MDPI

Systematic Review

Towards Objective Quantification of Hand Tremors and Bradykinesia using Contactless Sensors: a Systematic Review

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Abstract: Assessing the progression of movement disorders such as Parkinson's Disease (PD) is key in adjusting therapeutic interventions. However, current methods are still based on subjective factors such as visual observation, resulting in significant inter-rater variability on clinical scales such as UPDRS. Recent studies show the potential of sensor-based methods to address this limitation. The goal of this systematic review is to provide an up-to-date analysis of contactless sensor-based methods to estimate hand dexterity UPDRS scores in PD patients. 224 abstracts were screened and 9 articles selected for analysis. Evidence obtained in a cumulative cohort of $n = 187$ patients and 1385 samples indicates that contactless sensors, particularly the Leap Motion Controller (LMC), can be used to assess UPDRS hand motor tasks 3.4, 3.5, 3.6, 3.15 and 3.17, although accuracy varies. Early evidence shows that sensor-based methods have clinical potential and might, after refinement, complement or serve as a support to subjective assessment procedures. Given the nature of UPDRS assessment, future studies should observe whether LMC classification error falls within inter-rater variability for clinician-measured UPDRS scores to validate its clinical utility. Conversely, variables relevant to LMC classification such as power spectral densities or movement opening and closing speeds could set the basis for the design of more objective expert systems to assess hand dexterity in PD.

Keywords: Tremor; Bradykinesia; Parkinson´s Disease, UPDRS, Leap Motion, Contactless

1. Introduction

Parkinson´s Disease (PD) is a movement disorder caused by the degeneration of the dopaminergic neurons of the *substantia nigra pars compacta*, a reduction of striatal dopamine, and is characterized by the potential presence of Lewy bodies [1]. PD requires constant monitoring to track progression and perform therapeutic adjustments. Monitoring is currently performed with questionnaires such as the Unified PD Rating Scale (UPDRS) [2].

UPDRS rates different aspects of PD through visual observation of a series of tasks. These tasks are designed to monitor, among others, the most important symptoms of PD, also known as cardinal signs: resting tremors, asymmetry, bradykinesia, and a positive response to dopaminergic replacement therapy. In the case of hand dexterity, these tasks are related to bradykinesia and hand tremors, performing tasks such as finger tapping. UPDRS then rates these tasks on scales from zero (no symptoms) to four (patient is unable to perform the task), through visual observation. While the criteria to identify zeroes and fours are mostly clear, intermediate scores are considerably more ambiguous, which irrevocably leads to sensibility and reliability problems [3]. UPDRS is commonly complemented with patient diaries, which, although helpful, can also be biased by the subjective view of the patient [4]. The fact that this ambiguity introduces variability in assessments is well documented [3,5]. Furthermore, the relationship between PD and similar conditions also accompanied by hand tremor, such as Essential Tremor (ET), is still unclear [6].

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A solution to minimise subjectivity is to introduce sensor-based measurements [7], which provide a reproducible and objective assessment of hand tremor and bradykinesia. The Leap Motion Controller (LMC) has been proposed for this task [8]. Capturing hand movements via contactless sensors has the potential to reduce ambiguity, providing neurologists with more objective assessments of hand dexterity that may lead to more accurate therapeutic adjustments. At the same time, variables that provide meaningful information for the estimation of UPDRS scores could be used to establish more objective assessment scales, allowing for a finer resolution in hand dexterity assessment and better adjusted pharmacologic therapies.

The goal of this article is to provide a systematic review of recent advances in hand dexterity assessment using contactless sensors in PD patients, in the domains of hand tremor and bradykinesia. This review aims to provide further insight into the feasibility and reliability of this paradigm, as well as suggesting best practice guidelines for both engineers and clinicians on how to proceed from this point.

2. Materials and Methods

As a basis for this systematic review, we searched the databases Pubmed, ScienceDirect, IEEE Xplore and Cochrane for articles matching the search query:

(Parkinson `OR` *Tremor)* `AND` *(Leap Motion* `OR` *Contactless* `OR` *Infared* `OR` *Lidar)*

on March 31, 2021. This search yielded the following results:

- 28 matches in Pubmed
- 168 in ScienceDirect, including 10 duplicates
- 18 in IEEE Xplore, including 5 duplicates
- 3 in Cochrane, including 3 duplicates

The search was complemented by 7 additional articles selected from the references of search matches, yielding 224 abstracts for screening. The abstracts of these matches were filtered according to the following criteria:

1. Research articles
2. Related to PD
3. Related to hand tremor or bradykinesia

This filtering reduced the abstracts to 47 full-text articles assessed for eligibility. These full-text articles were selected for analysis if they met the following *inclusion criteria*:

1. Articles presenting a method to measure hand tremor or bradykinesia using a contactless approach
2. In patients with PD
3. Aiming to link sensor data to clinical functional performance scores (MDS-UPDRS-III or similar)

Conversely, articles were excluded if they met at least one of the following *exclusion criteria*:

1. Articles not related to hand tremor or bradykinesia. 13 articles were excluded with this criterion.
2. Articles without participants (technical or otherwise conceptual papers). 7 further exclusions.
3. Articles aiming to test a novel rehabilitation tool or otherwise not linking sensor data to clinical functional performance scores. 9 further exclusions.
4. Articles not using contactless sensors. 3 further exclusions.
5. Articles aiming to classify between PD patients and controls exclusively and not to assess symptom severity. 6 further exclusions.

Finally resulting in *n=9* articles for the qualitative and quantitative analysis [9–17]. Of the selected articles, 6 were first identified in the Pubmed search, 1 in ScienceDirect, and 2 were selected from the additional articles. This procedure was conducted in accordance with the PRISMA guidelines. A.G. was responsible for the selection and data collection process. The following data were sought from the articles: cohort data, procedure data (assessment method, sensor implementation), classification data, and classification accuracy. No studies are clinical trials and no bias assessment was conducted. Both the PRISMA flow diagram and checklist are included in Appendix A.

3. Results

All identified articles use some form of video source, including hand detection and tracking. Six of the nine articles use the LMC [10–14,17–19], while 3 use other video sources [9,15,16]. Essentially, all studies follow the same structure: given a dataset of PD patients performing a certain MDS-UPDRS III task (*e.g.*, finger tapping) rated by one or more neurologists and captured with a sensor, the resulting task score (or a linear regression model) is inferred using points of interest of the hand, defined by a series of features, with a classification method, as depicted in Figure 1.

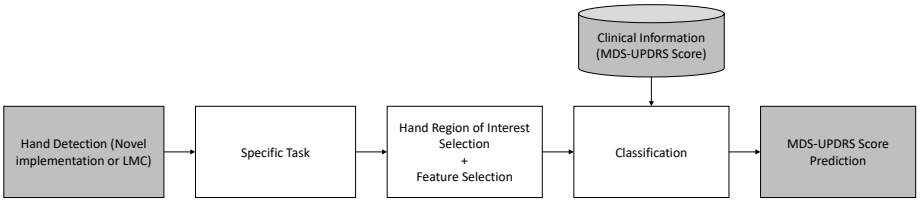

Figure 1. Study design flow diagram.

The identified studies implement one or more of the following UPDRS specific tasks:

- Task 3.4, Finger Tapping: The patient taps the index finger on the thumb 10 times as quickly and as big as possible. Out of the nine identified studies, seven analyse this task [9,11–16].
- Task 3.5, Hand Movements: The patient makes a tight fist, then opens the hand 10 times as fully and as quickly as possible. Out of the nine studies, three analyse this task [11–13].
- Task 3.6, Pronation-Supination: The patient extends the arm with the palm down, then runs the palm up and down alternately 10 times as fast and as fully as possible. The three same studies as above analyse this task [11–13].
- Task 3.15, Postural Tremor: The patient stretches the arm with the palms down. Tremor in this posture is observed for 10 seconds. Out of the nine studies, four analyse this task [10–12,17].
- Task 3.17, Kinetic Tremor: The patient performs at least three finger-to-nose maneuvers. Tremor in this movement is observed. Out of the nine studies, two analyse this task [10,17].

Table 1 summarizes the implemented tasks and signal of interest of each study. With the exception of task 3.5, the choice of hand region of interest for each task is consistent.

Table 2 presents the study devices, cohorts, total number and type of samples, as well as the main study goals. The studies either aim to predict the UPDRS rating of a given sample [9,10,15,17] or build a linear regression model relating variables extracted from the signals described in Table 1 and UPDRS scores [11–14,16]. In this study, we refer to sample as an instance of either hand of a PD patient performing a UPDRS task.

Cumulatively, the nine identified studies have a cohort of $n = 187$ patients and 1385 samples.

In the following, we divide the qualitative analysis into two subsections. Section 3.1 compares the results of studies that aim to evaluate the scores of UPDRS tasks related to tremor, 3.15 (Postural Tremor) and/or 3.16 (Kinetic Tremor), while Section 3.2 compares the results of studies that aim to evaluate bradykinesia with Tasks 3.4 (Finger Tapping), 3.5 (Hand Movements) and 3.6 (Pronation-Supination).

3.1. Tremor

Four studies aimed to assess hand tremor in PD using contactless sensors [10–12,17]. All studies used the LMC and either the center of the palm [10,17] or changes in fingertip velocity [11,12]. Butt *et al.* suggest the use of a 14 Hz lowpass filter, which should not affect the detection of Parkinsonian tremors. The studies also differed greatly in the choice of variables, as well as in the resulting accuracy, if classification was attempted.

Vivar *et al.* [10] proposed the use of histogram-based variables, computing an addition and subtraction of data points within a sliding window of 449 samples that advances through the data. Standard features are then computed from these histograms, with contrast and homogeneity providing the best performance. This yielded the best performance in this task group, with an accuracy over 97% classifying scores of 0, 1 and 2.

Lugo *et al.* [17] performed a similar study, using a significantly shorter windowing of 15 frames, as well as a different choice of variables. The resulting performance was worse at 74%, albeit the sample size was larger and a patient with a score of 3 on both hands was included.

Finally, Butt *et al.* [11,12] did not aim to estimate UPDRS scores but rather find variables correlated with said scores. The first study found no correlations between the chosen variables (signal strength and power in the 8-12 Hz band). The second study used the same variables and identified a correlation of $R = 0.59$ with signal strength.

Table 3 summarizes the differences in these studies. Overall, data indicate that detecting resting tremor is feasible, but kinetic tremor is more difficult to identify.

3.2. Bradykinesia

Seven studies aimed to assess at least one UPDRS task related to bradykinesia using contactless sensors [9,11–16]. These studies used a mixture of LMC and video, and differed greatly in choice of signals and variables. As all of these studies implemented Task 3.4 (Finger Tapping) but only three included additional tasks [11–13], we provide the results of these subsections in two separate tables. Table 4 summarizes the results for Task 3.4, where all studies used the Euclidean distance between the thumb and the fingertip as signal of interest, and Table 5 presents the results of the remaining tasks. The following subsections offer a detailed analysis of each task.

3.2.1. Task 3.4 (Finger Tapping)

With the exception of Khan *et al.* [9], all studies used the Euclidean distance between the tip of the index finger and the thumb as signal of interest. All studies are also reasonably consistent in the choice of variables: number of repetitions, amplitudes, variability of amplitude (particularly a decrease in amplitude with subsequent repetitions), speeds (generally considered as opening and closing speeds separately), accelerations, and frequency domain analysis. We can divide these seven studies into two groups: two that classify UPDRS scores [9,15] and five that use linear regression instead [11–14,16].

The two studies aiming at classification [9,15] used video instead of an LMC. Interestingly, the resolution and frequency employed by Khan *et al.* [9] is significantly lower, with a smaller number of participants but a significantly larger number of samples and a more complex classification task, as they aim to classify ternary scores of 0, 1 and 2 instead of classifying scores binarily as lesser or equal to one *vs.* greater than one [15]. Both

obtained the best results when using support vector machines, with overall accuracies of 82% for Khan [9] and 84% for Williams [15].

The remaining five studies used linear regression [11–14,16]. Some, but not all studies report the correlation of each of the variables individually. Overall, correlated variables fall within the $[0.5, 0.6]$ range, with Butt *et al.* [12] reporting significantly higher correlations for opening ($R = 0.836$) and closing ($R = 0.804$) speeds. Table 6 provides a direct comparison of the correlations of these studies. Overall, data indicate that assessing UPDRS scores with video is feasible, and opening and closing speeds show good correlations with UPDRS scores.

3.2.2. Task 3.5 (Hand Movements)

Concerning Task 3.5 (Hand Movements), no classification has been implemented yet. Lee *et al.* [13] explored the correlation of a 120 Hz linearly interpolated signal analyzed through amplitudes, frequencies, velocities and slopes. The number of participants was small (eight), but a large number of samples was collected by measuring with and without deep brain stimulation. They employed the angle between the fingers and the palm as signal of interest. As they did not explore the regression coefficients on each task individually but rather build a global linear regression model, only the velocity of Task 3.5 is reported as showing a relevant correlation of $R = 0.69$.

Butt *et al.* [11,12] also implemented this task in their two studies, using the Euclidean distance between palm and fingertips. Again employing a 14 Hz lowpass filter, they explored a very similar set of variables, using number of repetitions, speeds, the variability of frequency and amplitude, and power spectral density. They do report the individual correlation of each of the explored variables, showing significant correlations in most variables. Interestingly, the correlations vary substantially between both studies.

Table 7 offers a comparison between the correlations of these three studies. Overall, data indicate good correlations for opening and closing speeds. No study has attempted to classify UPDRS scores so far.

3.2.3. Task 3.6 (Pronation-Supination)

The same three studies as in the previous subsection implemented Task 3.6, using the same variables as in the previous task but focusing on a different point of the hand, the roll angle of the palm. All three studies report worse results with Task 3.6, as summarized in Table 8. Overall, data only shows good correlations for amplitude and variability of amplitude. No study has attempted to classify UPDRS scores so far.

4. Discussion

In this systematic review, we analyzed recent advances in sensor-based, UPDRS-inspired tremor and bradykinesia assessment in PD patients.

Concerning tremor, it seems that the coordinates of the palm center are a good predictor of UPDRS scores. Larger windows as well as statistical variables seem to be a better choice. Although the studies did not include patients with higher scores (three and four) classifying these should be easier as tremor is expected to be more severe. Although the limited number of studies does not yield definite conclusions, it would seem that classifying tremor UPDRS scores scores is nearly as accurate as classifying PD patients and healthy controls.

	Finger Tapping	Hand Movements	Pronation-Supination
Opening Speeds	409 (4)	240 (2)	96 (1)
Closing Speeds	409 (4)	240 (2)	96 (1)
Number of Repetitions	96 (1)	192 (2)	96 (1)
Frequency	313 (3)	192 (2)	96 (1)
Amplitude	169 (2)	96 (1)	336 (3)

	Finger Tapping	Hand Movements	Pronation-Supination
Opening Speeds	0.576	0.673	0.009
Closing Speeds	0.588	0.670	0.025
Number of Repetitions	0.728	0.585	0.257
Frequency	0.326	0.499	0.488
Amplitude	0.370	0.647	0.573

Figure 2. Number of samples and (number of articles) using different variables and UPDRS bradykinesia tasks (top) and sample-weighted correlations (bottom).

Figure 2 summarizes the number of samples, studies and sample-weighted correlations of all UPDRS bradykinesia tasks. The number of repetitions, opening and closing speeds, combined with changes in amplitude as the task progresses, seem to best characterize the rating in Task 3.4 (Finger Tapping). Implemented classification schemes in this scenario can already achieve excellent results, with accuracies over 80% when discriminating scores of 0, 1 and 2. As is the case with tremor, including higher scores would probably not decrease accuracy as these represent patients that are either almost (3) or fully (4) incapable of performing the task.

For Tasks 3.5 (Hand Movements) and 3.6 (Pronation-Supination) no full classification has been implemented yet. Early results seem to suggest that this task is more difficult to rate, as correlations between variables and neurologist ratings are somewhat lower, in the 0.5-0.6 range. A significant exception is variability of amplitude, which seemed to perform better in [11].

In spite of the limitations of this study, as the number of relevant studies is still small, available early evidence points to the LMC offering a feasible, objective alternative to visual observation to capture and rate hand motility in PD, as well as in other related diseases. Evidence shows that sensor-based methods have clinical potential and might, after refinement, complement or even replace subjective assessment procedures. A significant advantage of a sensor-based approach is that a linear regression model could provide a much higher resolution than current UPDRS assessment. Apart from this advantage, a sensor-based assessment also shows potential to link objective tremor and bradykinesia assessment to dopaminergic replacement therapy (DRT) dosage directly. In this sense, a more accurately adjusted dose might help maximize the period in which DRT is effective as dosage needs to be subsequently increased and OFF periods become longer.

Nevertheless, a substantial number of additional studies in several domains are required. Future research should focus on including more than one clinician rating, as well as procedure standardization. Once pilot trials achieve UPDRS classification predictions that fall within the inter-rater range, designing expert systems that offer a much finer resolution of tremor and bradykinesia should become feasible.

Author Contributions:

Conceptualization, methodology and validation, data curation, writing, A.G. and C.E.; Formal analysis, A.G.; Supervision, project administration, C.E.; All authors have read and agreed to the published version of the manuscript. Please turn to the CRediT taxonomy for term explanation.

Funding:

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Data Availability Statement:

Data is contained withing the article and supplementary material.

Conflicts of Interest:

The authors declare no conflict of interest.

Table 1. Study tasks and signal of interest

Reference	Finger Tapping	Hand Movements	Pronation-Supination	Postural Tremor	Kinetic Tremor
Khan [9]	Index finger position				
Vivar [10]				Palm center x coordinate	Palm center x coordinate
Butt 1 [11]	Thumb-Index fingertip distance	Sum of all Palm-Fingertip distances	Palm roll angle	Fingertip velocity average	
Butt 2 [12]	Thumb-Index fingertip distance	Sum of all Palm-Fingertip distances	Palm roll angle	Fingertip velocity average	
Lee [13]	Thumb-Index fingertip distance	Palm-Phalanxes median cosine angle	Palm roll angle		
Cakmak [14]	Thumb-Index fingertip distance				
Williams 1 [15]	Thumb-Index fingertip distance				
Williams 2 [16]	Thumb-Index fingertip distance				
Lugo [17]				Palm center coordinates	Palm center coordinates

Table 2. Study cohorts and goals

Reference	Resolution	N	Sex M/F	Age Range or Mean (SD)	Number of Samples	Study Goals
Khan [9]	352x288@25Hz	13	8/5	50-75	387	Classify UPDRS scores in 0, 1 or 2
Vivar [10]	LMC@40Hz	20	11/9	69 (14)	39	Classify UPDRS scores in 0, 1 or 2
Butt 1 [11]	LMC@35Hz	16	11/9	68 (7)	96	UPDRS Linear regression
Butt 2 [12]	LMC@35Hz	16	11/9	69 (9)	96	UPDRS Linear regression
Lee [13]	LMC@120Hz	8	6/2	44-60	144	UPDRS Linear regression
Cakmak [14]	LMC@100Hz	24	17/7	57 (9)	378	UPDRS Linear regression
Williams 1 [15]	1920x1080@60Hz	20		67 (10)	40	Classify UPDRS scores in <=1 or >1
Williams 2 [16]	1920x1080@60Hz	37	24/13	68 (10)	73	UPDRS Linear regression
Lugo [17]	LMC@40Hz	33	21/12	65 (12)	132	Classify UPDRS scores in 0, 1, 2 or 3

Table 3. Tremor classification results

Reference	Signal of Interest	Signal Preprocessing	Variables	Results
Vivar [10]	Palm center x coordinate	None	Sum and difference of histograms	Bagged Tree classifier, 97% accuracy
Butt 1 [11]	Fingertip velocity average	14 Hz Lowpass	8-12 Hz Power spectral density, signal strength	No significant correlations found
Butt 2 [12]	Fingertip velocity average	14 Hz Lowpass	8-12 Hz Power spectral density, signal strength	$R = 0.59$ for signal strength
Lugo [17]	Palm center coordinates	15-Frame Windowing	Square Euclidean and Chi Square distance, Earth Mover's distance, Manhattan distance, Shannon entropy, Log energy enthropy	Unspecified classifier, 73.81% accuracy

Table 4. Finger Tapping classification results

Reference	Signal Preprocessing	**Variables**	**Results**
Khan [9]	Moving average filter, Standard deviation outlier removal	Average of the Cross-Correlation between normalized maxima and minima, total taps, tapping speed, tapping speed variation, differences between first and second half of the task, opening velocity, closing velocity, zero crossing rate, signal energy, facial movements	SVM classifier, 82% accuracy
Butt 1 [11]	14 Hz Lowpass	Number of repetitions, speeds, variability of frequency and amplitude, power spectral density	Significant correlations for opening speed ($R = 0.515$) and closing speed ($R = 0.602$)
Butt 2 [12]	14 Hz Lowpass	Number of repetitions, speeds, variability of frequency and amplitude, power spectral density	Significant Correlations for number of repetitions ($R = 0.728$), closing speed ($R = 0.804$) and opening speed ($R = 0.836$)
Lee [13]	120 Hz Linear interpolation	Amplitudes, frequencies, velocities and slopes	Significant correlations for velocity and frequency ($R = 0.45$), $R = 0.86$ combining all tasks
Cakmak [14]	None	Mean and standard deviation of speed, acceleration, frequency	root mean square error of 4.37 points (7.8%) for UPDRS-III and 2.12 points (10.7%) for bradykinesia
Williams 1 [15]	PCA	Power spectral density, frequency, peaks, ratio of maxima to minima, standard deviation of peaks	SVM classifier, 84% accuracy
Williams 2 [16]	Savitzky-Golay	Amplitude, speed, amplitude variability, power spectral density	Significant correlations for speed ($R = 0.56$), amplitude variability ($R = 0.61$) and rhythm regularity ($R = 0.50$), $R = 0.69$ using all variables

Table 5. Hand Movements and Pronation-Supination classification results

Reference	Signal Preprocessing	**Variables**	**Hand Movements Results**	**Pronation-Supination Results**
Butt 1 [11]	14 Hz Lowpass	Number of repetitions, speeds, variability of frequency and amplitude, power spectral density	Significant correlations for variability of frequency ($R = 0.685$) and number of repetitions ($R = 0.630$)	Significant correlation for variability of amplitude ($R = 0.858$)
Butt 2 [12]	14 Hz Lowpass	Number of repetitions, speeds, variability of frequency and amplitude, power spectral density	Significant correlations for opening speed ($R = 0.647$), Variability of amplitude ($R = 0.647$), closing speed ($= 0.639$) and number of repetitions ($R = 0.539$)	Significant correlation for variability of frequency ($R = 0.488$)
Lee [13]	120 Hz Linear interpolation	Amplitudes, frequencies, velocities and slopes	Significant correlation for velocity ($R = 0.69$), $R = 0.86$ combining all tasks	Significant correlation for amplitude ($R = 0.56$), $R = 0.86$ combining all tasks

Table 6. Finger Tapping correlation (R) results. Amplitude refers to amplitude or variations thereof. Frequency refers to frequency or variations thereof. [1] Combination of all elements. [2] No distinction between opening and closing speeds

Reference	Opening Speeds	Closing Speeds	Number of Repetitions	Frequency	Amplitude
Butt 1 [11]	-0.515	-0.602			
Butt 2 [12]	-0.836	-0.804	-0.728	-0.006	-0.188
Lee [13]	0.45[1]	0.45[1]		0.45[1]	
Williams 2 [16]	-0.56[2]	-0.56[2]		-0.5	0.61

Table 7. Hand Movements correlation (R) results. Amplitude refers to amplitude or variations thereof. Frequency refers to frequency or variations thereof. [1] No distinction between opening and closing speeds

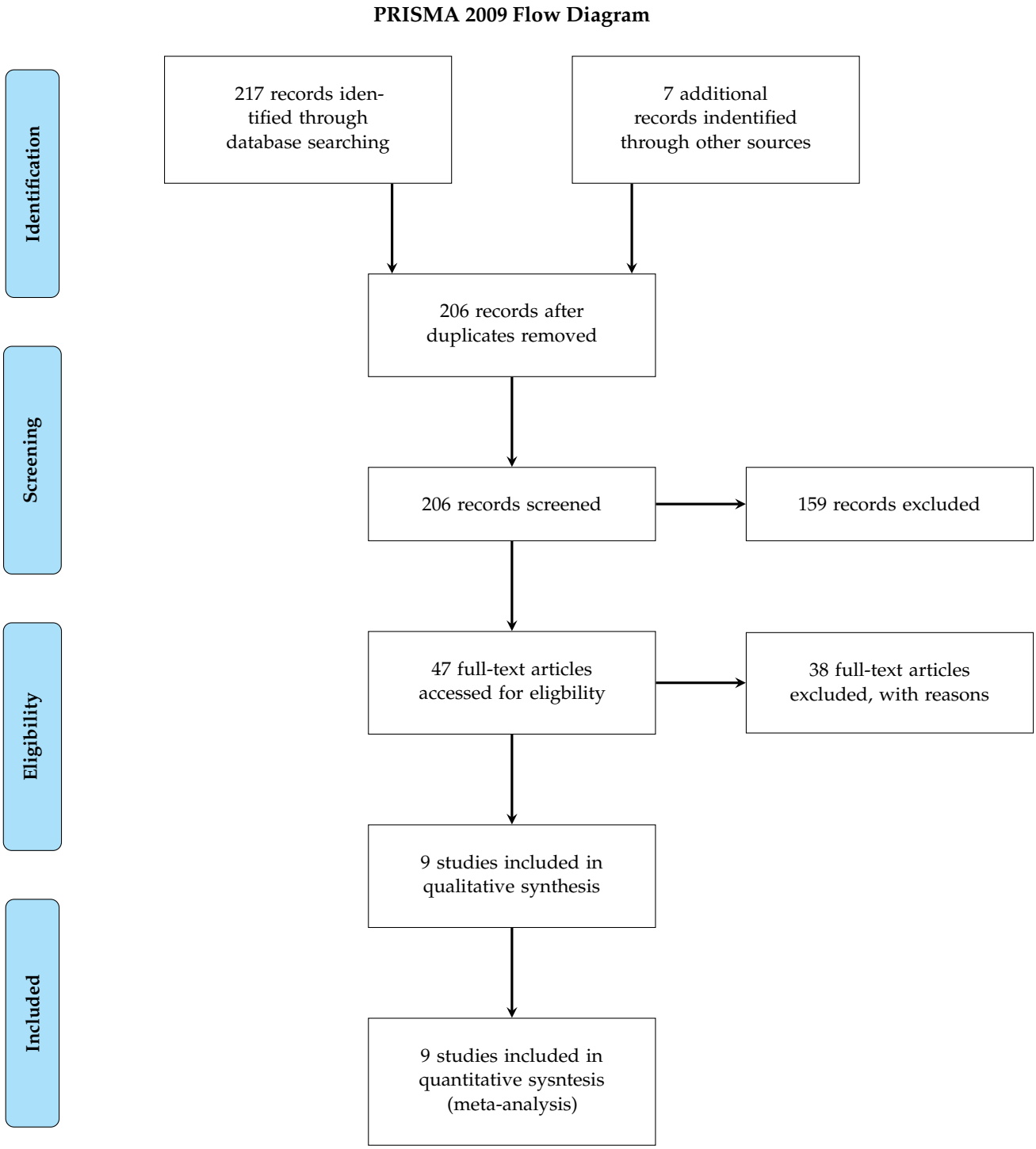
Reference	Opening Speeds	Closing Speeds	Number of Repetitions	Frequency	Amplitude
Butt 1 [11]			-0.63	-0.685	
Butt 2 [12]	-0.647	-0.639	-0.539	0.313	-0.647
Lee [13]	0.69[1]	0.69[1]			

Table 8. Pronation-Supination correlation (R) results. Amplitude refers to amplitude or variations thereof. Frequency refers to frequency or variations thereof

Reference	Opening Speeds	Closing Speeds	Number of Repetitions	Frequency	Amplitude
Butt 1 [11]					-0.858
Butt 2 [12]	-0.009	-0.025	-0.257	-0.488	0.307
Lee [13]					0.56

Appendix A. PRISMA Guidelines

Appendix A.1. PRISMA Flow Diagram



Appendix A.2. PRISMA Checklist

Table A1. PRISMA Checklist (Part 1/2).

Section and Topic	Item	Checklist item	Location where item is reported
Title			
Title	1	Identify the report as a systematic review	1
Abstract			
Title	2	See the PRISMA 2020 for Abstracts checklist	1
Introduction			
Rationale	3	Describe the rationale for the review in the context of existing knowledge	1
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses	2
Methods			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses	2
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted	2
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used	2
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process	2
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process	3
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect	2
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information	N/A
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process	N/A
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results	N/A
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5))	3
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions	N/A
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses	3
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used	3
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression)	N/A
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results	N/A
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases)	N/A
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome	N/A

Table A2. PRISMA Checklist (Part 2/2).

Section and Topic	Item	Checklist item	Location where item is reported
Results			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram	12
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded	2
Study characteristics	17	Cite each included study and present its characteristics	3
Risk of bias in studies	18	Present assessments of risk of bias for each included study	N/A
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots	3-5
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies	N/A
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect	3-5
	20c	Present results of all investigations of possible causes of heterogeneity among study results	N/A
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results	N/A
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed	N/A
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed	N/A
Discussion			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence	5-6
	23b	Discuss any limitations of the evidence included in the review	6
	23c	Discuss any limitations of the review processes used	N/A
	23d	Discuss implications of the results for practice, policy, and future research	6
Other Information			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered	N/A
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared	N/A
	24c	Describe and explain any amendments to information provided at registration or in the protocol	N/A
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review	6
Competing interests	26	Declare any competing interests of review authors	7
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review	8

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