Treating severely brain-injured patients with apomorphine: study protocol for a double blind randomized placebo-controlled trial using behavioral and neuroimaging assessments

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Summary for lay people: Patients who survive coma may develop disorders of consciousness. Treating these patients to improve recovery is extremely challenging. Apomorphine, a drug which stimulates dopamine neurons, exhibits promising clinical effects and safety in preliminary studies. However, its efficacy for the recovery of consciousness in large studies and its neural mechanisms remain to be definitely demonstrated. This trial aims to quantify the efficacy of apomorphine in treating patients with disorders of consciousness and to identify the brain networks it targets, using standardized clinical scales and advanced brain imaging techniques. Confirmatory results would open new and much needed therapeutic options for brain-injured patients.

Background: Patients who survive severe brain injury may develop chronic disorders of consciousness. Treating these patients to improve recovery is extremely challenging because of the absence of international guidelines and scarce therapeutic options (Schnakers and Monti, 2017).

Among pharmacological treatments, apomorphine, a potent direct non-specific dopamine agonist with a high affinity for D2 receptors, has exhibited promising behavioral effects and safety of use in small-sample pilot studies (Fridman et al., 2009, 2010). However, despite the improvement compared to historical data, the lack of a control group could not eliminate the possibility that the effect was a result of spontaneous recovery, and the true efficacy of apomorphine for the recovery of consciousness remains unclear (Gosseries et al., 2014). In addition, the underlying neural mechanisms of this treatment are still unknown. An upregulation of central thalamic activity through a modulation of the anterior forebrain mesocircuit has been proposed as a possible explanation (Schiff, 2010a, 2010b) but the absence of neuroimaging and neurophysiological data prevent definitive confirmation. This clinical trial aims to 1) verify

and quantify the efficacy of apomorphine subcutaneous infusion in patients with disorders of consciousness, 2) better identify the rate and the phenotype of responders to treatment, 3) evaluate tolerance and side effects occurrence in this specific patient population and 4) investigate the neural networks underlying its modulating action on consciousness using multimodal outcome measurements.

Methods/design: This study is a prospective double-blind randomized placebo-controlled trial. Forty-eight patients diagnosed with disorders of consciousness (i.e., unresponsive wakefulness syndrome and minimally conscious state) will be randomized to receive a 30-day regimen of either apomorphine hydrochloride or placebo via daily 12-hour subcutaneous infusions. Patients will be monitored at baseline 30 days before initiation of therapy, during treatment and for 30 days after treatment washout, followed by a two-year remote follow-up. In an initial study phase, up to six patients will be treated in an open-label fashion.

Behavioral outcome measures will include weekly assessments using standardized scales such as the Coma Recovery Scale – Revised (CRS-R) (Giacino et al., 2004) and the Nociception Coma Scale – Revised (NCS-R) (Chatelle et al., 2012) during the inpatient phase. Tolerance and safety of use will be monitored using a specifically designed Adverse Events Questionnaire filled weekly by the referent physician, from treatment initiation to the end of the inpatient phase. Long-term behavioral follow-up will be performed at 6, 12 and 24 months post-treatment by telephone interview using the Glasgow Outcome Scale – Extended (GOS-E) (Levin et al., 2001) as well as phone-adapted versions of the CRS-R and the Adverse Events Questionnaire.

Neurophysiological and neuroimaging measures will complement clinical evaluations and provide data on brain activity. Resting-state high-density electroencephalography (EEG) will be acquired weekly during the whole inpatient phase. In addition, participants will be assessed before and after treatment with Magnetic Resonance Imaging (MRI), Positron Emission Tomography (PET), EEG during auditory paradigms and 24-hours EEG recordings.

To measure changes in circadian rhythm, body core temperature (Matsumoto et al., 2013) and body movements (Cruse et al., 2013) will be recorded with non-invasive portable devices throughout the whole duration of the inpatient phase (Figure 1).

Statistical analyses will be performed blindly to detect changes in behavioral status, circadian rhythmicity, brain metabolism and functional connectivity both at the individual level (comparing before and after treatment) and at the group level (comparing the apomorphine and the placebo arms). Behavioral response will be determined by changes of diagnosis using the CRS-R, and further analyses will also look at changes between the non-responding and the responding patient subgroups. Age, gender, etiology, time since injury and diagnosis will also be included as regressors.

Hypotheses: Based on the mesocircuit hypothesis, we postulate a modulation in the activity of the network's anterior forebrain structures following administration of apomorphine (Figure 2),

which will translate into the following changes: 1) A behavioral improvement such that the CRS-R diagnosis and total score will improve in responding patients, while NCS-R scores may also increase, reflecting a higher perception of pain; along with long-term functional recovery measured by sustained higher GOS-E and CRS-R scores at follow-up compared to the placebo group; 2) A relative recovery of sleep-wake cycles measured by a normalization of circadian rhythmicity as well as an increase in total body movements; 3) A metabolic improvement with significant increase of whole-brain glucose uptake, with highest increase of values found in the striatum, thalamus and frontoparietal cortical areas measured with PET; 4) A modulation of dynamic connectivity in response to apomorphine measured by resting-state fMRI analyses (seed-based and whole-brain connectivity measures) and changes of resting-state EEG connectivity metrics (notably increased mean alpha spectral connectivity, participation coefficient and delta modularity).

Additionally, we can expect improvements after treatment in less specific measures of recovery such as sleep cycle architecture on 24-hours EEG hypnograms and the probability of consciousness given by a machine learning multivariate classifier derived from EEG recordings during auditory paradigms (Engemann et al., 2015).

While improvements can be expected as well in the placebo arm due to spontaneous recovery and placebo effect, we hypothesize that responding patients in the apomorphine arm will exhibit significantly higher increases in these different markers of recovery.

Discussion: New multimodal approaches using neurophysiology and neuroimaging allow a more accurate diagnosis of patients with disorders of consciousness but the current available treatments remain inefficient. This study aims to verify the efficacy of apomorphine for the recovery of consciousness in the first randomized placebo-controlled double-blind trial using multimodal measurement methods. The results will contribute to define the role of dopamine agonists in the treatment of this challenging population of patients and help identify the neural underpinnings underlying the modulation of consciousness networks by apomorphine. Notably, this trial is designed to bring objective neuroimaging and neurophysiological evidence to further assess the validity of the mesocircuit hypothesis and its modulation by pharmacological agents, which may open new therapeutic perspectives.

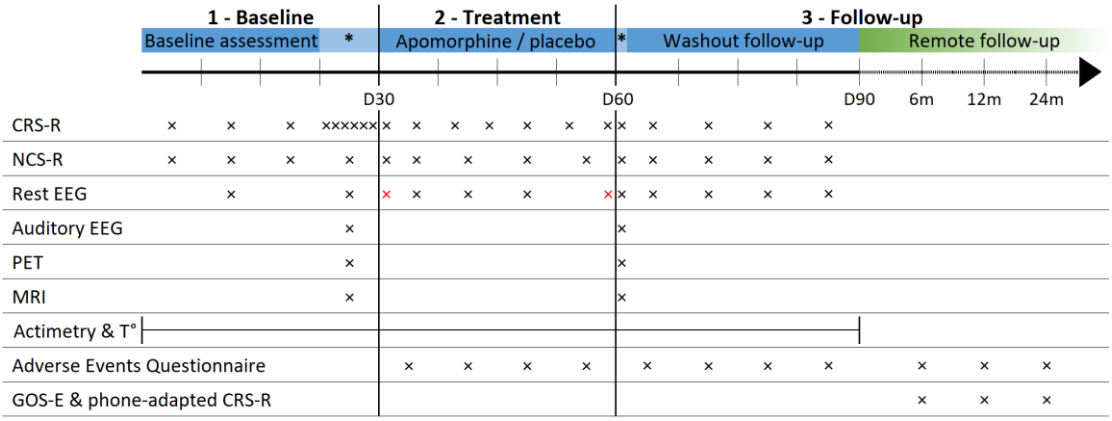

Figure 1. Timeline of the study protocol. * : multimodal assessment; Blue segments: inpatient phase; Green segment: outpatient follow-up; CRS-R: Coma Recovery Scale – Revised; NCS-R: Nociception Coma Scale – Revised; EEG: electroencephalography; PET: positron emission tomography; MRI: magnetic resonance imaging; T°: body core temperature; GOS-E: Glasgow Outcome Scale – Extended; Red crosses: 24-hours EEG

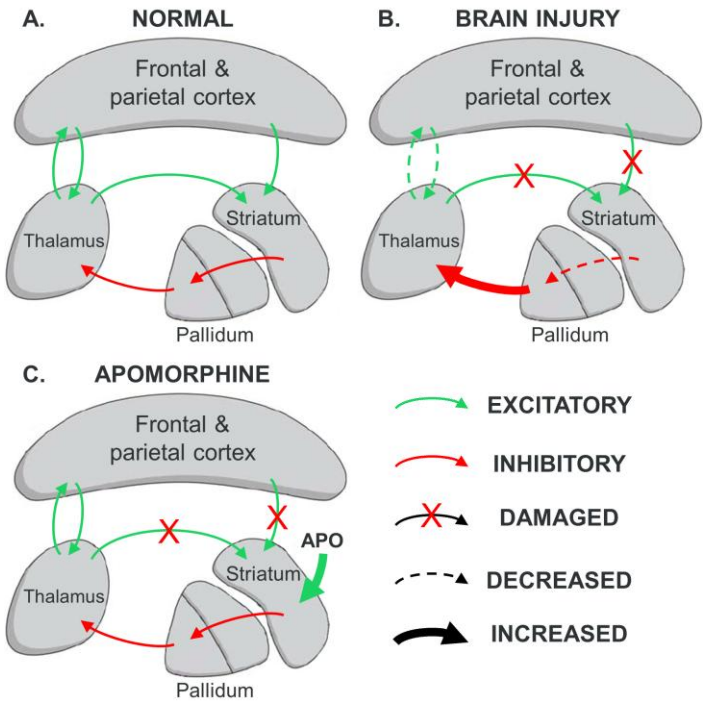

Figure 2. The mesocircuit hypothesis. (A) Normal wakeful condition. Dopamine neurons in the striatum inhibit the pallidum, which prevents it from inhibiting the thalamus. Thalamic projections activate cortical networks and get positive feedback in return. Excitatory inputs from both the cortex and the thalamus activate the striatum to maintain the loop. (B) Brain injury. Withdrawal of thalamostriatal and corticostriatal projections following widespread neuronal deafferentation leads to reduced activity of the striatum, resulting in an inhibition of thalamic activity and decreased cortical activation. (C) Postulated action of apomorphine (APO) on brain

injury. The facilitating action of apomorphine on striatal dopamine neurons could substitute for the missing inputs and restore the inhibitory striatopallidal projections, thus freeing the thalamus and its output towards the cortex.

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