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Abstract

Purpose: To determine the role of noradrenergic modulation in the control of motor output, we compared the acute effect of Reboxetine (REB), a noradrenaline reuptake inhibitor, to a placebo (PLA) on knee extensors motor performance and cortical and spinal excitability. **Methods:** Eleven young males took part in two randomized experiments during which they received either 8 mg of REB or a PLA. The torque produced during a maximal voluntary contraction (MVC) and its variability (i.e. coefficient of variation) during submaximal contractions ranging from 5 to 50% MVC were measured. Paired electrical (PES) and transcranial magnetic stimulation (TMS) were used to assess changes in voluntary activation during MVC, and corticospinal (motor evoked potential - MEP) and spinal excitability (Hoffman (H) reflex) during contraction at 20% MVC. **Results:** MVC torque and torque steadiness increased respectively by 9.5 and 24% on average in REB compared with PLA condition ($P<0.001$). Voluntary activation tested by TMS and PES was greater (~3%; $P<0.05$) in REB than PLA condition. The increase in voluntary activation in REB condition was significantly correlated with subjects' initial voluntary activation level when tested by TMS ($r=-0.62$; $P=0.048$) and PES ($r=-0.86$; $P<0.01$). The maximal amplitudes of H reflex and MEP and, the slope of their recruitment curves were enhanced by REB ($P<0.05$). The ratio between the TMS-induced EMG silent period (SP) and the corresponding MEP (SP/MEP) was reduced in REB condition ($P<0.01$). **Conclusion:** The present findings indicate that voluntary activation and accuracy in force control can be increased by an enhanced level of noradrenaline concentration. This improvement in motor performance is accompanied by changes located at both cortical and spinal levels.

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Abstract

Purpose: To determine the role of noradrenergic modulation in the control of motor output, we compared the acute effect of Reboxetine (REB), a noradrenaline reuptake inhibitor, to a placebo (PLA) on knee extensors motor performance and cortical and spinal excitability. **Methods:** Eleven young males took part in two randomized experiments during which they received either 8 mg of REB or a PLA. The torque produced during a maximal voluntary contraction (MVC) and its variability (i.e. coefficient of variation) during submaximal contractions ranging from 5 to 50% MVC were measured. Paired electrical (PES) and transcranial magnetic stimulation (TMS) were used to assess changes in voluntary activation during MVC, and corticospinal (motor evoked potential - MEP) and spinal excitability (Hoffman (H) reflex) during contraction at 20% MVC. **Results:** MVC torque and torque steadiness increased respectively by 9.5 and 24% on average in REB compared with PLA condition ($P<0.001$). Voluntary activation tested by TMS and PES was greater (~3%; $P<0.05$) in REB than PLA condition. The increase in voluntary activation in REB condition was significantly correlated with subjects' initial voluntary activation level when tested by TMS ($r=-0.62$; $P=0.048$) and PES ($r=-0.86$; $P<0.01$). The maximal amplitudes of H reflex and MEP and, the slope of their recruitment curves were enhanced by REB ($P<0.05$). The ratio between the TMS-induced EMG silent period (SP) and the corresponding MEP (SP/MEP) was reduced in REB condition ($P<0.01$). **Conclusion:** The present findings indicate that voluntary activation and accuracy in force control can be increased by an enhanced level of noradrenaline concentration. This improvement in motor performance is accompanied by changes located at both cortical and spinal levels.

Key words: force steadiness, knee extensor muscles, reboxetine, cortical excitability, spinal excitability

Introduction

The noradrenergic system is involved in the control of many higher functions such as arousal, attention, stress response, memory, sensory information processing and long-term synaptic plasticity through its action on the synaptic transmission in the prefrontal cortex. Modulation of prefrontal functions by noradrenaline has been largely investigated and perturbation of the noradrenergic signaling has been shown to be involved in the pathogenesis of many neuropsychiatric disorders (for review articles, see (1-3)). Surprisingly, much less is known regarding the noradrenergic actions on the motor system and the functional consequences in human.

Previous studies reported that increasing central noradrenergic concentration using reboxetine (REB), a noradrenergic reuptake inhibitor, improves motor function in hand muscles of healthy subjects (4-6) and stroke patients (7, 8). The presence of a REB effect appeared however to be task specific and was mostly reported during visuomotor tasks (6). Concomitantly to the improved motor performance under REB, Plewnia et al. (4, 5) and Kuo et al. (9) observed an increase in corticospinal excitability and a decrease in short-interval intracortical inhibition in healthy individuals by using transcranial magnetic stimulation (TMS). Furthermore, using functional magnetic resonance, Wang et al. (7) reported that the improvement in motor function under REB in paretic patients resulted from a rearrangement of cortical interactions, supporting a role for cortical-related mechanisms in these adaptations.

Even though an extensive animal literature demonstrated a significant role for noradrenergic projections in the modulation of spinal excitability, its role at the spinal level in humans is still unclear. By increasing intrinsic excitability of motor neurons, monoaminergic inputs have proven to play a role in adjusting motoneuronal excitability, allowing thereby

motor units to discharge at a higher rate in response to ionotropic inputs (for reviews in animal, see (10, 11)). Based on the results of animal studies, a noradrenergic modulation of spinal excitability in humans is likely and needs further investigations.

Therefore, given the paucity of the literature on the impact of noradrenergic modulation on motor control, the present work investigated the influence of REB on maximal force and force steadiness during submaximal isometric contractions (12, 13). The latest task was chosen because, along with a sufficient maximal force, accurate control of force is necessary to perform adequately most functional tasks (14). Associated changes in spinal and corticospinal excitability were assessed by recording the Hoffmann (H) reflex and motor evoked potential (MEP) induced by TMS in the knee extensor muscles which play an important role in everyday activities. As the size of the H reflex, induced by Ia-afferents activation, depends on the excitability of spinal motor neurons and modulation of Ia synaptic transmission (15), whereas MEP estimates both the excitability of cortical and spinal motor neurons, by comparing the concurrent changes of both responses we aimed to identify the relative modulation in excitability at spinal and cortical levels (16). Contrary to previous studies, we recorded H reflexes and MEPs in the contracting muscle which is more functionally relevant and enabled us to investigate the duration of TMS-induced intracortical inhibition by measuring the silent period (SP) in the ongoing EMG activity. This parameter has been shown to assess long-lasting cortical inhibition mediated by type B gamma-aminobutyric ($GABA_B$) receptors (17) that ensure the stability of cortical network activity (18).

Material and methods

Subjects

Eleven recreationally active male subjects (age: 23.0 ± 2.1 yr; height: 1.82 ± 0.08 m; mass: 80.1 ± 8.5 kg) completed this study. Prior to their participation in the study, all volunteers received written information regarding the nature and purpose of the experimental protocol. All the subjects passed a medical screening and an electrocardiogram at rest to exclude any contraindication to REB and/or TMS. Subjects had the opportunity to ask questions before signing the written statement of consent. The experimental protocol was approved by the Ethical Committee of the Erasmus Hospital (Brussels).

Ergometric device

The neuromuscular parameters were recorded while the subjects sat on an adjustable chair such that the hip and knee joints were at 100° (angle between trunk and thigh) and 80° (full extension = 0°), respectively. The chair had a long back-rest and the head of the subject was secured in a custom-made headrest to ensure a stable position during the experiment. A force transducer was rigidly connected to the front of the chair by a custom made fixing system (for detailed description of the setup, see (19)). The right leg was attached to the transducer using a velcro strap that was placed ~2 cm above the lateral malleolus. To limit trunk movement during contractions, the subject was secured to the chair by a harness. Headrest and transducer positioning were recorded for each subject to reproduce identical setup conditions in the two experimental sessions (19).

Torque and electromyographic recordings

The isometric torque produced by the knee extensor muscles was measured using a force transducer (linear range, 0–2,500 N; U2000 load cell, Maywood Instruments Ltd, Basingstoke, UK). Torque was calculated by multiplying the output from the transducer by the lever arm measured as the distance between the center of the transducer and the axis of rotation of the knee joint. Voluntary and electrically evoked electromyographic (EMG) activities were recorded from rectus femoris (RF), vastus medialis (VM), vastus lateralis (VL) and long head of the biceps femoris (BF) by means of self-adhesive bipolar electrodes (Ag-AgCl, 10 mm diameter, interelectrode center to center distance: 5 cm). The EMG electrodes were placed over the muscle belly of each muscle whereas the reference electrodes were located over the lateral condyle of the tibia. The locations of EMG electrodes were marked with indelible ink to ensure similar recording conditions during the two experimental sessions. All EMG signals were amplified (× 1,000) and filtered (10 Hz - 1 kHz) by a custom-made differential amplifier. All signals were acquired on a computer at a sampling rate of 2 kHz with a data-acquisition system (Model MP 150, Biopac Systems, Santa Barbara, CA, USA) and analyzed off-line with associated AcqKnowledge software.

Electrical stimulation

Single and paired rectangular pulses of 1 ms duration were delivered to the femoral nerve by a constant current stimulator (DS7A Digitimer, Welwyn Garden City, UK) triggered by a digital timer (Master-8, AMPI, Jerusalem, Israel) through self-adhesive electrodes (Ag-AgCl, 10-mm diameter). The cathode was positioned over the nerve in the femoral triangle, and the anode midway between the greater trochanter and the iliac crest (20).

The evoked EMG responses were the Hoffmann reflex (H reflex) and M wave. Stimulus intensity was optimized for the VM because pilot experiments performed in our lab indicated that reflex responses were more stable in this muscle. This was confirmed by Doguet and Jubeau (21) who also observed a better inter-day reliability in VM than in VL.

Unlike previous works investigating the effect of noradrenergic modulation on corticospinal excitability at rest (4, 9), we determined the H-reflex and M-wave recruitment curves during submaximal isometric contractions at 20% of maximal voluntary contraction (MVC). As muscle activation favors a constant spinal synaptic transmission, such an approach reduces the intra-subject variation and assesses the corticospinal pathway in a more functional condition (22). Stimulus intensity was increased gradually by steps of 1 mA until the H reflex reached maximal amplitude (Hmax) and by steps of 2 mA thereafter until the M-wave amplitude reached a plateau (Mmax). Three to eight stimulations were induced at each step depending on the response variability.

Voluntary activation was tested by the superimposed stimulation method using paired supramaximal electrical stimuli (PES) delivered at 10-ms interval during the MVC plateau and at rest immediately after the end of the MVC (19, 23). The stimulation intensity used to test voluntary activation was set 30% above that required to induce Mmax.

Transcranial magnetic stimulation

A double-cone coil (130 mm outer diameter) was positioned over the cortex to elicit MEP in the right knee extensors with a Magstim 200 stimulator (Magstim, Dyfed, UK). The junction of the double cone coil was positioned 1–2 cm to the left of the vertex. During each experiment, the position of the coil was determined to induce the greatest MEP response for a given stimulus

in VM (see protocol) and this position was marked on the scalp. The recruitment curve was performed at 20% MVC by increasing the stimulation intensity in steps of 3% of the maximal stimulator output (3-8 stimulations at each step) until the MEP amplitude reached a plateau (MEPmax).

To assess voluntary activation by TMS, the stimulator output was set to evoke the greatest superimposed response and MEP in VM with a minimal MEP size in the biceps femoris while the subject was sustaining a 50% MVC with the knee extensors. The mean TMS intensity used to test voluntary activation corresponded to 58.3 ± 3.0% (range: 55-63%) of the stimulator output.

Drugs

Oral administration of REB, a selective and specific noradrenaline reuptake inhibitor, was used to increase basal extracellular noradrenaline levels in the nervous system (24). A single dose of 8 mg of REB was used in the present study, similarly to previous studies investigating the impact of REB on motor performance in hand muscles (5-7), to compare our data with results reported in upper limb muscles.

During the two experimental sessions, subject received a capsule with either 8 REB or a placebo (PLA) consisting of 20 mg of lactose. Subjects ingested the capsule 85 min before the beginning of the recordings as plasma concentration was reported to be high and relatively stable between 85 and 140 min following the ingestion of a single oral dose of 8 mg of REB (4). REB and PLA were administrated in a randomized order, and, both experimenters and subjects were unaware of the capsules content. The drug treatment was supervised by a medical doctor who was available in case of side effects during and after the experiments. The only side effects

reported by three subjects under REB were: perturbed sleeping the night following the experiment and feeling a little bit warmer than usual before the start of the experimental recordings. This last feeling was also reported by one subject during the session under PLA.

Experimental protocol

Subjects took part in three experimental sessions, one familiarization session and two experimental sessions spaced by one week and conducted at the same time of the day to limit diurnal variation in muscle force (25). The familiarization session was dedicated to accustom subjects to the setting conditions and the protocol to minimize learning and anxiety effects. They practiced isometric contractions at different levels during the torque-matching task and experienced electrical motor nerve stimulation and TMS. The course of the familiarization session was similar to the real experimental sessions. During the experimental sessions, the protocol was planned so that all the recordings started 85 min following drug intake and completed within one hour (see reason above; (4)). Exercise, caffeine or alcohol consumption was forbidden during the 24 h preceding each session.

After the ingestion of the drug (REB or PLA), subjects were progressively equipped with a heart rate monitor (Polar H1 sensor and RS300X watch, Kempele, Finland), EMG electrodes and installed on the experimental chair. Thereafter, they warmed-up by performing a series of ten submaximal contractions and two brief MVC. The optimal location and stimulation intensity for TMS and electrical stimulation were then determined during brief (~3s) submaximal contractions (at 20 and 50% MVC), and at rest for electrical stimulation.

The experimental recordings (Fig. 1) started with two to three 3-s MVCs, separated by 1 min of rest, during which paired electrical supra-maximal stimuli were induced. They were

followed by two to three PES evoked at rest to determine the resting potentiated mechanical response. After 3 min of recovery, subjects performed an MVC and two contractions at 75% and 50% MVC. TMS was applied during the torque plateau of each contraction. Each contraction was repeated two to three times and separated by at least 1 min of rest. The order of the two submaximal contractions was randomized across subjects but kept constant for each subject across all experimental sessions. A brief MVC was finally performed with a single superimposed electrical stimulation to record the superimposed Mmax that was used to normalize the MEP. After a rest period of 4 min, the experimental session continued with the torque-matching task. For each of the four levels (5, 10, 20 and 50% MVC), subjects first performed a 5-s contraction to experience and match the required torque. This was followed by the recording of two 15-s isometric contractions maintained as steady as possible and separated by 30 s of rest. A visual feedback of the torque was provided on a 22-in. monitor, located in front of the subject. The gain of the displayed signal was adjusted so that the target line was always in the middle of the screen and torque fluctuations were visually similar for the different contraction levels. Target torques were presented in a random order for each subject. After a rest period of 4 min, the experimental session ended with the recording of the H-reflex, M-wave and MEP recruitment curves.

FIGURE 1

Data analysis

MVC torque and associated average value of the rectified EMG (aEMG) of VM, VL, RF, and BF were determined for a 500-ms period during the plateau of the MVC. The coefficient of variation (CV) of the torque exerted during the torque-matching task and the corresponding aEMGs was determined for the steadiest 5-s period. The values for the two contractions at each target were averaged.

The peak-to-peak amplitude and area of the H reflex, MEP and M wave were measured. As the amplitude and area of the evoked responses exhibited similar features, only the former parameter is reported in the manuscript. H-reflex and MEP responses were normalized to Mmax to account not only for potential changes in excitability of the muscle fiber membrane and slight variation in the position of the EMG electrodes between sessions, but also to reduce inter-individual differences. As active threshold, corresponding to the lowest intensity inducing a small response (9), is usually considered not sensitive enough to detect spinal and corticospinal excitability changes (4, 9), only maximal amplitudes and slopes of the ascending part of the recruitment curves for H reflex, M wave and MEP were analyzed. These responses represent a greater portion of the motor neuron pool and are usually considered as a more reliable measure of spinal and corticospinal excitability (9). Maximal response amplitude (Hmax, Mmax and MEPmax; Fig. 2A) was determined by averaging the five largest responses obtained during the recruitment curve. The ascending limb of the recruitment curve for H reflex, M wave and MEP were fitted by a Boltzmann sigmoid (Fig. 2B-D; (26, 27)) to determine the following parameters: 1) the stimulus intensities corresponding to 50% of the maximal amplitude of the evoked responses (respectively H_{50}, M_{50}, MEP_{50}); and 2) the slope (H_{slope}, M_{slope}, MEP_{slope}) of the ascending limb of the recruitment curve (Fig. 2B-D). The slope was calculated for the part of the curve corresponding to the stimulus intensity associated with H_{50}, M_{50} and MEP_{50} and was obtained using the following equation:

$$\frac{m(Hmax\ or\ MEPmax\ or\ Mmax)}{4}$$

where *m* is the inverse of the Boltzmann equation slope (22, 26, 27). Before to calculate the slope, the amplitude of the responses was expressed as a percentage of Mmax and its intensity as a percentage of the stimulus intensity associated with M_{50} or MEP_{50}. The r-squared quantifying

how the Boltzmann sigmoid fits the data was high for all recruitment curves and ranged between 0.93-0.99.

FIGURE 2

The duration of the cortical SP associated either with the MEP recorded during MVC or the MEP responses used to calculate MEPmax during the contraction at 20% MVC was measured to assess the level of intracortical inhibition. SP duration was determined in the contracting muscle as the interval between the TMS induced artifact and the return of continuous EMG activity. To reduce the inter-subject variability and the possible confounding effect of a change in MEP amplitude on SP duration, the ratio between SP and the corresponding MEP was calculated (SP/MEP; (16, 28)).

The superimposed torque induced by TMS or PES during MVC was measured as the difference between the superimposed peak torque and MVC torque (20, 23). Peak torque of the response induced by PES was measured at rest whereas it was estimated rather than measured directly for TMS (23). For each subject, a linear regression between the amplitude of the superimposed torque evoked by TMS and voluntary torque was performed for intensities of 50, 75 and 100% MVC. The *y*-intercept was taken as the amplitude of the estimated resting response (ERT; (23)). Voluntary activation level (% of maximum), tested either using PES or TMS, was calculated according to the following equation: [1 – superimposed torque /torque induced at rest in response to PES (or ERT for TMS)] $\times$ 100 (19, 20, 23).

Statistical analysis

Prior to comparing each dependent variable, the normality of the data was controlled using a Shapiro-Wilk normality test. Depending on the distribution of the data for each variable, paired Student t-test or Wilcoxon signed-rank test was used to compare all parameters between PLA and REB conditions, except those recorded during the torque-matching task. The coefficient of variation (CV) for torque at 5, 10, 20 and 50% MVC and associated aEMG were analyzed using a two-factor (condition x torque level) ANOVA with repeated measures. When a significant main effect was found, a Bonferroni's post hoc test was used to compare differences between selected data points. Depending on the distribution of the data, Spearman rank correlation coefficient (r_s) or Pearson correlation coefficient (r_p) was calculated to explore the correlation between individual changes in voluntary activation induced by REB (as compared with PLA) and initial voluntary activation level tested either using TMS or PES under PLA condition. For all comparisons, the statistical level of significance was set at 0.05. Data are reported as means ± SD within the text, and means ± SEM in the figures.

Results

MVC and electrically-induced responses

The mean MVC torque was 9.5% greater in REB (267.4 ± 51.0 N·m) than in PLA (244.1 ± 43.6 N·m) condition (Fig. 3; $P<0.001$). For all muscles, there was no difference in aEMG between conditions (all P-values >0.47). The aEMG in PLA and REB conditions were respectively 619.9 ± 232.2 and 651.2 ± 233.0 µV for VM, 412.6 ± 121.0 and 427.8 ± 120.6 µV for VL, 384.1 ± 108.3 and 369.2 ± 122.4 µV for RF, and 60.3 ± 26.9 and 65.3 ± 28.3 µV for BF.

The mean peak torque produced by PES at rest was similar in both conditions, respectively 90.7 ± 16.4 and 92.2 ± 17.6 N·m for PLA and REB (P=0.566).

FIGURE 3

Voluntary activation and MEP during MVC

Voluntary activation was significantly greater in REB than in PLA condition (Fig. 4), when tested either by TMS (3.0%; P<0.001) or PES (2.8%; P=0.046). The increase in voluntary activation in REB condition and the subjects' initial voluntary activation level were significantly correlated when tested either by TMS (r_s=-0.62; P=0.048) or PES (r_p=-0.86; P<0.01).

FIGURE 4

The amplitude of the MEP recorded during MVC did not differ significantly (P=0.270) between PLA (50.2 ± 11.6% Mmax) and REB (53.9 ± 15.7% Mmax) conditions. Mmax amplitude was similar (P=0.415) in both conditions (13.3 ± 5.2 and 12.6 ± 5.5 mV in PLA and REB, respectively). There was no drug effect for SP duration (96.1 ± 8.1 and 95.5 ± 7.2 ms for PLA and REB, respectively; P=0.565) or SP/MEP ratio (18.0 ± 8.9 and 18.7 ± 10.4 $ms \cdot mV^{-1}$ for PLA and REB, respectively; P=0.755).

Torque variability

The ANOVA for torque variability indicated no interaction between drug condition and torque level (P=0.709), but a significant main effect was found for torque level (P<0.001) and drug condition (P<0.001; Fig. 5A). The CV for torque was significantly lower in REB than in PLA condition for all torque levels (range for post-tests P-values: 0.001-0.027). In addition, CV

was greater at 50% MVC compared with the other torque levels (all post-tests P-values <0.001). The mean aEMG for agonist muscles (Fig. 5B) and biceps femoris (Fig. 5C), expressed as % of their value recorded during knee extensors MVC, increased as a function of the torque level (ANOVA: P<0.001). Regardless of the muscle, no drug effect (ANOVA P-values >0.67) or drug and torque level interactions were found (P-values >0.62).

FIGURE 5

Recruitment curves

Results obtained from the analysis of the evoked potentials recorded during the recruitment curves are presented for one subject in Fig. 2 and as mean values in table 1. The Mmax and the slope (M_{slope}) of the ascending limb of M-wave recruitment curve were similar in both REB and PLA conditions (table 1). In contrast, the Hmax and MEPmax as well as the slopes (H_{slope} and MEP_{slope}) of their recruitment curves were significantly greater in REB than in PLA condition (table 1). SP duration was similar in both conditions whereas SP/MEP ratio was significantly less in REB than in PLA condition (table 1).

TABLE 1

Discussion

The purpose of the present study was to further explore the effect of noradrenergic neuromodulation on the maximal force and fine control of muscle force and associated changes in corticospinal and spinal excitability. To that end, we compared data obtained after the ingestion of 8 mg of REB, a reuptake inhibitor of noradrenaline, to those recorded in PLA condition. Our results showed an increase in both maximal force and force steadiness under

REB. The motor performance improvements were accompanied by a greater corticospinal excitability which is at least partly related to an increase of the motoneuronal excitability of the spinal level.

Modulation of spinal and corticospinal excitabilities

The changes in corticospinal excitability associated with REB intake differ depending on the level of muscle activation. When assessed during MVC, REB had no effect on MEP amplitude and SP/MEP ratio. This finding agrees with our previous observations (19, 20). In contrast, the analysis of the recruitment curve performed at 20% MVC indicated that REB substantially increased corticospinal excitability and decreased intracortical inhibition. The lack of REB effect during MVC is likely due to the fact that, at the time the superimposed stimulation is induced, motor neurons are either already activated or in a refractory state (29).

Similarly to the MEP, the analysis of the H reflex recorded at 20% MVC revealed that its maximal amplitude and the slope of the ascending part of its recruitment curve were increased by REB, indicating a greater spinal excitability and gain in the reflex loop (15, 22). These results contrast with a previous study showing that REB increased MEP without affecting the maximal H-reflex amplitude recorded in the abductor pollicis brevis at rest (4). This observation, together with the increased MEP amplitude, led the authors to conclude that REB mainly enhanced cortical excitability. The discrepancy with our results may be explained by the fact that voluntary activation brought motor neurons closer to their firing threshold (21, 22), thereby augmenting the sensitivity of the method to detect small changes in spinal excitability.

The concurrent changes in SP/MEP ratio, MEP and H reflex in the present study suggest that noradrenaline reuptake inhibition influences both spinal and cortical levels. At the cortical

level, noradrenaline is known to modulate excitability in a task specific way by regulating both glutamatergic facilitation and GABAergic inhibition through complex mechanisms that have been investigated in animal preparations (for a review, see (1)). A similar impact of noradrenergic modulation on cortical excitability in humans is supported by previous pharmacological studies that reported an increase in intracortical facilitation and a reduced short-interval intracortical inhibition under REB (4, 9). Our results, showing a decreased of the SP/MEP ratio, also suggest a reduced long-latency intracortical inhibition. Since changes in this ratio may be partly driven by the increase in MEP, we additionally compared the SP duration associated with MEPs of similar amplitude (expressed as % of Mmax) in PLA and REB conditions. This procedure enables to test a similar proportion of the motor neurons pool and avoid the influence of MEP size on SP duration. In that condition, the mean SP duration was significantly briefer (P=0.001) in REB (126 ms) than in PLA (141 ms), which is consistent with the SP/MEP ratio results. At the spinal level, our results are in line with animal studies showing that noradrenaline increases the intrinsic excitability of motor neurons (11). The main mechanism by which noradrenaline is thought to facilitate motor neurons excitability is the induction of plateau potentials by the activation of L-type calcium channels (30) and by the depolarization of the resting membrane potential (31). Through these mechanisms, noradrenaline does not directly excite motor neurons, but potentiates the action of excitatory synaptic inputs (11). In addition to an increase in motor neuron excitability, an effect of noradrenergic modulation on presynaptic inhibition is not excluded (32), which may have facilitated muscle afferent feedback to the motor neuron pool, contributing to increase its responsiveness.

Maximal torque

The present results confirm those of our previous study regarding MVC torque (19). In that work, we administered two separate doses of 8 mg of REB, one the evening before the experiment and one upon arrival at the laboratory, and reported a 9% increase in MVC torque in the REB condition. In the present work, we administrated a single dose of REB to be able to compare our results with studies that investigated the impact of a similar dose on motor performance in hand muscles (5-7). A single 8 mg dose of REB appears to be sufficient to increase the MVC torque produced by the knee extensors. As the torque evoked at rest by the paired electrical stimulation was unchanged by REB, our data point towards voluntary activation enhancement being the main mechanism of torque increase. The absence of aEMG changes during MVC in the REB condition may be surprising at first, but it is known that surface EMG is not sensitive enough to detect small changes in motor unit discharge rate (33).

The observation of a greater voluntary activation in REB than in PLA condition is in line with the study of Wang and colleagues (7) who investigated the impact of REB on grip power in hemiparetic stroke patients and the associated changes in cortical activation using functional magnetic resonance imagery. They observed that REB increased grip power on the paretic side whereas power was unchanged in the unaffected hand. The increase in power in the paretic side was associated with a partial normalization of cortical activity and cerebral connectivity that most probably resulted in an enhancement of the initially reduced motor output. Similar mechanisms may have contributed to the increase in MVC torque we observed in REB condition. Indeed, unlike hand muscles (25, 34), most healthy individuals are unable to fully activate their knee extensor muscles (19, 35). Knee extensors could therefore be more responsive to noradrenaline reuptake inhibition induced by REB. This view point is supported by the

negative correlation observed between the gain in voluntary activation and subjects' initial capacity.

Torque steadiness

The lower torque variability (expressed as CV) observed in REB compared with PLA condition suggests that noradrenergic neuromodulation also contributes to refine motor control. As mentioned in the introduction, studies investigating the impact of REB on fine motor control are sparse and controversial in healthy subjects. For example, it has been shown that REB has a positive effect on motor control during tasks involving upper limb movements and requiring adjustments of motor performance based on a visual feedback (5, 6). In contrast, REB did not reinforce the performance or training-dependent improvements of simple and skilled finger movements performed without visual feedback (5, 6). The task chosen in the present study had an important visuomotor component and required high attention to continuously adjust the torque level to match the target. In agreement with the above observations, our results thus support a role for noradrenergic modulation in increasing accuracy during visuomotor tasks.

Torque fluctuation during steady submaximal contractions is influenced by the variability of motor units discharge rate and changes in common input to motor neurons (36-38) that are modulated at cortical and subcortical levels (36). Through its impact at cortical and spinal levels, noradrenaline may contribute to modulate the common input signal sent to the motor neuron pool and adjust the gain of motor neurons, improving thereby the effective neural input sent to the muscle (38). The greater torque steadiness observed in the present study under REB is most likely the result of complex mechanisms (see introduction) that need to be addressed in further research works.

In conclusion, the present findings indicate that voluntary activation and accuracy in force control can be increased by an enhanced level of noradrenaline concentration. This improvement in motor performance is accompanied by changes located at both cortical and spinal levels.

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Conflict of interest

The authors report no conflict of interest. The results of the present study do not constitute endorsement by ACSM. The findings are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation.

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Figure legends

Figure 1. Overview of the experimental protocol. The recordings started 85 min after drug intake with voluntary activation testing using electrical and transcranial magnetic stimulation (TMS), followed by the torque matching task, the H-reflex and M-wave recruitment curve and ended with motor evoked potential (MEP) recruitment curve. MVC, maximal voluntary contraction; PES, paired electrical stimulation; SES, single electrical stimulation.

Figure 2. Changes induced by REB intake on spinal and corticospinal excitability in a representative subject. Panel A illustrates traces of Hmax, MEPmax and Mmax in PLA and REB conditions recorded in vastus medialis during an isometric contraction at 20% MVC. Panels B, C and D illustrate the recruitment curves for M wave, H reflex and MEP, respectively in PLA (open circles) and REB (filled circles) conditions. The thick lines represent the slope of the ascending part of recruitment curves occurring at the stimulus intensity associated with H_{50}, M_{50} and MEP_{50} which are indicated by the dashed lines on the graphs.

Figure 3. Effect of REB on MVC torque. Individual changes (thin lines) and mean change (thick line) induced by REB intake are compared with PLA condition. Significant difference between REB and PLA condition: *P < 0.05.

Figure 4. Effect of REB on voluntary activation tested either by TMS (A) or PES (B). Individual changes (thin lines) and mean changes (thick lines) induced by REB intake are compared with PLA condition. Significant difference between REB and PLA condition: *P < 0.05.

Figure 5. Effect of REB on torque variability and associated EMG activities during sustained submaximal contractions ranging between 5 and 50% MVC. Panel A illustrates CV of torque

579 (%) at the four different contraction levels in REB and PLA conditions. Panel B and C illustrate,
580 respectively the mean value for the EMG activity of the agonist muscles (average value of vastus
581 medialis, vastus lateralis and rectus femoris aEMG) and of the biceps femoris. All EMG values
582 are expressed as a percentage of their value recorded during knee extensors MVC. Significant
583 difference between REB and PLA condition: *$P < 0.05$.

584

Table 1

Table 1. M-wave, H-reflex and MEP parameters recorded in vastus medialis in Placebo and Reboxetine conditions at 20% MVC.

	Placebo	Reboxetine	P-value
M wave			
Mmax (mV)	15.1 ± 6.0	14.9 ± 5.7	0.846
M_{slope} (%Mmax· $\%I_{M50}^{-1}$)	4.6 ± 3.2	4.2 ± 2.2	0.765
H reflex			
Hmax (%Mmax)	35.8 ± 16.1	41.2 ± 16.8	0.007
H_{slope} (%Mmax·$\%I_{M50}^{-1}$)	1.0 ± 0.6	1.4 ± 0.6	0.001
MEP			
MEPmax (%Mmax)	47.5 ± 18.4	55.4 ± 17.5	0.019
MEP_{slope} (%Mmax·$\%I_{MEP50}^{-1}$)	1.0 ± 0.8	1.5 ± 0.6	0.016
SP (ms)	141 ± 22	136 ± 14	0.369
SP/MEP ($ms \cdot mV^{-1}$)	28.2 ± 16.0	22.0 ± 11.9	0.007

Mmax, Hmax and MEPmax: maximal amplitude of the M wave, H reflex and MEP, respectively. M_{slope}, H_{slope} and MEP_{slope}: slope of the ascending part of the recruitment curve for M wave, H reflex and MEP, respectively. $\%I_{M50}$ and $\%I_{MEP50}$: percentage of the stimulus intensity corresponding to 50% of Mmax and MEPmax, respectively. Data are mean values ± SD for eleven subjects. P-values < 0.05 indicate a significant difference between Reboxetine and Placebo conditions.

Figure 1

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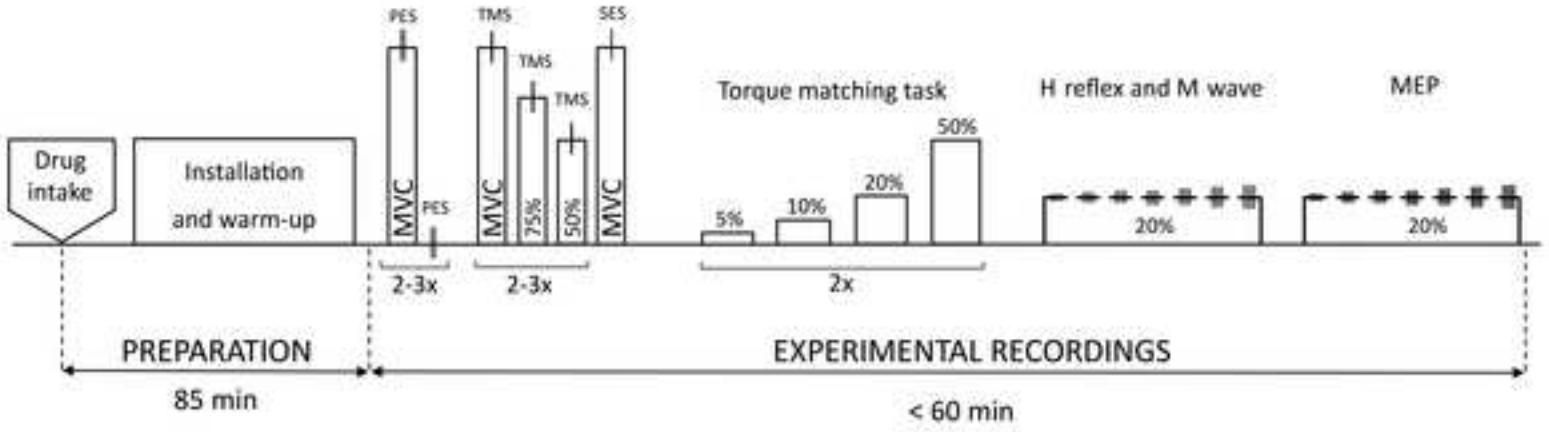
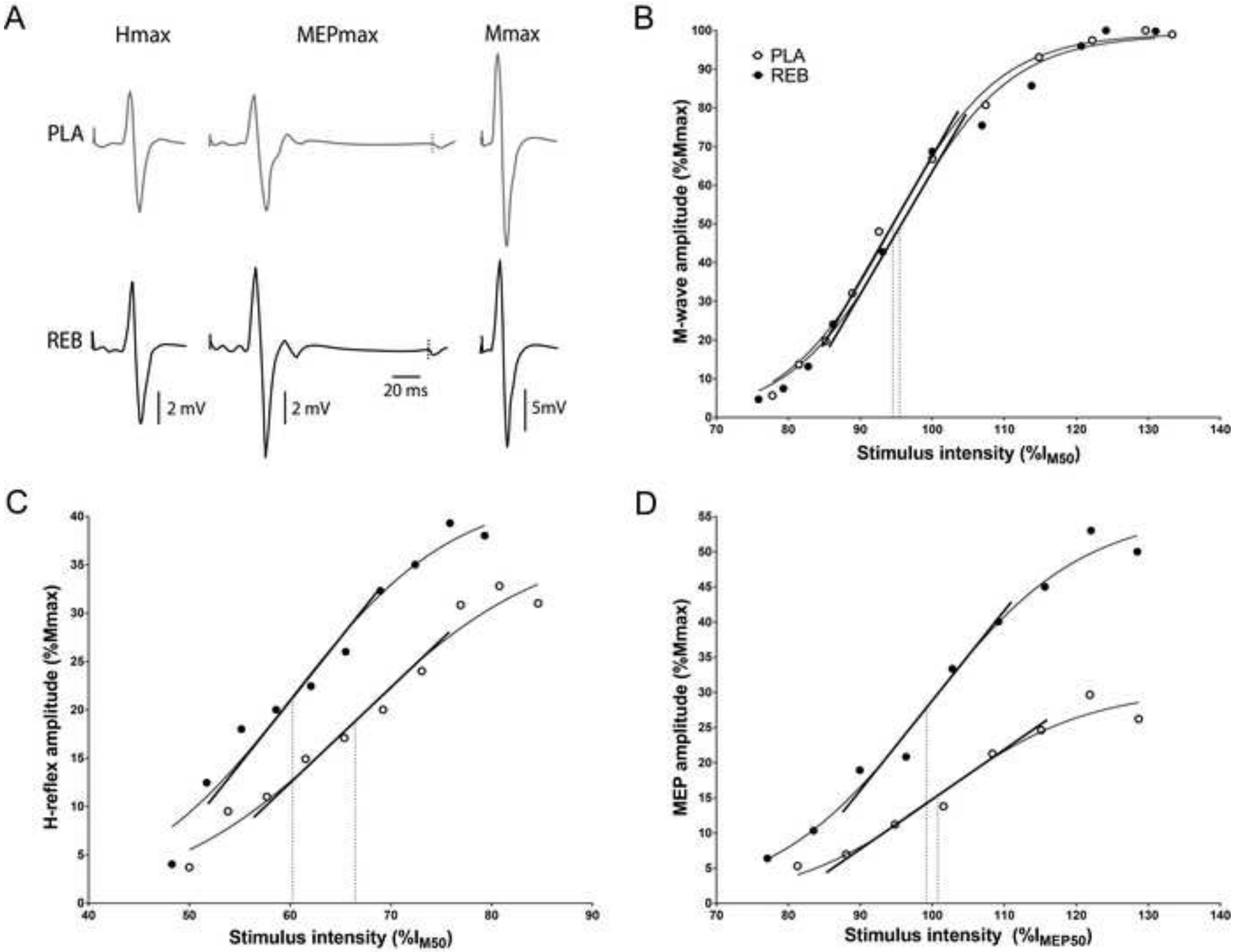


Figure 2



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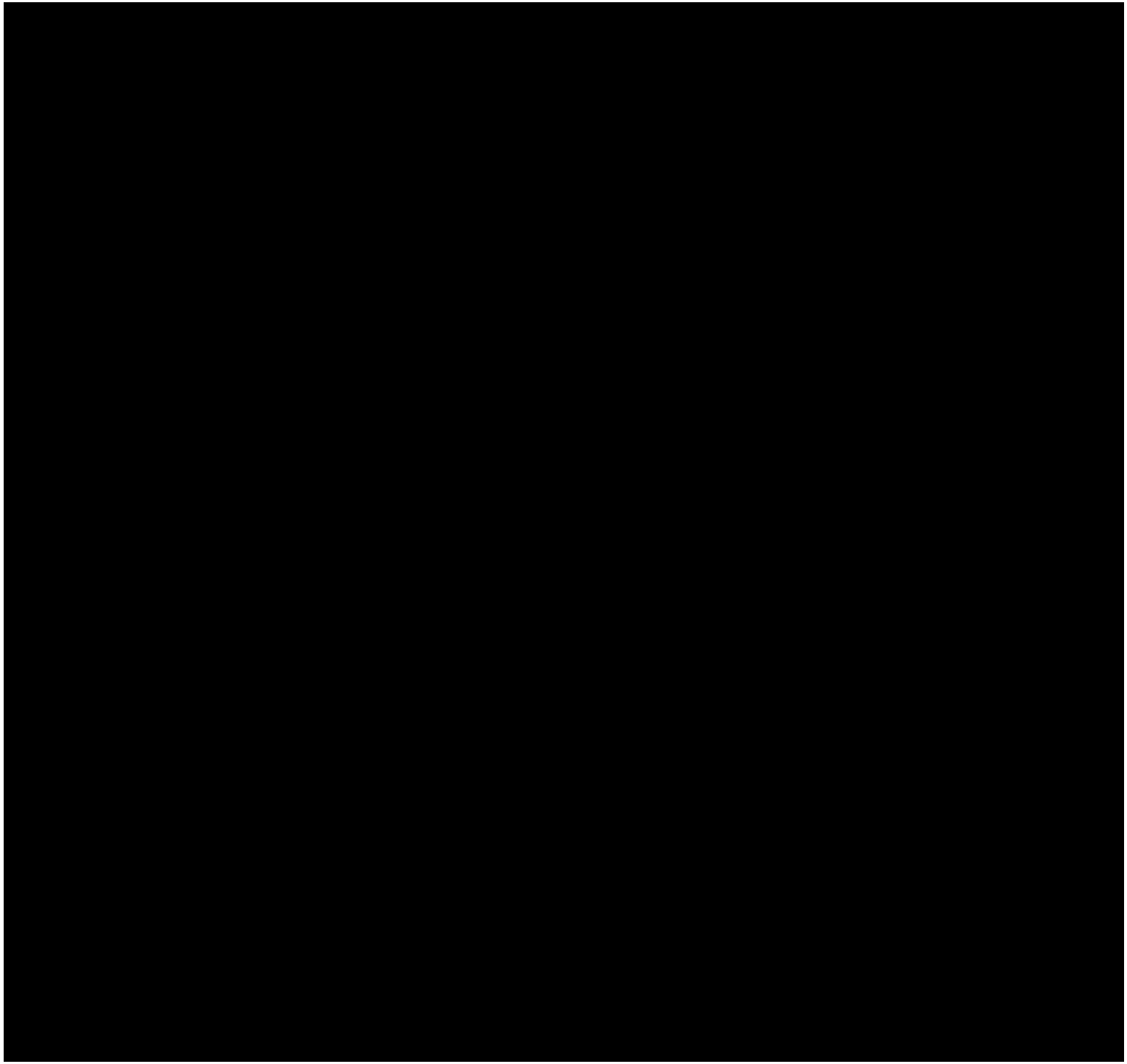

Figure 4

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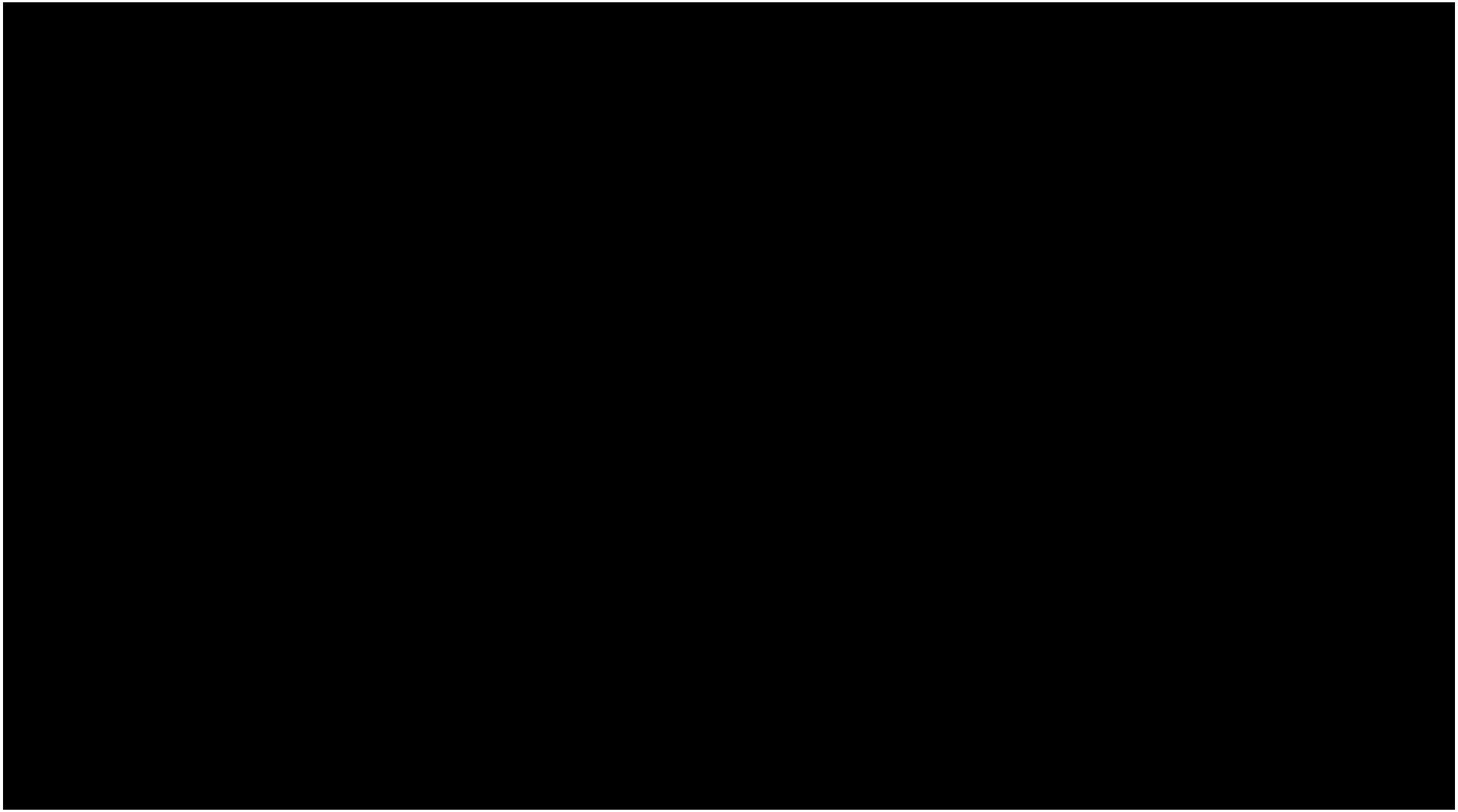

Figure 5

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