**Pathological Beta Burst Dynamics are Conserved Across Different Movements in Parkinson’s Disease**

Raumin S. Neuville, Ross. W. Anderson, Matthew N. Petrucci, Jordan E. Parker, Kevin B. Wilkins, Anca Velisar, Helen M. Bronte-Stewart

1Stanford University School of Medicine, Department of Neurology and Neurological Sciences, Stanford, CA, USA
2Stanford University School of Medicine, Department of Neurosurgery, Stanford, CA, USA

1University of California School of Medicine, Irvine, CA
2Smith Kettlewell Research Institute, San Francisco, CA, USA

Corresponding Author:
Helen Bronte-Stewart MD MSE
John E. Cahill Family Professor,
Director, Stanford Movement Disorders Center (SMDC)
Department of Neurology and Neurological Sciences,
300 Pasteur Drive
Stanford University School of Medicine
Stanford CA 94305

Email: hbs@stanford.edu

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Highlights

- Prolonged beta burst durations represent pathological neural activity in Parkinson’s disease
- Beta band peak frequencies are similar across rest, fine, limb and axial movements
- Beta burst dynamics are similar among rest and different movement states
- Conservation of Parkinsonian neural characteristics across different activity states supports the feasibility of closed loop deep brain stimulation systems in daily life

Abstract

Background: Resting state beta band (13 – 30 Hz) oscillations represent pathological neural activity in Parkinson’s disease (PD). It is unknown whether the peak frequency or dynamics of beta oscillations change among rest, fine, limb and axial movements. This will be critical for the development and feasibility of closed loop deep brain stimulation (DBS) algorithms during resting and movement states.

Methods: Subthalamic (STN) local field potentials (LFPs) were recorded from a sensing neurostimulator (Activa® PC+S, Medtronic Inc.,) and synchronized to kinematic recordings in twelve PD participants off medication/off STN DBS during thirty seconds of repetitive alternating finger tapping, wrist-flexion extension, stepping in place, and free walking. Beta power peaks and beta burst dynamics were identified by custom algorithms; beta burst dynamics were compared among rest and movement tasks.
Results: Resting state burst durations were longer in a PD beta band, which was elevated above the 1/f physiological spectrum compared to an overlapping band (p < 0.001). Beta power peaks were evident during fine, limb, and axial movements in 98% of movement trials; the peak frequencies were similar during movements and at rest. Burst duration, average and peak power were also similar among the four movement tasks across the group but varied within individuals.

Conclusions: Prolonged burst durations were a feature of PD bands elevated above and not of PD bands overlapping the 1/f spectrum. The conservation of rest/movement band peak frequency and burst dynamics during different activity states supports the feasibility of successful closed loop DBS algorithms driven by beta burst dynamics during different activities and at rest.
Introduction

Exaggerated resting state beta band (13 – 30 Hz) oscillations and synchrony are pathophysiological markers of hypokinetic aspects of Parkinson’s disease (PD). When averaged over time, these oscillations appear as elevated portions of the local field potential (LFP) power spectral density (PSD) above the broadband 1/f spectrum (He, 2014; Shreve et al., 2017). Beta band power is attenuated on dopaminergic medication and during subthalamic (STN) deep brain stimulation (DBS); the degree of attenuation has been correlated to the degree of improvement in bradykinesia and rigidity, whereas averaged resting state beta band power is less robustly correlated with PD motor signs (Bronte-Stewart et al., 2009; Brown et al., 2001; Cassidy et al., 2002; Eusebio et al., 2011; Kühn et al., 2009, 2008, 2006; Levy et al., 2002; Priori et al., 2004; Quinn et al., 2015; Ray et al., 2008; Weinberger et al., 2006; Whitmer et al., 2012; Williams et al., 2002).

Recently, it has been shown that physiological resting state beta oscillations are represented by short duration fluctuations in power (beta bursts) in the striatum and cortex of healthy non-human primates (Feingold et al., 2015). These authors suggested that the precise temporal dynamics of beta bursts may be more reliable markers of PD than averaging beta activity over periods of time. Burst dynamics in PD have been studied during rest (Tinkhauser et al., 2017), but less is known about real time beta burst dynamics during movement and whether beta burst dynamics differ during fine motor or limb movements and/or during gait and freezing of gait (FOG) (Anidi et al., 2018; Lofredi et al., 2019). The duration of beta bursts is a relevant neural control variable for closed loop DBS systems, which can precisely target (shorten) the duration
of beta bursts, but it is not known how this variable may change between movements, possibly necessitating a different response from a closed-loop algorithm.

In this study, we investigated whether beta band peak frequency and beta burst dynamics were conserved or were different during fine, limb, and/or axial movements in PD people. We also tested the hypothesis that bands within the PD LFP spectrum, which overlapped the 1/f spectrum, should consist of mainly shorter duration (physiological) bursts and that a band, in which PSD power was elevated over the 1/f spectrum, should consist of mainly longer duration (pathological) bursts.

Methods

Human Subjects

Fourteen participants (10 male) with clinically established Parkinson’s disease (PD) underwent bilateral implantation of DBS leads (model 3389, Medtronic, Inc., Minneapolis, MN, USA) in the sensorimotor region of the subthalamic nucleus (STN) using a standard functional frameless stereotactic technique and microelectrode recording (MER) (Brontë-Stewart et al., 2010; Quinn et al., 2015). Long-acting dopaminergic medication was withdrawn over 24 hours (72 hours for extended release dopamine agonists) and short-acting medication was withdrawn for over 12 hours before surgery and before each study visit. One participant took an extra short-acting carbidopa/levodopa tablet 5 hours before the experiments and was included as their resting state LFP spectra were similar 6.25 hours and 8.5 hours later, suggesting resolution of an attenuating effect of medication on beta power (Trager et al., 2016). The preoperative selection criteria and assessment of participants have been previously described (Bronte-Stewart et al., 2009; de
Solages et al., 2010; Taylor Tavares et al., 2005). The dorsal and ventral borders of each STN were determined using MER, and the base of electrode 0 of the Medtronic 3389 lead was placed at the MER defined ventral border of the STN (de Solages et al., 2011, 2010; Marceglia et al., 2006). The DBS leads were located in the STN, Supplementary Information, Fig. S1. All participants signed a written consent and the study was approved by the Food and Drug Administration (FDA), Investigational Device Exemption (IDE) and the Stanford School of Medicine Institutional Review Board (IRB). Each participant was classified as tremor dominant (TD) or akinetic rigid (AR) phenotype based on previously described criteria (Quinn et al., 2015; Shreve et al., 2017; Trager et al., 2016). The age of the group (mean ± SD) was 57.2 ± 9.4 years and the disease duration from symptom onset was 7.7 ± 3.7 years. Four participants were TD and eight were AR phenotype. Unified Parkinson’s disease Rating Scale motor (UPDRS III) scores (mean ± SD) in the pre-operative off- and on-medication state were 39.2 ± 14.8 and 23.2 ± 14.1, respectively. Two TD participants were excluded because of prominent tremor, during which their beta band power was attenuated such that no peak was detected in both hemispheres, leaving a total of twelve participants and 24 STNs (Shreve et al., 2017).

**Experimental Protocol**

All experiments were performed within two months after DBS lead placement in the off medication/off DBS state. Recordings were collected in the Stanford Human Motor Control and Neuromodulation Laboratory. Experiments started with a resting state recording, during which each participant sat still for 30 seconds. Participants completed four different movement tasks: (1) repetitive alternating finger tapping (RAFT) on an engineered keyboard (Bronte-Stewart et al., 2000; Taylor Tavares et al., 2005; Trager et al., 2015) (2) instrumented repetitive wrist-
flexion extension (rWFE) using wearable sensors (Koop et al., 2008, 2006; Louie et al., 2009), (3) stepping in place (SIP) on dual force plates (Nantel et al., 2011), and (4) free walking (FW). During the RAFT task, participants were seated with their elbow flexed at approximately 90 degrees and the wrist was supported by a pad alongside a customized engineered keyboard. Visual and auditory feedback was minimized, as the participants had their eyes closed and wore headphones that played white noise to limit auditory feedback from the key tapping. With the index and middle fingers placed on individual keys, participants were instructed to tap each key in an alternating pattern as fast and regularly as possible for 30 seconds. For the instrumented rWFE task, participants were seated and instructed to raise their arm to a 90-degree angle and flex and extend their hands at the wrist as fast as possible for 30 seconds. During the SIP task, participants were instructed to perform alternating stepping on dual force plates for 100 seconds. For the FW task, all participants walked for approximately one minute that included portions of forward walking and turns. All movements were self-paced.

**Data acquisition and analysis**

Local field potentials (LFPs) from the STN were recorded from the electrode pair of the DBS lead, which had the greatest resting state beta band peak power and with the least artifact (electrode pairs 0-2 or 1-3 of the Medtronic 3389 lead; Supplementary Information, Table S1). The pre-amplified LFP was high-pass filtered at 2.5 Hz and low-pass filtered at 100 Hz. LFP data was sampled at a rate of 422 Hz (10-bit resolution). The gains used for the experiments were set at 2,000 with a center frequency of 2.5 Hz. The uncompressed LFP data were extracted via telemetry using the ActivaTM PC+S tablet programmer and then transferred to a computer for offline analysis in MATLAB (version 9.5, The MathWorks Inc. Natick, MA, USA). LFP data
used for analysis was from the first 30 seconds of movement or from the maximum length of continuous movement without cueing. The power spectral density (PSD) diagrams during the resting and movement states were calculated using Welch’s method, which used a 1 second Hanning window with 50% overlap (Welch, 1967). The peak frequency in the beta band was detected using a peak detection algorithm (de Solages et al., 2010); if more than one peak was detected, the peak with the greatest power was chosen. In two movement episodes, the algorithm failed to detect a peak, which was evident on visual inspection. For each STN, we defined the movement band as ± 3 Hz band surrounding the peak beta frequency of the PSD during movement, for a total of a 6 Hz bandwidth. The data acquisition and analysis of the kinematic recordings was not included in the analysis of this manuscript and has been described previously (Anidi et al., 2018; Blumenfeld et al., 2017; Quinn et al., 2015; Syrkin-Nikolau et al., 2017).

**LFP burst dynamics determination**

Figure 1 demonstrates the method used to determine the movement band burst dynamics. Simulation of physiological LFP activity was performed using pink (1/f) noise, generated using the MATLAB routine dsp.ColoredNoise in a period of 36 seconds, with a sample frequency of 422 samples/second and the amplitude matched to the roll off of the *in vivo* human data.
(Anderson et al., 2020; He, 2014); a simulated 1/f PSD from pink noise is represented as the grey trace in Fig. 1A.

![Figure 1](image.png)

**Figure 1.** Method for determining burst durations (A) PSD diagrams of 30 seconds during a participant’s resting state (red) versus pink noise (gray). The yellow, shaded area represents the 6 Hz band centered on the peak of the elevated portion in the PSD. The green-dashed lines display the band (non-pathological) where there was no elevation of the resting state PSD above the pink noise or simulated 1/f activity. (B) Consecutive, 6 Hz envelopes of the filtered, rectified and squared resting state LFP during the resting state within the non-pathological, high frequency range. The red lines signify the median power of the troughs from each envelope. (C) The envelope of a 6 Hz band centered around the peak of the of the beta band (shaded yellow in A). The threshold for determining burst durations, represented by the red line, was calculated by multiplying the average median trough powers

The resting state PSD from a representative person with PD (red trace, Fig. 1A) revealed a broad band (11-30 Hz) where LPF power was elevated above the 1/f spectrum and a higher frequency band (45-63 Hz) that overlapped with the 1/f spectrum, Fig. 1A. The band in the PD spectrum, which overlapped with the 1/f spectrum was used to determine the baseline or threshold, from which burst dynamics from elevated bands would be calculated. To do this, the band was first
filtered into equal consecutive 6 Hz overlapping bands, using a 6-Hz bandwidth, zero-phase 8th order Butterworth filter, and then squared. An envelope was formed by interpolating the consecutive peaks of the squared signal; the envelopes of each band are represented in Fig. 1B. The median power of the local minima (troughs) of the envelope of each band was determined, red lines Fig. 1B. Using a similar process, the envelope of a 6 Hz band around the peak of the elevated portion of the PD PSD (shaded yellow, Fig. 1A) is shown in Fig. 1C. The threshold or baseline power, which would determine the timing and duration of bursts in elevated beta band, was chosen as four times the average of the median of the trough powers from the 45-63 Hz band and is represented as the red line on Fig. 1C (Anderson et al., 2020). The duration of a burst was calculated as the time between consecutive crossings of the envelope across the baseline threshold, Fig. 1C. Average and peak power of each burst was measured as the average and highest instantaneous power of the burst, respectively.

Statistics

The primary outcome variables were movement peak frequency, mean burst duration, mean burst power (mean of the total burst average power), and mean burst peak power. Normalization of all power values was completed through division by the average power of the squared and rectified signal in the 45-63 Hz frequency band during the resting state (Anidi et al., 2018). One-way ANOVAs compared peak frequencies in the PSDs and variation in burst metrics among the different movement tasks and resting state with each STN treated individually. Analyses were corrected for multiple comparisons using Bonferronni correction. In the presence of a violation of Mauchly's test of sphericity, the Greenhouse-Geisser correction was applied. A Wilcoxon
signed ranks test was used to compare between elevated and overlapping bands during resting state as the data failed normality when using the Shapiro-Wilk test. There was one trial per movement task for each participant.

**Results**

*Frequency bands of elevated power exhibit longer burst durations than those of overlapping bands in the PD spectrum*

We tested whether the distribution of PD burst durations was shifted towards longer durations in a frequency band, whose average power was elevated over the 1/f curve (Fig. 2, insert yellow shaded region) compared to the distribution in a band whose power lay within the confidence intervals of the simulated, 1/f PSD (Fig. 2, insert green shaded region, 33-39 Hz). To determine the physiological burst duration, we first found the average peak frequency across all participants (mean ± SD) during the resting state to be 20 ± 3 Hz. Using a 6 Hz band centered around 20 Hz (17-23 Hz), we determined the physiological mean beta burst duration from the simulated 1/f curve, which was 178 ± 16 ms. We then defined physiological burst durations as those shorter than the mean plus 2 standard deviations of the physiological beta band which was 210 ms.
The distribution of resting state PD burst durations, compiled from all 24 STNs, from the elevated band and the overlapping band is demonstrated in Fig. 2. The mean burst duration was longer in the elevated band compared to that in the overlapping band (1020 ± 1580 ms and 160 ± 40 ms respectively, p < 0.0001). In the elevated PD beta band, 65.7% of burst durations were longer than the upper limit of simulated physiological beta burst durations (210 ms); in the overlapping PD band, 76.7% of bursts had physiological (short) durations. This demonstrates that in the resting state, neural activity in the bands elevated above the 1/f curve were dominated by longer (pathological) burst durations, whereas the neural activity in the PD overlapping band consisted of mainly shorter (physiological) burst durations.

Figure 2. Burst duration distributions of elevated and overlapping band during the resting state for all STNs. Burst durations above the threshold of 210 ms were labelled as prolonged (red) and those below were labelled as physiological (black). Five points in the elevated band are not shown as they represented durations > 5000 ms. The insert shows a resting state (red) and a pink noise (gray) PSD diagram. The elevated and overlapping bands are represented by the yellow and green highlighted area, respectively.
**Movement peak frequency was conserved among different movements**

Beta peaks were evident and appeared similar in frequency during the four movement tasks in the PSDs from a representative AR PD participant as shown on Fig. 3A. The synchronized neural (movement band) and kinematic recordings of each task by the same participant are demonstrated for the contralateral hand in repetitive alternating finger tapping (RAFT, Fig. 3B), and repetitive wrist flexion-extension (rWFE, Fig. 3C), and for stepping in place (SIP, Fig. 3D). The participant demonstrated progressive bradykinesia in both the RAFT and rWFE and normal SIP. The movement band power fluctuated over time as the representative participant performed different movements, Fig. 3B-D.

**Figure 3.** Neural and kinematic signals of the movement tasks from one participant. (A) LFP PSD diagrams during the four different movement tasks from one participant. The yellow highlighted area represents the patient-specific movement band. Movement band envelope (upper panel) and kinematic (lower panel) synchronized recordings from, (B) repetitive alternating finger tapping (RAFT), (C) repetitive wrist flexion-extension (rWFE), and (D) stepping in place (SIP)
Among the full cohort of 24 STNs, peaks of elevated beta power were detected in 98% of movement episodes during the different tasks, demonstrating that exaggerated beta band oscillations and synchrony were present during fine motor, limb and axial movements in addition to at rest. The frequencies of the peaks were similar among the different movements across the group (p = 0.65) and between the more and less affected STNs within individuals (p = 0.20). As demonstrated for the group’s resting state data in Fig. 2, the group mean movement band burst duration, mean and peak power were longer and greater in the elevated band (yellow region, Fig 3A) than that in the overlapping band (33-39 Hz), regardless of task, (p = 0.001 (burst duration), p < 0.0001 (mean burst power and peak power); Supplementary Information, Table S2).

Movement band burst metrics during different movements

Overall for the 24 STNs, the mean burst duration was similar among movements, Fig. 4A (p = 0.12); however, the patterns of burst durations among tasks varied among participants, Fig. 4B and C. Within an individual, the mean burst durations of the more affected and less affected STNs also differed among tasks, Fig. 4B and C. Across the group there was no difference between movement band burst duration between the movement tasks and resting state (p = 0.16).
Figure 4. Distribution of mean burst duration of the four movement tasks for twelve participant cohort (24 STNs). (A) In the box plots, the boundary of the box closest to the x-axis represents the 25th percentile, the center line represents the median, and the highest boundary indicates the 75th percentile. Whiskers above and below the box represent the maximum value of the data above the 75th percentile that is within 1.5 times the interquartile range (IQR) and the minimum value of the data below the 25th percentile that is within 1.5 times the IQR, respectively. (B,C) Mean burst durations for each STN shown for the more and less affected sides.
A similar result was seen for the means of the movement band mean burst power, which was not different among movements for the group, $p = 0.20$, Fig. 5A. However, there was variation in the mean burst power among movements, within individuals and between STNs within the same participant, Fig. 5B and C. A similar result was seen for the means of the movement band peak power among movements ($p = 0.138$). There was no difference between movement band mean burst power and peak power between the movement tasks and resting state ($p = 0.077$ and 0.079 respectively).

**Discussion**
A substantial literature supports the presence of exaggerated STN beta band neural oscillations and synchrony in the resting state in Parkinson’s disease (PD), but less is known about the characteristics of STN beta dynamics during fine motor, limb and axial movement in PD. The results of this study demonstrate that pathological beta neural activity is still present during ongoing movement and, for the first time, we have shown that the peak frequency of the movement beta band was conserved among fine, limb and axial movements in freely moving people. Mean movement band burst dynamics (duration, average and peak power) were also similar among the different movements for the group, although there were differences among movements within individuals, and between the more affected and less affected STNs of individual participants. When comparing resting state to movement, there was no difference in peak frequency and burst dynamics.

Both pathological and physiological neural activity is represented in the PD LFP spectrum

Physiological neural activity consists of short periods of neural synchrony that are important for normal neurophysiological processing, and these may be represented by short duration fluctuations of elevated power (bursts), whereas pathological neural activity in Parkinson’s disease is characterized by prolonged durations of exaggerated beta band neural synchrony (Bronte-Stewart et al., 2009; Brown, 2003; Eusebio et al., 2011; Foffani et al., 2003; Giannicola et al., 2010; He, 2014; Kühn et al., 2008, 2006; Levy et al., 2002; López-Azcárate et al., 2010; Moshel et al., 2013; Öz Kurt et al., 2011; Priori et al., 2004; Ray et al., 2008, p. 2; Shreve et al., 2017; Tan et al., 2013; Wang et al., 2014; Weinberger et al., 2006; Whitmer et al., 2012; Yang et al., 2014). The results of this study demonstrated that the majority of burst durations in the PD spectral band that overlapped the 1/f spectrum were in the physiological range, whereas the
The majority of the burst durations in the PD (beta) band that was elevated above the 1/f spectrum were in the pathological range. The mean burst duration was significantly longer in the elevated band compared to the mean burst duration of that overlapping band, which was similar to that reported for the beta band in the normal non-human primate in both the striatum and motor cortex (Feingold et al., 2015). This demonstrates that both pathological and physiological neural activity is present in the same PD spectrum, and this suggests that if a spectral band is not elevated above the 1/f curve in a PSD, then neural information processing using those frequency bands is largely physiological.

*The clinical significance of the conservation of beta band peak frequency and burst dynamics across movements*

Several studies have demonstrated that beta power decreased before, at the onset of, and during movement in human participants with PD and in non-human primates (Anidi et al., 2018; Blumenfeld et al., 2017; Hell et al., 2018; Johnson et al., 2016; Jounidi et al., 2013; Kühn et al., 2004; Litvak et al., 2011; Syrkin-Nikolau et al., 2017, Fischer 2018, Lofredi 2019). This has led to a frequent generalization in the literature that beta power ‘goes away’ during movement. The results of this study demonstrate that beta peaks were still evident during movement, and that the peak frequency, and overall beta burst dynamics were conserved among fine motor and limb movements and during gait. This may alleviate concerns regarding the implementation of closed loop DBS in freely moving people. Up to now, closed loop DBS classifier algorithms have used estimates of resting state beta band power as the control variable (Afzal et al., 2019; Little et al., 2016a, 2016b, 2013; Piña-Fuentes et al., 2019; Piña-Fuentes et al., 2017; Rosa et al., 2017, 2015; Velisar et al., 2019). Such algorithms require knowledge of the peak frequency of the band of
interest and until now it was not known whether the same beta band could be used to drive closed loop DBS when the person is working at their computer, when eating or dressing and when walking. The conservation of the choice of the band of interest (determined by the peak frequency) among fine, limb, and axial movements suggests that the same classifier algorithms will be appropriate across rest and movement states. In addition, advances in technology (Summit™ RC+S, Medtronic Inc.) have made it possible to use beta band burst duration and power as the control variable and will require calculation of patient-specific beta band dynamics. The conservation of beta band burst dynamics across movement states has demonstrated that these advanced methods of closed loop DBS will be feasible in the home environment. Patient-specific calibrations of burst duration and power thresholds to drive closed loop DBS will be an improvement to the current ‘one-size fits all’ DBS parameter settings.

**Limitations**

Due to the limited number of investigative devices (Activa™ PC+S, Medtronic Inc. MN, USA) allocated to centers, the sample size was small but comparable to previous studies (Anidi et al., 2018; Blumenfeld et al., 2017; Quinn et al., 2015; Syrkin-Nikolau et al., 2017). There were a larger number of akinetic rigid compared to tremor dominant PD participants in this cohort, so a phenotypic comparison was not possible due to insufficient statistical power. The interaction between neural and kinematic characteristics was outside the scope of this study.

**Conclusion**
The results of this study demonstrated that exaggerated beta power was evident during fine motor, limb and axial movements and that the peaks of the frequency band of elevated power (the movement band) were similar during such different movements. Importantly, overall the burst characteristics of the movement band were no different during different movements involved in normal daily activities, although there were differences among individuals and between the more affected and less affected STNs within individuals. It was evident that Parkinsonian LFP fluctuations (bursts) were longer in duration and greater in power in a frequency band, which was elevated above a simulated broadband 1/f spectrum compared to a band, which overlapped the 1/f spectrum, in which burst durations were largely physiological. The mean LFP burst durations in the physiological, overlapping band at rest and during movement were similar to that reported in the normal non-human primate in both the striatum and motor cortex (Feingold et al., 2015). This supports the hypothesis that normal physiological information processing may involve short periods of neural synchrony, whereas pathological sensorimotor processing in the beta band in PD may be related to longer periods of neural synchrony. Pathological beta bursts persisted through state changes and serve as a resolute biomarker for PD. This is critical for future closed loop DBS systems, which will require an input that is both indicative of the disease state as well as robust through the patient’s activities of daily living.

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Declaration of Competing Interest

Helen Bronte-Stewart is a member of the Medtronic Inc. Clinical Advisory Board.

Author Contributions

Raumin Neuville: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Data Curation, Writing – Original Draft and Review & Editing, Visualization, Supervision, Project administration. Ross Anderson: Methodology, Software, Validation, Formal analysis, Investigation, Writing – Original Draft and Review & Editing, Visualization, Supervision. Matthew Petrucci: Methodology, Validation, Supervision. Jordan Parker: Methodology, Validation. Kevin Wilkins: Formal Analysis, Writing – Review & Editing, Visualization. Anca Velisar: Software, Investigation. Helen Bronte-Stewart: Conceptualization, Methodology, Writing – Original Draft & Review & Editing, Supervision, Funding acquisition.
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