

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

Julius Welzela\*, Günther Deuschl**a**, Julian Keil**b**, Miriam Güthe**a**, Gesine Hermann**a**, Walter Maetzler**a**, and Jos Becktepe**a**

aUniversity Hospital Schleswig-Holstein, Kiel, Germany

bDepartment of Psychology, University of Kiel, Kiel, Germany

\*Correspondence should be addressed to J.W. (j.welzel@neurologie.uni-kiel.de)

**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.

Chart

Description automatically generated with low confidence

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

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), auditive-visual (av) and auditive-only (ao)

**Groups** -> essential tremor patients (ET) and healthy controls (HC)

# 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.

A picture containing diagram

Description automatically generated

Figure 3: Pupil times series data of a single participant. (A) Raw times series separate for all trials.

(B & C) Distributions for baseline and trial part of epoch.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | 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. | | | | |

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.

## Tremor force

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

For the differences in the tremor relevant frequency spectrum, we found a statistical significant difference between each group 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

Description automatically generated with medium confidence

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

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.

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

Boulay, C. (2020). *LabRecorder* (1.14).

Kothe, C., Boulay, C., Delmore, A., & Stenner, T. (2020). *LabStreamingLayer* (1.15.0).

Peirce, J., Gray, J. R., Simpson, S., MacAskill, M., Höchenberger, R., Sogo, H., Kastman, E., & Lindeløv, J. K. (2019). PsychoPy2: Experiments in behavior made easy. *Behavior Research Methods*, *51*(1), 195–203. https://doi.org/10.3758/s13428-018-01193-y

Pupil Labs. (2021). *Pupil LSL Relay* (2.0). PupilLabs.

# Acknowledgements

# Author contributions

Lorem ipsum dolor sit amet, consectetuer adipiscing elit. Maecenas porttitor congue massa. Fusce posuere, magna sed pulvinar ultricies, purus lectus malesuada libero, sit amet commodo magna eros quis urna. Nunc viverra imperdiet enim. Fusce est.

# 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, a 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)

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. In the experimental blocks feedback was give in the following order: 1. Visual only (vo), 2. visual-auditive (va) and 3. auditive only (ao). Prior to training the individual maximum force (MF) was determined. Participants were asked to apply maximum pressure with the thumb and index finger three times for 1 second. The maximum of the respective averages of samples was used as MF. The target force to match for the rest of the experiment was 15% of the MF. In the training block, the task was first trained in each of the three feedback conditions and subjects were allowed to repeat the training if necessary. Trials from the training were not included in the data analysis. The subsequent main blocks, comprise four randomized trials each from the three feedback conditions. The subjects were asked to reach a target as quickly as possible using the force sensor in their right hand. The force sensor in their right hand. In the last of the three main blocks, however the subject is instructed not to use the force sensor and instead to use only the passively follow the tasks. Accordingly, the sequence of the blocks is not randomized, the passive condition is always the last to be processed and serves as a baseline for the recording of pupillometry data. The processing time for each of the main blocks is approximately 6.5 minutes. At the beginning of each trial, a written cue is first displayed for 1 s indicating the nature of the task is displayed, either "auditory only" for the unisensory-auditory feedback Condition ao, in which the only cue to the proximity of the bar to the target is a changing "visual only" for the vo condition, in which the bar and the target are shown on the screen but no are shown on the screen but no sound is heard, and "auditory & visual" for the multisensory the multisensory feedback condition av (see Figure 4). The cue as well as all stimuli described in the following are presented against a gray background (hex color code: #808080). In each trial, the cue is first followed by a rest period of variable length(Range: 1 - 1.5 s; see Figure 5), during which a blank, black screen is shown. Subsequently, the subject is shown a fixation cross on a gray background centered in the middle of the screen is presented (hex color code: #000000; see Fig.5), which the subject is asked to fixate with his gaze. The presentation duration of the fixation cross varies between 1.5 and 2.5 s. In the subsequent Force phase, as in the experiment of Archer et al. (2018), the subject's task is to move to a target area as quickly as possible using the force sensor in his or her hand as quickly as possible and to hold the position there until the force phase ends. Phase ends. Unlike in the original study, however, the force phase ends after only 6 sin order to obtain more trials for the same total duration of the experiment. In this way a better signal-to-noise ratio can be obtained for the EEG data analysis. The target area is centered horizontally and vertically on the computer monitor marked by a white bar (height: 27.522° visual angle, width: 0.997° visual angle, Hex color code: #ffffff). If a visual stimulus serves as a cue to the set position (in the feedback-conditions vo and av; see Figure 5, left and right), the subject is presented with an additional is shown another red bar in addition to the white target area (height: 27.522°visual angle, width: 0.997° visual angle, hex color code: #732626), which the test person can the force sensor to move it horizontally in order to move to the target area. Target. How strongly the bar responds to the pressure applied to the force sensor, is varied from trial to trial (see UV SoF in the independent variables section). In trials with auditory cue stimulus (feedback conditions ao and av, cf. Figure 5 middle), the distance to the target area is signaled by a changing tone signaled (frequency between 440 and 660 Hz). The volume was set before the experiment calibrated to a comfortable volume for the subjects before the experiment.

Data processing

Preprocessing for force and pupil.

Four force data measures at each feedback condition were calculated using Python: mean force (%MVC), unfiltered force error (RMSE), RMSE low-pass filtered into the 0–3 Hz range, and sum of power of force between 4–12 Hz. We chose to evaluate force tremor between the 4–12 Hz range since this range is where a majority of the tremor is contained. The middle 25speriodofeachtrialwasanalysedtoensurethatsubjectshad reached a constant level of force. The low and high visual feedback measures (mean force, RMSE unfiltered, RMSE 0–3 Hz, sum of power in 4–12 Hz) were subtracted to obtain a high-low difference measure (mean ForceH-L, Force Unfiltered ErrorH-L,Force 0-3 Hz ErrorH-L, and Force TremorH-L). Each measure was tested for homogeneity by conducting a Levene’s test, and was followed by either an independent samples t-test or a Mann-Whitney U-test (significance at P 5 0.05).

Statistics

Descriptive and Tremor and Pupil

Diagram

Description automatically generated

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.