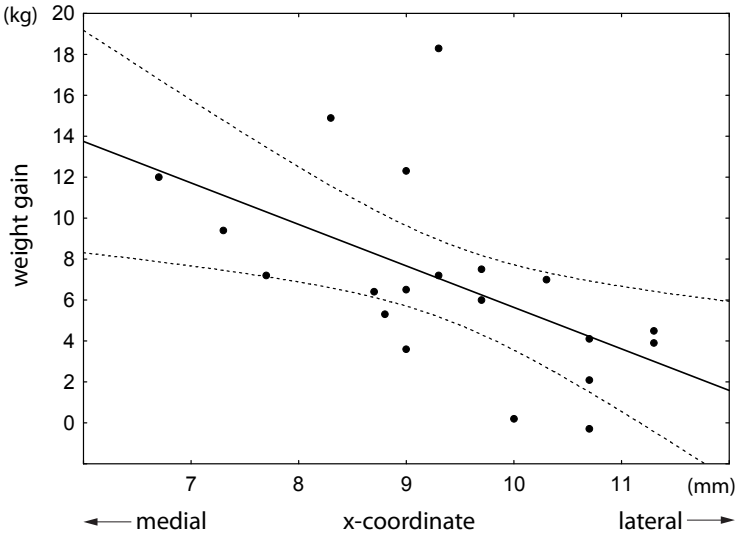

FIGURE 2

Weight gain in 20 patients with Parkinson's disease in relation to the mediolateral position of the active contact with bilateral STN-DBS ($r=-0.55$, $p<0.01$). Only one active contact (more medial contact from both hemispheres) was used in each patient. The x-coordinate represents the distance of the active contact from the wall of the third ventricle. Each millimeter in the medial direction was associated on average with a 1.6-kg increase in body weight. Dotted lines denote the 95% confidence interval of the regression line.

Study 2: Using RM-GLM analysis, the change in *cortisol* over TIME in response to STN-DBS was significant (F= 6.81, p=0.004). The only significant interaction was between POSITION (x-axis) and TIME (F= 6.28, p=0.005). With the additional RM-GLM analysis adjusted for the confounding effects (AGE, PD duration, LEDD change, UPDRS change, stimulation intensity STIM), the interaction of POSITION (x-axis) and TIME remained significant (F=6.5 p=0.007). None of other factors or interactions were significant in either of the two analyses. *Cortisol* changes (TIME 0-1, TIME 0-17) correlated inversely with the distance of the active contact from the wall of the third ventricle in the mediolateral direction (x-axis), calculated as the mean of the x-coordinates of the left and right hemispheres (TIME 0-1: r=0.59, p=0.006; TIME 0-17: r=0.71, p=0.0004; Figure 3). The correlation remained significant regardless of calculation method of the x-coordinate. While *state-anxiety* and *BDI* scores did not change throughout the study, *trait anxiety* became significantly worse one year after surgery compared to the pre-operative state, increasing from 39 ± 8.8 to 47 ± 10.5 (T=3.13, p=0.01). When modeling the cortisol level with the RM-GLM restricted to the group of patients in which anxiety was assessed, we observed a significant trait ANXIETY versus TIME interaction effect (F=7.03, p=0.004; Figure 3-A). Post hoc analyses revealed significant differences in cortisol levels in TIME 17 only (p= 0.003). Using Pearson analysis, postoperative trait-anxiety inversely correlated with cortisol levels in TIME 17 (r=-0.70, p=0.004).

Finally, for weight gain the RM-GLM showed a significant effect of ANXIETY (F=5.87, p =0.03) and ANXIETY versus TIME interaction (F=5.03, p=0.002). Differences in weight gain assessed with Fisher post hoc tests were significant in TIME 5 (p=0.02), TIME 11 (p=0.009) and TIME 17 (p=0.001).

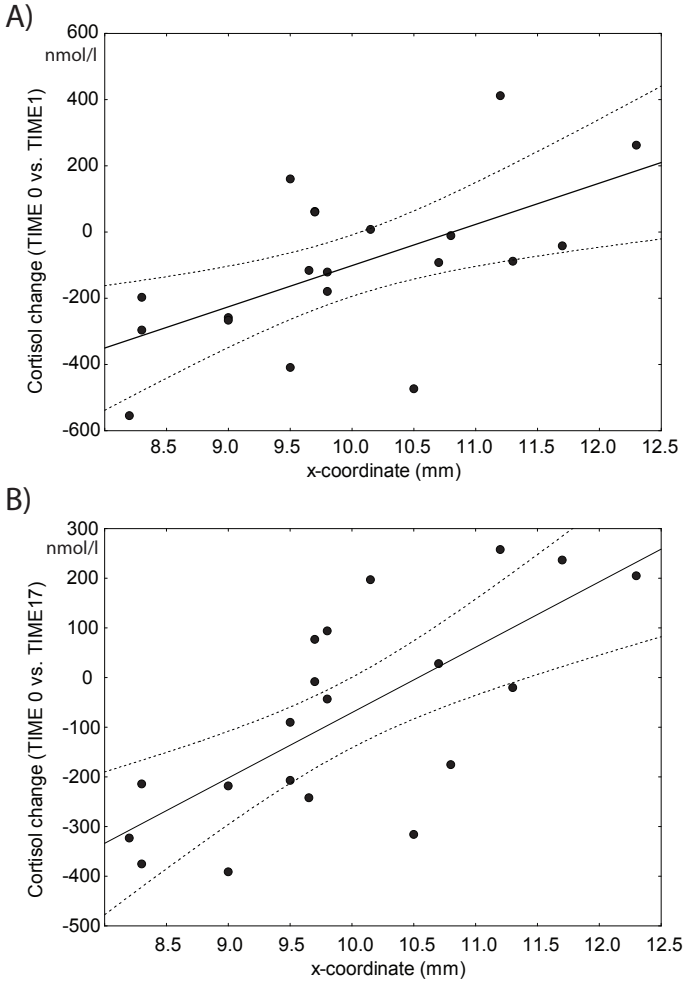

FIGURE 3
Morning plasma cortisol changes in the 1st (A) and 17th (B) month of stimulation relative to prestimulation state in relation to the mediolateral position of the active contact in bilateral STN-DBS (A - 1st month: p=0.006, r=0.59; B - 17th month: p=0.0004, r=0.71). The x-coordinate represents the distance of the active contact from the wall of the third ventricle. Dotted lines denote the 95% confidence interval of the regression line.

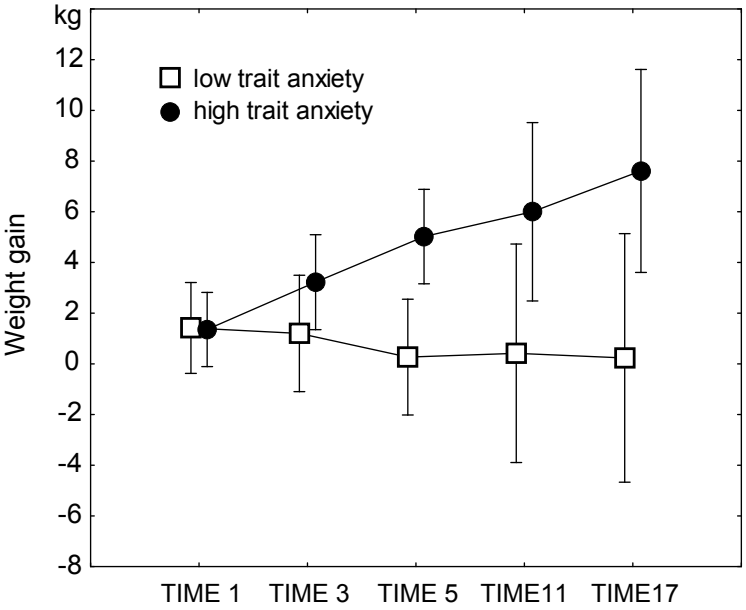

FIGURE 4

Weight gain over the period of the study in relation to anxiety. From 5th month after initiation of the STN-DBS, patients with higher trait anxiety experienced significant greater weight gain than patients with lower anxiety (Fisher post hoc test: at 5th month, p=0.02; 11th month, p=0.009; 17th month, p=0.001).

DISCUSSION

Study 1: We observed weight gain inversely related to the distance of the contacts from the wall of the third ventricle (Figure 1), and patients with at least one contact located medially in the STN experienced significantly greater weight gain than those with both active contacts located laterally. Thus, our results are consistent with the hypothesis that STN-DBS exerts a regional effect on adjacent structures involved in energy balance. Similar to other studies(Hamel, Fietzek et al. 2003, Herzog, Fietzek et al. 2004, Godinho, Thobois et al. 2006), we found an inverse correlation between unilateral motor outcome (measured for rigidity, akinesia and tremor using hemi-body UPDRS-III subscore) and contralateral position of the active contact. Thus, patients with the lowest motor score (best motor condition) had contacts located more laterally from the wall of the third ventricle. Such results most likely reflect the internal organization of the STN with the sensorimotor part located dorsolaterally in the nucleus(Hamani, Saint-Cyr et al. 2004). In conclusion, our findings support the hypothesis that weight gain in PD patients treated by STN-DBS may, at least in part, result from the regional effect of stimulation on adjacent structures involved in the central regulation of energy balance or reward**.**
Study 2: We also observed that the initiation of STN-DBS was associated with morning cortisol changes in close relation to the mediolateral position of the active electrode in the STN (Figure 3). Thus, the present findings are consistent with the hypothesis that STN-DBS exerts influence on the HPA axis in relation to the mediolateral position of the stimulating contact. In agreement with previously published work (Chang, Li et al. 2012)postoperative trait anxiety significantly worsened in our study. Furthermore, we observed that patients with higher postoperative trait anxiety had one of two active contacts located more medially in the STN and showed significantly lower morning cortisol than those with lower anxiety. Thus, we may speculate that stimulation of medial areas of the STN acts on the

HPA axis analogously to chronic stress. Finally, we observed that weight gain was closely associated with anxiety as well as with cortisol levels in the present study. Our findings are broadly consistent with a number of studies highlighting the role of anxiety and chronic stress with overeating, enhanced reward processing and obesity (Dallman 2010)

CONCLUSIONS

1. We observed that weight gain inversely related to the distance of the contacts from the wall of the third ventricle (Figure 3), and patients with at least one contact localized medially in the STN experienced significantly greater weight gain than those with both active contacts localized laterally (Figure 5). Thus, our results are consistent with the hypothesis that STN-DBS exerts a regional effect on adjacent structures involved in food intake or energy balance.

2. We found inverse correlation between the unilateral motor outcome (measured for rigidity, akinesia and tremor using the hemi-body UPDRS-III subscore) and the contralateral position of the active contact (Figure 4). Thus, patients with the lowest motor score (best motor condition) had contacts localized more laterally from the wall of the third ventricle. Such results most likely reflect the internal organization of the STN with the sensorimotor part localized dorsolaterally in the nucleus.

3. We observed that the initiation of STN-DBS was associated with morning cortisol changes in close relation to the medio-lateral position of the active electrode contact in the subthalamic nucleus. Patients with at least one contact localized more medially in the STN experienced a significantly greater decrease of cortisol than those with one or both active contacts more laterally. Thus, the present findings are consistent with the hypothesis that the STN-DBS exerts influence on the HP axis in relation to the mediol-lateral position of the stimulating contact.

4. We observed that patients with higher postoperative trait anxiety had one of two active contacts localized more medially in the STN (Figure 7) and showed significantly lower morning cortisol than those with lower anxiety (Figure 8). Thus, we may speculate that the stimulation of medial areas of the STN acts on the HP axis in a similar manner as chronic stress.

5. We found that patients with higher anxiety and lower cortisol increased their body weight more than those with lower anxiety (Figure 9). Our findings are broadly consistent with a number of studies highlighting the role of anxiety and chronic stress in overeating, enhanced reward processing and obesity.

Seznam publikací doktoranda v tomto uspořádání:

1. publikace, které jsou podkladem disertace

a) s impact factorem

Serranova, T., Sieger, T., **Růžička, F.**, Vostatek, P., Wild, J., Štastná, D., Bonnet, C., Novák, D., Růžička, E., Urgosik, D., Jech, R., 2014. Distinct Populations of Neurons Respond to Emotional Valence and Arousal in the Human Subthalamic Nucleus. Submitted to Proceedings of the National Academy of Sciences of the United States of America.

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b) bez IF 0

2. publikace bez vztahu k tématu disertace

a) s IF

Sieger, T., Bonnet, C., Serranova, T., Wild, J., Novak, D**., Ruzicka, F**., Urgosik, D., Ruzicka, E., Gaymard, B., Jech, R., 2013. Basal ganglia neuronal activity during scanning eye movements in Parkinson's disease. PloS one 8, e78581.**IF- 3.73**

Jech, R., Mueller, K., Urgosik, D., Sieger, T., Holiga, S., **Ruzicka, F**., Dusek, P., Havrankova, P., Vymazal, J., Ruzicka, E., 2012. The subthalamic microlesion story in Parkinson's disease: electrode insertion-related motor improvement with relative cortico-subcortical hypoactivation in fMRI. PloS one 7, e49056. **IF- 3.73**

b) bez IF 0

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