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Does arousal interfere with operant conditioning of spike-wave discharges in genetic epileptic rats?

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Summary One of the ways in which brain computer interfaces can be used is neurofeedback (NF). Subjects use their brain activation to control an external device, and with this technique it is also possible to learn to control aspects of the brain activity by operant conditioning. Beneficial effects of NF training on seizure occurrence have been described in epileptic patients. Little research has been done about differentiating NF effectiveness by type of epilepsy, particularly, whether idiopathic generalized seizures are susceptible to NF. In this experiment, seizures that manifest themselves as spike-wave discharges (SWDs) in the EEG were reinforced during 10 sessions in 6 rats of the WAG/Rij strain, an animal model for absence epilepsy. EEG's were recorded before and after the training sessions. Reinforcing SWDs let to decreased SWD occurrences during training; however, the changes during training were not persistent in the post-training sessions. Because behavioural states are known to have an influence on the occurrence of SWDs, it is proposed that the reinforcement situation increased arousal which resulted in fewer SWDs. Additional tests supported this hypothesis. The outcomes have implications for the possibility to train SWDs with operant learning techniques.

Introduction

Neurofeedback (NF) is a behavioural treatment for several mental and behavioural disorders, and considered an alternative or additional treatment to medical treatments of epilepsy. The origin of NF in the field of epilepsy dates back to the early seventies of the last century when it was demonstrated in cats that the sensorimotor rhythm (SMR) could get under operant control (Wyrwicka and Sterman, 1968) and that SMR trained cats had elevated seizure thresholds

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(Sterman, 1972). Next, SMR training proved to be effective in epileptic patients with poorly controllable seizures (Cott et al., 1979; Sterman and Egner, 2006). Later, studies with patient groups (Lantz and Sterman, 1988; Andrews and Schonfeld, 1992) and meta-analyes (Sterman, 2000; Tan et al., 2009) verified the effectiveness of SMR training as a treatment for epilepsy. Others demonstrated that volunteers and patients can be trained to improve self-control over slow cortical potentials (SCP) (Elbert et al., 1979) and that SCP training might be effective as adjunctive treatment in drug-refractory epilepsy patients (Birbaumer et al., 1991; Rockstroh et al., 1993; Kotchoubey et al., 1996, 2001).

Most studies about the efficacy of NF employ subject groups with mixed seizure types, with partial epilepsies being preponderant (Monderer et al., 2002). As far as we know, no study has been published yet that systematically investigated whether efficacy of NF training is dependant of seizure type, including absences. Although absence epileptic patients were included in the Kotchoubey et al. (2001) study, success of the treatment has not been differentiated by seizure type. The reason for the absence of such studies might most often be that large homogenous patient groups are not readily available.

Experiments employing animal models provide the possibility to overcome this problem. Animal experiments have additional advantages: they permit control of possibly confounding factors such as genetic variability (by using inbred strains), age, age of onset, medication, and environmental conditions including upbringing and learning history. Furthermore, uncontrollable factors that might exert great influences on efficacy outcomes in humans e.g. expectancies that mediate the placebo effect (Kirsch, 1997) play a less significant role in animal experiments.

The WAG/Rij strain is a valid animal model for human absence epilepsy (Coenen and van Luijtelaar, 2003; Depaulis and van Luijtelaar, 2006). Clinical features of rats from this strain resemble clinical features in humans with absence epilepsy. The EEG of a WAG/Rij rat during a seizure also has the typical Spike-and-Slow-wave pattern (Sitnikova and van Luijtelaar, 2007), though the frequency at which spikes and waves occur during a discharge train is 7—11 Hz in comparison to 2.5—4 Hz in humans; but there is no reason why the frequency should be the same across species. Spike-wave discharges (SWDs) in both species are also accompanied by a decrease of consciousness, as was revealed by outcomes of visual and auditory evoked potential studies, and in time estimation tasks. The evoked potentials made during SWDs mimicked most those of slow-wave sleep (when the level of consciousness has decreased) and the occurrence of SWDs influenced the accuracy of the estimation of time elapsed in both species (Meeren et al., 2001; van Luijtelaar et al., 1991a,b).

The aim of this study is to investigate whether NF can be utilized to alter the frequency of SWD occurrences in WAG/Rij rats. It will be tried to bring SWDs under operant control by providing the rats with incentives contingently after SWD onsets, thus reinforcing SWDs. It is expected that the number of SWDs will increase with conditioning training and will be higher than the number of SWDs that occurred spontaneously during a previous (non-reinforced) baseline measurement. To test whether the change in frequency of SWD occurrences achieved by reinforcement remains stable in non-reinforced sessions, the number of SWDs during a post-measurement will be recorded as well.

Although the increase of the number of SWDs occurrences has no clinical application, we chose for increasing rather than decreasing SWDs, because the primary aim is to demonstrate if direct operant control of SWDs is possible at all. We did not choose to try to decrease the number of SWDs for three reasons. First, using punishment as a mean to decrease SWDs is no option, because it is ethically questionable and has unwanted side-effects including emotional responses like fear and aggression (Azrin and Holz, 1966). Second, the idea of reinforcing SWD-free periods is not feasible, because the total time that the rats are having SWDs is small compared to the total seizure-free time, which would require rewarding them almost continuously. Third, our study design is very similar to the design employed by Wyrwicka and Sterman (1968), which has proven to be effective. In both cases, a distinctive and easily identifiable EEG pattern with moderate frequency of occurrence was chosen for contingent reinforcement.

Methods

Animals and surgery procedure

Six male WAG/Rij rats, age 9 months, body weight between 302 and 341 g, bred and raised at the Biological Psychology Department of the Radboud University Nijmegen, were used as experimental subjects. Before surgery, rats were housed in pairs in standard cages with cage enrichment (Enviro Dry®) and a light—dark cycle of 12/12 h with white light on at 8 am. Rats had unrestricted access to food (standard rodent chow) and water before and during the experiment. Rats were handled before surgery and before the first EEG recording.

The experiment and its protocol were approved by the Animal Ethics Committee of the Radboud University Nijmegen.

Rats were implanted with a tripolar (Plastics One, Roanoke, VA, USA; type: MS333/2a) and a bipolar (type: MS303/2-A) stainless steel electrode set. Bare electrode wires' diameter was 0.2 mm, surrounded by 0.03 mm polyimide insulation with only the tip of the wires dismantled. Electrodes were implanted epidurally through circular holes in the skull (0.8 mm diameter for single wires of the tripolar electrode set; wires of the bipolar set shared one hole of 1.2 mm). The location of the bipolar electrode wires were 0.5 mm apart from each other at AP −1.8, L −3.2 (all coordinates in mm relative to bregma. AP = anterior/posterior; positive values: more anterior. L = lateral; positive values more left). The bipolar set was not used in this experiment. The location of the tripolar electrode wires were AP +4.7, L −1.7, used as ground; AP −1.8, L +3.2 (sensorimotor cortex); and above the cerebellum, not further specified. Differential EEG was measured between the last two electrodes. Anaesthesia was induced by Isoflurane (Nicholas Piramal (I) Limited, London, UK). Before surgery, rats were medicated with 0.1 ml atropine sulphate and 0.12 ml Rimadyl® (diluted; Vericore Ltd, Dundee, UK). Lidocaine was used as local analgesic. Body temperature was monitored and kept constant by a heating pad. Four stainless steel screws were attached to the skull to hold the electrode sets fixed to the skull by dentist's cement (Simplex Rapid; Association Dental Product Ltd, Purton, Swindon, Wiltshire, UK). 24 and 48 h after surgery rats were medicated again with 0.12 ml Rimadyl®.

After surgery, rats were housed individually in standard cages and a light—dark cycle of 12/12 h with white light on at 9 pm. Rats had unrestricted access to food and water. Rats had a 2-week recovery period before the first recording session. Cage enrich-