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Differential Frequency Modulation of Neural Activity in the Lateral Cerebellar Nucleus in Failed and Successful Grasps

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Abstract

The olivo-cerebellar system has an essential role in the detection and adaptive correction of movement errors. While there is evidence of an error signal in the cerebellar cortex and inferior olivary nucleus, the deep cerebellar nuclei have been less thoroughly investigated. Here, we recorded local field potential activity in the rodent lateral cerebellar nucleus during a skilled reaching task and compared event-related changes in neural activity between unsuccessful and successful attempts. Increased low gamma (40–50 Hz) band power was present throughout the reach and grasp behavior, with no difference between successful and unsuccessful trials. Beta band (12–30 Hz) power, however, was significantly increased in unsuccessful reaches, compared to successful, throughout the trial, including during the epoch preceding knowledge of the trial's outcome. This beta band activity was greater in unsuccessful trials of high-performing days, compared to unsuccessful trials of low-performing days, indicating that this activity may reflect an error prediction signal, developed over the course of motor learning. These findings suggest an error-related discriminatory oscillatory hallmark of movement in the deep cerebellar nuclei.

Keywords

Local Field Potentials; Cerebellum; Skilled Reaching; Deep Brain Stimulation

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Conflict of Interest

A.G.M. and K.B.B. have distribution rights related to intellectual property in Enspire DBS, Cardionomics and ATI. A.G.M. is a consultant to Spinal Modulation and Functional Neuromodulation.

INTRODUCTION

The cerebellum is known to play an integral role in both motor learning and kinematics; however, the specific role of the lateral cerebellar nucleus (LCN), or dentate nucleus, in adaptive motor control remains unclear. The dentate is reciprocally connected to contralateral premotor, motor, and associative cortices via the ventrolateral and mesial thalamic nuclei (Allen et al., 1978; Brodal, 1978), with limited projections from the periphery. Recent data suggest that Purkinje single cell spiking in the cerebellar cortex, which inhibit the deep cerebellar nuclei, is associated with failure or success of a trial (Greger and Norris, 2005; Roitman et al., 2009) and can predict performance errors (Kitazawa et al., 1998; Popa et al., 2012). If there is a predictive signal upstream of the LCN at the level of the cerebellar cortex, it follows that a distinctive modulatory signal may be processed in the LCN itself. In the current experimentation, we tested the hypothesis that local field potential (LFP) activity within the LCN could distinguish between successful and unsuccessful reaches during a skilled motor task. Such findings have important physiological implications, as LCN LFPs during reaching and grasp have not been studied to date. Furthermore, these findings represent an important technical milestone by advancing ongoing translational work in chronic stimulation of the LCN as a treatment for post-injury motor rehabilitation (Cooperrider et al., 2014; Machado et al., 2013) towards a closed-loop stimulation therapy, wherein stimulation is triggered by a neural signal.

METHODS

Animals

Male Long-Evans rats (200–225g) were housed in standard caging on a 12:12 hour light/dark cycle and food-restricted (12g of food/day) during experimental testing with unrestricted access to water. Behavioral testing was performed during the dark phase of the light cycle under controlled red lighting. Animal use was approved by the Institutional Animal Care and Use Committee of Cleveland Clinic.

Microelectrode Array (MEA) Implantation

Each animal was implanted unilaterally with a single five-electrode tungsten MEA (Figure 1; Model #385-TU0501-01, Alpha-Omega Engineering, Nazareth, Israel) in the LCN as described previously (Cooperrider et al., 2014), with laterality randomized across animals. Briefly, the dura mater was removed after a small craniectomy and the MEA was advanced with the most medial and anterior electrode of the array targeted to AP: -10.8 and ML: ± 3.6 from bregma and DV: -4 from brain surface. A reference screw was placed on the skull, adjacent to the lambda. The implant was secured with dental cement and animals were allowed to recover with food and water *ad libitum* for one week before the initiating of behavioral training.

Behavioral Testing

Each animal was trained to perform a reach and grasp task (Figure 2), which required it to reach through a narrow vertical aperture to retrieve a food pellet (45 mg, TestDiet, St. Louis, MO). The animal was placed into a clear Plexiglass box (25 cm long by 20 cm high by 8 cm

wide) with a 12 cm tall, 1 cm wide aperture on one of the narrow walls. A ledge was mounted on the outside of the box, 2 cm from the ground, and centered on the aperture. On this ledge were two small divots used to hold the food pellets, each offset 1 cm from the center of the aperture. This design restricts pellet reaching to a designated forelimb, in this case the limb ipsilateral to the implanted LCN (Whishaw and Pellis, 1990). An infrared beam (OPB856Z, Optek Technology, Carrollton, TX) with analog input to the recording system was mounted such that the paw would interrupt the beam immediately prior to pellet grasp. After each reach, a pellet was placed in the rear of the box to entice the animal to leave the test region between trials, allowing another pellet to be positioned for retrieval. Rats without any successful grabs after ten days of training with the desired forelimb were excluded from the study. Behavioral training was videotaped (60 frames/sec) and saved for offline analysis. An LED was mounted in the camera's field of vision and illuminated when the infrared beam was interrupted.

Data Collection

Behavioral and electrophysiological data were collected for two to three months post implant recovery. Animals performed the task for 15 minutes per session, during which time a wireless headstage (Model TB5653, TBSI, Durham, NC) was attached to the MEA to record LCN LFP activity.

LFP channels were sampled at 787.8 Hz, amplified (800x), and band-pass filtered (1.2 Hz – 300 Hz). Additional analog inputs were used to synchronize infrared beam interruption. Data were digitized and stored as binary files in Telespike (Alpha-Omega Engineering, Nazareth, Israel) for offline analysis.

Behavioral Analysis

Videotaped reaching performance was analyzed to classify trials into unsuccessful (MISS) or successful (HIT) retrieval attempts. A HIT was defined as a trial when the rat successfully grasped and consumed the pellet in a single reach. A MISS was defined as an unsuccessful retrieval and included either a failure to grasp the pellet or a dropping of the pellet prior to consumption. Following an unsuccessful reach and grasp, rats may make additional attempts to collect the missed pellet before “resetting” their behavior by retreating to the rear of the testing apparatus. These subsequent attempts were excluded from analysis. Videos were manually parsed and compared with infrared beam signal to acquire time stamps for the beam break and to categorize these time stamps as denoting MISSES or HITS.

To determine the mean time at which animals performed each component of the reach/retrieval behavior, a subset of fifty HIT and MISS trials were randomly selected from each animal for analysis. For HIT trials, the video frames that represented movement initiation, beam break, grasp, and consumption were noted. Initiation was defined as the frame in which the rat began to lift its paw to reach. The beam break frame was defined as the first frame showing interruption of the infrared beam, indicated by LED illumination. A grasp was defined as the first occurrence of flexion of the digits around the pellet. Consumption was considered as the first frame when pellet came in contact with the mouth. MISS trials were analyzed by noting the frame when initiation, beam break, failed grasp, the second

attempt, and the second grasp occurred. Initiation and beam break were defined the same as for HIT trials. The failed grasp was defined as the frame showing the first flexion of the digits but resulting in an unsuccessful grasp. The second attempt was defined as the frame when the paw began to cross the vertical front wall of the training apparatus following a failed trial. Times for each behavioral marker were averaged across trials per animal and animals then averaged together.

Electrophysiological Analysis

LFP data were further band-pass filtered (1.2 to 100 Hz) and analyzed using custom Matlab scripts (MathWorks, Natick, MA). Using the infrared beam break as event marker, the data were extracted in 900 ms snippets (–550 to +350 ms) and divided into three epochs: –550 – –350 ms, –350 ms – 0, and 0 – 350 ms, by electrode. The frequency axis was maintained at 1 Hz per bin. Any trial containing 100 consecutive milliseconds of LFP data beyond 3 standard deviations of the mean or anything beyond 4 standard deviations was eliminated as artifact. The remaining trials' time series data were separated into HIT or MISS and a median value computed to yield a single time series per animal per trial type by electrode. The time series were then subjected to a time-frequency analysis using complex Morlet wavelets with a time-bandwidth product of 7. This evoked analysis specifically allows for the examination of phase-locked oscillations. LFP data between –550 and –350 ms before beam break were classified as baseline, as these data represented activity occurring prior to the mean timing of reach behavior initiation (Figure 2). Each bin was compared to the baseline period to compute the standard deviation (z-score) for each frequency. Thereafter, each animal's electrodes were averaged together, followed by an overall average of all animals to evaluate if there was sustained predominance of oscillations in any frequency domain across animals. Beta band was defined as 12–30 Hz, low gamma as 40–50 Hz, and high gamma as 50–90 Hz.

Statistics

The power within each frequency band of interest was calculated and compared both between trial types (Trial type×Epoch) and to the baseline period of each trial type (Frequency band×Epoch) using Two-way repeated measure ANOVAs. Multiple comparisons were corrected using the Holm-Sidak post-hoc test. Video frame times from the behavioral analysis were compared using a paired t-test. Statistics were performed with Graphpad Prism Software (La Jolla, CA) and significance levels set at $p < 0.05$.

To determine whether there was a significant difference comparing high- and low-performing days within the same trial type, a non-parametric permutation analysis (Maris and Oostenveld, 2007) was performed to compare days with performance <50% of the maximal accuracy and >50% maximal accuracy. Evoked responses and their time-frequency spectrograms were computed for each animal for each condition (as above), and compared using parametric t-tests. Time-frequency points that exceeded a t-value corresponding to alpha level of 0.05 were thresholded to form clusters. The largest positive and negative clusters were retained and tested under a permutation distribution. Permutation was performed for each animal by pooling the trials from two conditions in a combined set, followed by random repopulation of conditions. Permutation was only carried out at trial

level, not at channel level. The data analysis described above was repeated to identify the largest cluster. This was repeated 1000 times. Using the permutation distribution of the largest cluster statistics, the observed clusters were tested. Monte-Carlo estimates of p-value were computed for each observed cluster. If $p < 0.05$, the cluster was identified as significant.

Histology

Prior to sacrifice, electrolytic lesions were created at each electrode of the MEA (DC-current, 40–200 μ A, 30 s–2 min). After pentobarbital overdose (100 mg/kg), the brain was harvested, submerged in 4% paraformaldehyde for one week, and transferred to 30% sucrose in PBS for an additional 48 hours. 20 μ m coronal cerebellar sections were cut, mounted, and then stained with Perls DAB (HT20, Sigma-Aldrich, St. Louis, MO) and 1% cresyl violet. Animals with incorrectly targeted MEAs were excluded from the analysis or used as controls.

RESULTS

Animals

Seven animals completed this study. Histology confirmed the positioning of the MEA in the LCN for all five electrodes of the array in six of the seven animals (Figure 1). Only three electrodes could be confirmed for the final animal. Thus, data from 33 electrodes were used in the analysis.

Reaching Analysis

Video analysis revealed that the mean time of reach initiation occurred at -322 ± 16 ms (mean $\pm$ SEM, Figure 2) for HIT and -328 ± 16 ms for MISS trials, and did not differ between trial types ($p = 0.28$). MISS trials resulted in an immediate second grab attempt before a behavioral “resetting”, marked by the rat retreating to the back of the testing apparatus, in $74 \pm 4.6\%$ of the sampled trials. Because this second attempt did not occur until 472 ± 51 ms after beam break, it is unlikely to have been represented in the spectral analysis of data that included data up to 350 ms after beam break. None of the sampled MISSES trials were drops, thus, the vast majority of analyzed MISSES trials were of the failure-to-grasp type.

LCN modulation during reach and grasp behavior

As shown in the time-frequency plots (Figure 3A), the wavelet analysis revealed strong task-related activity of beta and low gamma bands across both trial types. Individual animals' frequency modulation can be seen in Supplemental Figure 1. Comparing between trial types, there was no difference in the power of high gamma band between HITS and MISSES ($F_{(1,6)} = 0.10$, $p = 0.76$, Figure 3B) nor in the power of low gamma band ($F_{(1,6)} = 1.07$, $p = 0.34$, Figure 3C). However, there was a significant difference in power between HITS and MISSES in the beta band range both before and after beam break [$F_{(1,6)} = 11.5$, $p = 0.015$], Holm-Sidak post-hoc: $-350 - 0$ ms, $p = 0.034$; $0 - 350$ ms, $p = 0.0050$, Figure 3D]. This result can also be seen in individual animals using standard induced methodologies, averaging wavelet-derived spectral components on a trial-by-trial level (data not shown).

Comparing all frequency bands by trial type to the baseline, a significant main effect of epoch was found for both HITS and MISSES ($F_{(2,12)}=9.51$, $p=0.0033$, Figure 3E; $F_{(2,12)}=5.37$, $p=0.022$, Figure 3F). Neither HITS or MISSES demonstrated a change in high gamma power compared to the baseline epoch ($-350 - 0$: $p=0.69$, 0.89 ; $0 - 350$: $p=0.44$, 0.89 , respectively, Figure 3E-F, Holm-Sidak posthoc). However, both HITS and MISSES showed an increased low gamma power compared to the baseline epoch ($-350 - 0$: $p=0.049$, 0.045 ; $0 - 350$: $p=0.0029$, 0.045 , respectively, Figure 3E-F, Holm-Sidak post-hoc). The power of beta band modulation increased in both epochs after baseline in MISSES ($-350 - 0$: $p=0.040$; $0 - 350$: $p=0.0031$, Figure 3F, Holm-Sidak post-hoc), while only increasing in the $0-350$ ms epoch in HITS ($-350 - 0$: $p=0.11$; $0 - 350$: $p=0.0025$, Figure 3E, Holm-Sidak post-hoc).

LCN Modulation Classified by Performance

To investigate whether oscillatory patterns differed between high- and low-performing days, a nonparametric permutation analysis was implemented to find the largest significant cluster between the two stages of training by trial type. The high-performing days generally correspond to late-stage learning days, while low-performing days correspond to early training.

This analysis revealed no significantly different cluster between high- and low-performing HITS days (Figure 4). There was, however, a significant cluster at approximately 15–22 Hz, comparing MISSES trials, with an increase in power at this frequency range observed in the high-performing days. This cluster corresponds to the initiation and reach portion of the behavioral task.

DISCUSSION

We investigated how the spectral profile of the rat LCN is differentially modulated during successful and unsuccessful performance of a reach and grasp task. To our knowledge, this is the first analysis of LCN LFP activity in a behaving animal model. We observed significant modulation across two frequency bands during the task: low gamma (40–50 Hz) and beta (12–30 Hz). Low gamma band power increased throughout the entirety of the reaching task independent of the trial type, suggesting that modulation in this frequency range may be related to active movement itself. Power within the beta (12–30 Hz) band, however, was greater during MISSES trials than during HITS throughout the entirety of the task, including during pre-grasp reaching phases of behavior, before the outcome of the trial was known. The overall increase in beta power observed in MISSES trials may be primarily due to an increase in beta power of MISSES on high-performing days, suggesting that beta band in the LCN may represent an error prediction signal, acquired through the process of motor learning.

Beta and gamma band in the motor system

Beta band activity is observed in the motor system, including the primary motor cortex, basal ganglia, motor thalamus, and cerebellum (Aumann and Fetz, 2004; Baker et al., 1999; Sanes and Donoghue, 1993). Modulation of beta band (typically including 12–30 Hz) is

associated with an increased coherence and/or amplitude in pre-movement or hold phases of behavior (Baker et al., 1999; Donoghue et al., 1998; Pellerin and Lamarre, 1997), although higher frequencies of beta/gamma band (approximately 20–40 Hz) modulation have been occasionally observed during movement, particularly when a task is difficult or novel (Murthy and Fetz, 1992, 1996). In contrast, results from the current study show increased beta band (12–30 Hz) power throughout the extent of a missed trial, including the period prior to the missed grasp, and during the retrieval and consumption periods of correct trials. The source of this discrepancy may be ascribed to several factors. First, this movement-coincident beta modulation could be a unique feature of the LCN. Secondly, we may speculate that the increase of beta band power during failed trials may also occur at other nodes of the motor system but, because unperturbed failed trials are less frequently analyzed than correct trials, it has not yet been observed. Lastly, beta band modulation was recorded in the present study at the neuronal population level with LFPs. The majority of cerebellar electrophysiology studies to date have been conducted through single-cell recordings (D'Angelo et al., 2009; Gilbert and Thach, 1977; Shidara et al., 1993), thus limiting the number of prior studies that can contrast with the present data.

Low gamma band (including 30–50 Hz) activity in the motor system is present during movement, usually during isotonic contraction (Gwin and Ferris, 2012; Omlor et al., 2007; Seeber et al., 2014) although modulation has also been reported to occur during the hold or preparatory periods of behavior (Igarashi et al., 2013; Sanes and Donoghue, 1993). Considering that low gamma band modulation (40–50 Hz in this study) was increased in both HITS and MISSES throughout the dynamic movement of reaching and grasping, this finding may more directly represent the dynamics or kinematics of movement itself, consistent with findings that low gamma band modulation occurs during isotonic contraction. We cannot rule out, however, that low gamma band plays a similar functional role to beta band, as its pattern of activity displays a marked resemblance to that of beta band. Individual animal data reveal that the power modulation of one animal may partially underlie the effect seen in low gamma band (Supplementary Figure 1), but we cannot conclusively posit that the two frequency ranges execute two different functions.

Error-related cerebellar activity

The cerebellum has long been hypothesized to play a crucial role in the processing and correction of motor errors (Eccles, 1969; Glickstein and Yeo, 1990; Miall et al., 1993). One model of motor function implicates the cerebellum as part of a forward model, where a sensory prediction of the outcome of an ongoing motor program is formed (Eccles, 1969; Shadmehr and Krakauer, 2008; Shadmehr et al., 2010; Wolpert et al., 1995). Such a model requires that an efference copy, a copy of the cortical motor plan, be sent to the cerebellum for evaluation (Eccles et al., 1972) via the robust corticopontocerebellar pathway (Horne and Butler, 1995). Modulation of frequency bands in the LCN may function as a substrate for the prediction of outcome, as our data suggest that changes in beta band activity predict the success of the motor plan before the kinematics are realized, satisfying a criterion of a forward model (Shadmehr et al., 2010). Moreover, the observation that the increase in beta band activity of unsuccessful trials is predominant during high-performing days further suggests that this signal may reflect the successful implementation of an internal model

within the cerebellum, wherein an error prediction may be signaled or computed. These data suggest most strongly that beta band modulation may act as a predictor of error itself, and not a learning signal, as one would expect greater modulation in poor-performing or early-training days if such was the case. The lessened beta band modulation in low-performing days also does not support the interpretation that this modulation is reflective of motor error, as gross error greatly decreases as animals become more proficient.

Additionally, our results demonstrate increased beta band power of MISSES through the entirety of the reaching behavior and failed grasp. These findings suggest that the LCN may have both feedforward (prior to grasp) and feedback (during and after grasp) functions, in agreement with similar studies examining cerebellar Purkinje cell spike modulation (Greger and Norris, 2005; Popa et al., 2012).

One limitation of this study is that it does not assess oscillatory changes in LCN activity between HITS and MISSES at the pre-motor planning phases. Rather, our data shows that LCN oscillations can predict the outcome of a reaching trial at the onset of the movement, well before the grasp. Additionally, although it cannot be entirely ruled out that differential modulation between HITS and MISSES is due to postural or motoric differences, we think that this is unlikely as there does not appear to be a discernible difference in the kinematics of reaching before the pellet is reached. The latency between initiation of the reach and grasp of the pellet does not differ between trial types.

Beta band as a trigger for therapeutic stimulation

Our lab has previously shown that open-loop, continuous stimulation of the LCN improves motor performance after cortical ischemia (Cooperrider et al., 2014; Machado et al., 2009; Machado et al., 2013). The present findings suggest that the LCN may provide not only the optimal site for stimulation of the dentatohalamocortical pathway for therapeutic purposes (Machado and Baker, 2012), but also a practical target for recording neurophysiological signals that may predict the outcome of a reaching trial. We postulate that better post-ischemia rehabilitation outcomes may be achieved if we exploit the LCN's role in error prediction towards a closed loop paradigm of DBS to be utilized along with motor training. Future research will explore these concepts.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Glossary

LCN	lateral cerebellar nucleus
MEA	microelectrode array

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HIGHLIGHTS

We recorded local field potentials of the lateral cerebellar nucleus during reaching.

Modulation was apparent in the beta (12–30 Hz) and low gamma (40–50 Hz) bands.

Beta band modulation was increased in unsuccessful trials compared to successful.

This increased modulation was present even before the target was reached.

Figure 1. MEA design and electrode localization

A) Wireless transmitter connected to the MEA and a magnified view of the electrode configuration. B) Targeted locations of the five MEA electrodes plotted on a trace of the nearest coronal section (Paxinos and Watson, 1998) with the LCN shown in white and the interpositus shaded gray. Coordinates are anterior/posterior with the compass showing dorsal and medial directions. C) Nissl- and Perls-DAB-stained section showing an electrode in the LCN. The dotted line defines the approximate border of the LCN and red arrows highlight the electrode tract.

Figure 2. Video stills depicting key behavioral events for the reach/retrieval task
 Video stills highlight the behavioral markers used to define each phase of task performance. Mean $\pm$ SEM is displayed. The bolded line represents the time frame statistically analyzed following spectral analysis, while behavior outside of the time statistically analyzed is shown with a dotted line.

Figure 3. The LCN exhibits oscillatory changes during the reach and grasp task

A) Trials were segregated into HITS and MISSES. Analysis included 1195 HITS trials and 1254 MISSES trials. (Upper panel) Mean LFP is presented with shaded area representing the standard deviation (SD). (Lower panel) Time-frequency plots produced from wavelet analysis. The solid black line at -350 ms indicates the end of the baseline period and the solid black line at 0 signifies infrared beam interruption. The dashed black line at approximately -320 ms indicates the mean initiation of the reaching movement and the dashed line at approximately +25 ms indicates the mean grasp of the pellet. Data were band-

pass filtered between 1.2–100 Hz and normalized by computing the SD compared to the baseline period (–550 to –350 ms). B-D) Spectral data were divided into 3 epochs: baseline, before (–350 ms – 0) and after (0 – 350 ms) beam break. HITS and MISSES were compared across frequency bands with 2-way ANOVAs and Holm-Sidak post-hoc tests. * $p < 0.05$, ** $p < 0.01$. E-F) Epochs before and after beam break were compared to the baseline period for each frequency band with 2-way ANOVAs and Holm-Sidak post-hoc tests. #40–50 Hz significantly different from baseline, $p < 0.05$; *12–30 Hz significantly different from baseline, $p < 0.05$; **12–30 Hz significantly different from baseline, $p < 0.01$

Figure 4. Oscillatory Modulation of Low- vs. High-Performing Days

Trials were divided into HITS or MISSES, and days grouped by performance. The high-performing classification included days when performance was $>50\%$ of an individual's maximal performance and the low-performing classification included days when performance was $<50\%$ of maximal performance. As before, data are presented as SD compared to the baseline period. Trials were permuted between low and high conditions to

find the largest observed significant cluster that differed between conditions. A black border outlines the bounds of the largest significant cluster ($p < 0.05$)