

**Multisensory integration as a modulator of action tremor**

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**Essential tremor (ET) amplitude is modulated by visual feedback during target driven movements: In a grip force task, tremor amplitude increases during large scale visual feedback compared to a condition with low scale visual feedback. It has not been examined whether visual feedback exclusively modulates action tremor severity or if an increase of other afferent input like auditory sensation has a modulatory effect on tremor amplitude as well. Also, it is unknown whether the sensory feedback itself directly affects the tremor generating network or if the effect is rather indirect: enhanced sensory feedback during targeted driven movements might cause arousal/psychological stress. We hypothesized that (1) amplitude of ET is modulated by variation of auditory feedback in the absence of visual feedback in a force tremor paradigm; (2) increase of tremor amplitude coincides with pupillary dilation as a measure of arousal / psychological stress, independently of the quality of sensory feedback. 14 ET patients and 12 matched controlls conducted a computer-based experiment in which they were asked to match a target force in a force sensor using their thumb and index finger. The quality of the matching the target force was feed back to the participant visually, auditory or a combination of both. For the visual feedback, two bars were displayed on a screen, with the distance between these bars decreasing with approximation of the target force. Results showed a comparable deviation from the target force (RMSE) during the experiment during all three sensory feedback modalities. Additionally, tremor severity did not differ between sensory feedback modalities. The ANOVA revealed an effect of the scaling factor on the tremor severity (Power 4-12Hz) for the visual- and also for the auditory feedback condition. Pupillometry consistently showed a significantly increased pupil diameter during the large scale visual- and auditory feedback conditions compared to the low scale feedback conditions. Our findings suggest that action tremor in ET is firstly modulated not only by visual feedback but also by auditory feedback in a comparable manner and seems to be modality independent. Secondly arousal / cognitive stress, as measured here by the pupil size, could mediate the increase of tremor amplitude. Further work including neurophysiological measures is required to better understand the role of these two possible mechanisms underlying target-related tremor.**

# Introduction

﻿Tremor is the most common movement disorder and is defined as an involuntary, rhythmic, oscillatory movement of a body part. (Bhatia, Bain et al. 2018) Tremor might occur in complete rest or during specific motor activation conditions, for example while actively maintaining a position against gravity (postural tremor) or during voluntary movements (simple kinetic tremor) and especially target-driven movements (intention tremor). Various etiologies can be underlying and, in many cases, -including the large group of essential tremor- the etiology remains obscure. However, as a common pathophysiological substrate of action tremor syndromes an altered oscillating activity within a cerebello-thalamo-motor cortical network was demonstrated by neuroimaging and electrophysiological approaches.(Helmich, Toni et al. 2013)

Despite its´ central origin, Essential tremor amplitude can be affected by modulation of peripheral sensory afference: Either by stimulating muscle end points or peripheral nerves and thereby activating the target muscles at specific phases of the tremor cycle so that the muscle response suppresses the tremor. (Prochazka, Elek et al. 1992, Popović Maneski, Jorgovanović et al. 2011) Or by stimulating peripheral nerves to evoke afferent activity that either modulates the excitability of spinal motor neurons or consecutively interacts with the central oscillations.(Reis, Arruda et al. 2021, Shukla 2022)

Recordings of thalamic microelectrodes have shown, that the integration of somatosensory afferent and efferent signals within certain thalamic areas play a decisive role in the generation of tremor amplitude.(Pedrosa, Brown et al. 2018)

Apart from somatosensory afference, the amplitude of action tremor syndromes like ET and intention tremor in multiple sclerosis was shown responsive to visual feedback as well: in the absence of visual feedback the amplitude of target driven action tremor decreases and contrary, by an increase of visual information the tremor amplitude increases.(Keogh, Morrison et al. 2004, Feys, Helsen et al. 2006, Gironell, Ribosa-Nogue et al. 2012) A recent functional MRI study found -apart from the well-known cerebello-thalamo-motor cortical pathway- a widespread visually sensitive network including key regions in the visual cortex and parietal lobule associated with severity of essential tremor during a static grip force task.(Archer, Coombes et al. 2017) However, it has not been examined yet whether visual feedback exclusively modulates action tremor severity or if an increase of other afferent input like auditory sensation has a modulatory effect on tremor amplitude as well. It is unknown whether the sensory signal itself directly affects the tremor generating network or if the effect is rather indirect: enhanced sensory feedback during targeted driven movements might cause arousal/psychological stress. In this view, feedback about the tremor in general increases tremor amplitude. This can be tested when manipulating the scale of the feedback in any sensory condition.

Recently, a modulatory role of psychological stress (or rather arousal?), as measured by a coincident pupillary dilation, onto the rest tremor network of Parkinson´s disease was shown.(Dirkx, Zach et al. 2020) This effect is most likely exerted by direct bottom-up noradrenergic influences onto the thalamus and indirectly by top-down cognitive influences onto the cerebello-thalamo-cortical circuit. Since the thalamus is a key node not only within the PD resting tremor network but also action tremor networks as well, an amplification of action tremor by ascending arousal systems (i.e. noradrenergic systems) seems likely.

Also, a potential role of multisensory integration in tremor amplitude modulation has not been examined yet. Simultaneously incoming sensory feedback could lead to an amplification of the tremor modulating effect compared to monosensory condition. To test this we plan to examine the modulation tremoroulus activity by visual and auditory feedback, as standalone and in combination.

Therefore, our study aims at testing the following hypotheses:

1: Feedback scaling influences tremor severity in different sensory feedback conditions in ET patients, not HC.

2: Increased pupil dilation during the task is expected during more prominent feedback

3: The higher gain with increased scaling in tremor force is reflected in pupil dialation.

#### Vocabulary

**Feedback condition**-> high vs. low gain

**Feedback type** -> visual only (vo), visual-auditive (av) and auditive-only (ao)

# Results

## Clinical data

We found a significant correlation between the TETRAS Score and the Schmahmann scale (r = -.21, p = 0.005), this correlation however dropped to r = -.1 (p = 0.197) when including age as a partial factor in the analysis.

For the TETRAS score patients showed a significant correlation with age (r = 0.566, p = 0.035), not however with the

BDI-II score (r = -0.145, p = 0.637). In the Schahmann scale patients scored significantly fewer point than the healthy controls (t = 2.226, p = 0.037), even though there was no significant age difference between the groups.

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| --- | --- | --- | --- | --- |
|  | Group | Median | [25th/75th]  percentile | p-value\* |
| Age [years] | c | 63.00 | [46.0/66.0] | 0.147 |
| p | 65.50 | [61.0/74.0] |
| BDI Score [n] | c | 0.50 | [0.0/1.8] | 0.003 |
| p | 8.00 | [5.0/11.0] |
| Schmahmann Score [n] | c | 107.00 | [102.0/111.0] | 0.046 |
| p | 93.00 | [86.0/101.0] |
| Tetras Score  [n] | c | - | - | - |
| p | 41.00 | [31.6/47.4] |
| Table 1: c = control group, p = ET group, SD = standard deviation, - = not available, \* = Mann-Whitney-U test. | | | | |

## Tremor force

Mean Force (MF), Unfiltered force error (RMSE) and Force Power 0-3 Hz did not differ between conditions or groups.

For the differences in the tremor relevant frequency spectrum (4-12 Hz), we found a statistical significant difference between the groups in each of the feedback types, visual only (t[53]=39.00, p=0.018), auditiv-visual (t[53]=24.00, p=0.041) and auditiv only (t[53]=42.00, p=0.013).

These stayed significant when including clinical scores such as TETRAS in the analysis

Chart

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Figure 2: Single trial power averages. Split per feedback type (vo, va, ao) and feedback condition (high, low).

## Pupil Size

Pupil dilation also revealed significant differences between each feedback conditions in some of the feedback types, visual only (t[53]=2.00, p=0.187), auditiv-visual (t[53]=2.33, p=0.022) and auditiv only (t[53]=1.33, p=0.047).

# Discussion

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Figure 3: Pupil times series data of a single participant.

In summary, we found that Essential tremor amplitude is modulated by visual and auditory sensory feedback scaling, independently of the type of sensation. Increased sensory feedback coincided with an increase of pupil diameter in patients, but not in controls. Combined auditory and visual feedback evoked the largest increase in tremor amplitude and pupil diameter in patients, although the differences in the tremor amplitude were not significant.

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Figure 1: Single trial pupil size averages. Split per feedback type (vo, va, ao) and feedback condition (high, low).

To our best knowledge, this is the first study to show that auditory feedback modulates the amplitude of target tremor in ET, comparable to visual feedback. It is long known, that visual feedback modulates action tremor in different disease conditions like multiple sclerosis and ET.

# Conclusion

# References

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# Acknowledgements

# Author contributions

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# Competing interest statement

# Materials and Methods

Participants

The study was approved by the ethical committee of the Medical Faculty of Kiel (AZ 447/21) and was conducted in accordance with the Declaration of Helsinki. Participants gave informed consent before participation and received financial compensation after completion of the study. The data come from a cohort of 14 with essential tremor patients and 12 healthy control subjects. All patients were diagnosed with Essential Tremor by a specialist for neurology, healthy controls had no history of neurological or psychological disorders. All participants were right-handed and had no restrictions in vision or hearing.

Patients were asked to pause tremor related medication, all participants were instructed to reduce caffeine and nicotine as much as possible prior to the experiment. Covariates between groups were compares using Mann-Whitney-U tests. While there was no significant difference in age (t = 86.50, p = 0.147), the Becks-Depression-Inventory (BDI-II, t = 113.50, p = 0.003) and Schmahmann-Scale (t = 33.50, p = 0.046) revealed a statistically significant difference between the patients and control group. More information can be found in Table 1.

Experimental setup

The experiment consisted of a computer-based task which involved matching a target force. Data collected from participants included a force sensor (GSS) and pupillometry. For the collection of the force, an Arduino based force sensor was used. The weight cell (Adafruit, ADA4541) was connected to an amplifier (SparkFun, HX711) and digitized at 80Hz via a ArduinoUno. The Arduino was connected via a serial port to the stimulus presentation computer. The experiment presentation was done via PsychoPy (Peirce et al., 2019). Inside the presenting script the data of the serial port was used to feedback information to the participant in real time (delay < 10ms) and send to LSL (Kothe et al., 2020) for recording. Data fed back to participants was of visual and auditory nature. Pupil data was recorded using a Pupil Core (Pupil Labs, Berlin, Germany) module with a sampling rate of 240 Hz. Calibration was done prior to the experimental task while data was send to LSL during the experiment via the Pupil LSL relay (Pupil Labs, 2021). All data streams (Experimental Marker, GSS and Pupil data) were recorded using the LabRecorder (Boulay, 2020). For details see Figure 4, left side.

Diagram

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Figure 4: Experimental setup. (Left side) Datastreams (Force sensor, Pupil dialation and experimental triggers) are recorded via the Lab Streaming Layer. (Right side) Example epoch with timing of all elements.

Experimental procedure

The experiment lasted ~20 minutes and took place in a controlled laboratory environment on the computer (distance from the to the screen: approx. 90 cm) in the presence of a test administration. The experiment consisted of a training block and three subsequent experimental blocks, between which the subject could take short breaks. Prior to training the individual maximum force (MF) was determined. Participants were asked to apply maximum pressure to the force sensor with the thumb and index finger three times for 1 second. The maximum of the respective averages of samples was used as MF.

The task for the participants was to match a target force and holding it for a period of 30s (15% of the MF). They got feedback of their performance during every trial in form of sensory feedback. Three different sensory feedback types presented in the following order: 1. Visual only, 2. visual-auditive and 3. auditive only. Visual only (vo) feedback consisted of two vertical bars which were supposed to overlap in position when the target force was matched. Auditory only (ao) feedback was provided by a reference tone (440Hz) and another tone which varied in pitch depending on the distance to the target (between 120 and 880 Hz). Visual-auditiv feedback was a combination of the vo and ao type. Each experimental trial consisted of a written cue what type of feedback is being presented, a 30 s resting period a 1-1.5s fixation cross and a 30 s task period (see Figure 4, right side).

In total every participant conducted 12 experimental trials, four of each feedback type. The subjects were asked to match the target force as quickly as possible using the force sensor in their right hand and hold it for the remainder of the trial. During each trial the feedback was altered using one of two factors using different gain levels, resulting in different feedback types. The low gain and high gain resulting in an easier or harder task to match the target force (Archer ea., 2017).

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Here FP is the force produced by the subject, Ft is the target force, and G is the gain level used to manipulate the amplitude of feedback.

Data processing

Preprocessing for force and pupil.

The force data was first normalized to the participants MF by dividing every sample by the MF \* 0.15. Next, data was filtered between 0.1-15 Hz using a bandpass butterworth filter of order 10, executed by the scipy package (1.8.1) in python (3.8). After filtering, data was cut into trials to estimate power-spectral densities, using the the psd\_array\_welch function from the MNE package. For tremor relevant power, a frequency window 4-12 Hz was defined, for voluntary movement a 0-3 Hz frequency window was defined. Unfiltered force error (RMSE) during a trial was calculated by the root of the squared difference per sample to the target force.

The Pupil data was first cleaned of artifacts. Blinks were detected using outliers in gaze acceleration and PupilLabs confidence values and set to NaN in the time series. NaN values were subsequently interpolated using a fft convolution using a Gaussian kernel ranging 120 samples (~0.5 s). After cleaning the raw time series, data was cut into epochs. A divisive baseline correction was applied per epoch and changes in pupil size were estimated 5 s after epoch start until 10s before the epoch ended. The mean of the time window of interest was used for statistical analysis.

Preprocessing scripts of the GSS and pupil data can been found at GitHub (<https://github.com/JuliusWelzel/tremor_feedback_jw>).

Statistics

Clinical data were compared between groups using a Mann-Whitney-U test. Correlation analysis were conducted using a Pearson correlation if Levene’s test and Shapiro-Wilk test allowed it, otherwise spearman rank correlation were used. For the GSS data the interindividual difference between the means of the easy and hard feedback condition was calculated per feedback type. An t-tests between groups for every feedback condition was calculated. The same was done for the pupil size data. All statistical analysis were performed in Python (3.8) using the scipy package (v1.8.1) or pingouin package (v0.5.2).