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COORDINATION IN ADULTS WITH NEUROLOGICAL IMPAIRMENT – A SYSTEMATIC REVIEW OF UNCONTROLLED MANIFOLD STUDIES

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Highlights

- UCM studies in adults with neurological impairment are generally of good quality
- Several neurological diseases consistently reduce UCM synergy strength
- Anticipatory UCM synergy adjustments are deficient after neurological impairment
- The relationship between UCM synergy indices and function needs more investigation

ABSTRACT

Background: Analysis of sensorimotor synergies has been greatly advanced by the Uncontrolled Manifold (UCM) approach. The UCM method is based on partitioning inter-trial variance displayed by elemental variables into 'good' (V_{UCM}) and 'bad' (V_{ORT}) variability that, respectively, indicate maintenance or loss of task stability. In clinical populations, these indices can be used to investigate the strength, flexibility, stereotypy and agility of synergistic control. **Research question:** How are synergies affected by neurological impairment in adults? Specifically, this study aimed to determine *i*) the impact of pathology on V_{UCM}, V_{ORT}, and their ratio (synergy index); *ii)* the relationship between synergy indices and functional performance; *iii*) changes in anticipatory synergy adjustments (ASAs); and *iv*) the effects of interventions on synergies. **Methods:** Systematic review of UCM studies on adults with neurological impairment. **Results:** Most of the 17 studies had moderate to high quality scores in the adapted Critical Review Form and the *UCM reporting quality checklist* developed for this review. *i)* Most of the studies found reduced synergy indices for patients with Parkinson's disease (PD), olivo-ponto-cerebellar atrophy, multiple sclerosis and spinocerebellar degeneration, with variable levels of change in V_{UCM} and V_{ORT}. Reduction in synergy indices was not as consistent for stroke, in three out of six studies it was unchanged. *ii)* Five of seven studies found no significant correlations between scores on motor function scales and UCM indices. *iii)* Seven studies consistently reported ASAs that are smaller in magnitude, delayed, or both, for patients compared to healthy controls. *iv)* Two studies reported increased synergy indices, either via increase in V_{UCM} or decrease in V_{ORT}, after dopaminergic drugs for patients with PD. There were similar synergy indices but improved ASAs after deep brain stimulation for patients with PD. **Significance:**

UCM can provide reliable and sensitive indicators of altered synergistic control in adults with neurological impairment.

Key-words: uncontrolled manifold, synergy, neurological impairment

1. Introduction

Effective rehabilitation of movement-related disorders depends on our understanding of the ways in which atypical movement results from pathology, how pathology results from imprecise or insufficient movement, and how movement practice enhances task-specific performance and prevents health issues [1]. Advancements in the understanding of physiological and pathophysiological movement are thus fundamental for the development of effective clinical interventions. For this reason, "physical therapists need to own the human movement system and its management from the science to the practice" [2]. Clinicians and researchers in physical rehabilitation can be thought of as *applied movement scientists* [1,3].

Most physical therapists are familiar with the term synergy. It can, however, have different meanings. In clinical practice, synergy refers to muscles that are activated together to produce coordinated movement [4]. Pathological synergies refer to disrupted or non-selective recruitment of muscles leading to uncoordinated or stereotypical movement [5–7]. As many therapy approaches aim to improve motor function by breaking, re-balancing, reinforcing, or creating synergies[8], the investigation of synergies is fundamental to advancing clinical practice. In traditional movement science, synergies refer to neurally-established patterns of shared activity between muscles [9–11].

In the last two decades, the analysis of synergies has been greatly advanced by the Uncontrolled Manifold (UCM) approach. The UCM approach makes a unique contribution to the investigation of synergies with respect to applied movement science and neuroscience. In this approach, a specific definition of synergy is used. Synergies refer not only to a pattern of shared activity between motor elements [9–11], but also to a particular *task-specific* organization.

Synergies allow stable and flexible performance in tasks like reaching for an object, standing up, walking, or jumping [12,13]. The UCM approach thus defines and quantifies synergies with respect to function: a synergy exists when elements of the neuromuscular system are organized to stabilize important, functionally-relevant performance variables [12].

The label "uncontrolled" derives from the hypothesis that a special kind of variability of the redundant degrees of freedom of the neuromuscular system need not be controlled. Variability can be partitioned into two components (see Figure 1). One is a set of values compatible with a desired value of an important performance variable, such as for example the hand position when reaching for a target. This set of values is the UCM. In reaching for a target, because of redundancy, several combinations of shoulder, elbow and wrist angles will lead to the same hand position. Movement variability within this set of equivalent combinations (the UCM) does not affect task performance. Variability within the UCM is *good* in the sense that it contributes to stability while affording flexibility. Therefore, the central nervous system (CNS) does not have to correct deviations of the system if they are within the UCM; degrees of freedom are "uncontrolled", free to vary and solve the movement task flexibly. In contrast, some combinations of elements (joint angles in the reaching example) interfere with performance (hand position) and would thus be outside the UCM. This is *bad* variability because it negatively affects stability of performance, so it needs to be constrained [12,13].

The UCM method tests whether trial-to-trial movement variability is interpretable as stabilizing particular performance variables. First, one needs to choose candidate elemental variables (degrees of freedom at a given level of analysis) assumed to be independently controlled by the CNS. Because of the theoretical control assumption, the choice needs to be well justified. For example, separate joint angles, muscle activations or forces may be considered elemental

variables independently controlled by the CNS in typical individuals. However, the ability of patients with neurological pathologies to control muscles or joints independently may be impaired. For them, correlated patterns of joint motions, muscle activations or forces (called modes) would be more appropriately considered as elemental variables for UCM analysis. Second, a suitable task-relevant performance variable that is affected by variations in the elemental variables also needs to be chosen for analysis [12,13]. Examples of performance variables stabilized by synergies include the position of the center of mass in transfer and standing tasks, hand position and orientation in reaching tasks, total force in finger pressing tasks[14–16].

Data from elemental variables across several trials of a task are used to compute projections of variance onto the performance variable's UCM (V_{UCM}) and its orthogonal component (V_{ORT}). A ratio of the normalized magnitudes of variance along these two dimensions, the synergy index (SI), is computed as $(V_{UCM}- V_{ORT})/V_{TOT}$, where V_{TOT} is total variance and all variance indices are computed per dimension [12,13,17,18].

UCM indices V_{UCM}, V_{ORT} and SI can be used to investigate synergies in healthy and clinical populations. Higher values of V_{UCM} compared to V_{ORT} indicate more flexibility: the availability of varied movement patterns to accomplish the same task. Such flexibility is very useful to deal with changing circumstances, such as unexpected perturbations [19], fatigue of one of the elements [20], and secondary tasks [21]. Low V_{UCM} compared to V_{ORT} indicates stereotypy and decreased possibility to take advantage of redundancy. The SI indicates synergy strength. Stronger synergies (with higher proportions of V_{UCM} to V_{ORT}) indicate flexibility and adaptability, while weaker synergies (lower proportions of V_{UCM} to V_{ORT}) may reflect low performance stability. Lastly, the ability to switch between different synergies with anticipatory synergy adjustments (ASAs) (to turn synergies "on and off") in preparation for an action is of utmost importance in many functional

situations [22,23]. Agility requires the ability to attenuate a synergy in preparation for a quick change in that variable. Otherwise, the individual would have to fight his or her own synergy [18,24,25].

Around a decade ago, Latash and Anson argued for the use of UCM to investigate synergies in clinical populations [4]. Given the importance of synergy research in the application of movement science, the objective of this study was to review the evidence generated by UCM research in studies on individuals with neurological impairments. This review addresses the specific research questions proposed by Latash and Anson [4]: *i*) the relationship between pathology and changes in V_{UCM} and V_{ORT}, *ii*) the relationship between strength of synergies and performance in everyday functional tasks, *iii*) the relationship between functional deficits and ASAs, and finally, *iv*) the effects of interventions on pathologically changed synergies. With this literature review, we hope to contribute to evidence-based and theory-based developments in rehabilitation practice [3,26].

2. Methods

2.1. Search strategy

A search of scientific publications in the electronic databases PubMed and Scopus was conducted up to August 2018 with no date limits. The term "Uncontrolled Manifold" was used in isolation and in combination with (boolean operator AND) the keywords "Atypical", "Clinical", and "Rehabilitation". Study selection was conducted by two independent reviewers (P, V.A. and S, R.R) in four stages. First, databases were searched using the key terms. Then, the reviewers identified relevant candidate studies based on titles and abstracts. In this step, the full article was

assessed if reviewers couldn't decide whether it fulfilled the eligibility criteria. In the third stage, potentially relevant studies were read in full. In the fourth and final stage, the lists of references from the selected articles were inspected for additional eligible studies that were not found in the previous stages. The final selection was decided by consensus between both investigators, consulting a third investigator (V, D.V) in case of disagreement. There are no review protocols registered for this topic.

2.2. Criteria for selection of articles

Studies were eligible for inclusion in this review if they met the following criteria: research papers published in peer-reviewed journals using the UCM method in adults with neurological impairments. Case studies, review articles, and studies that assessed only healthy subjects were excluded. No limits on language or year of publication were used.

2.3. Quality assessment

Two reviewers (V, D.V. and P, V.A.) independently evaluated the quality of the selected articles. Reviewers were not blinded to the identity of authors of research papers or journal of publication. An adapted version of the Guidelines for Critical Review Form for Quantitative Studies [27,28] was used as a generic quality assessment (see Table 1a). In this adapted version, items referring to '*intervention*' in the Critical Review Form were either reformulated to refer to the task used in the UCM investigation, or suppressed. Specifically, the items below were changed:

‘Was the intervention described in detail?’ was changed to ‘Was the *task used for UCM analysis* described in detail?’

‘Could the intervention be replicated in practice’ was changed to ‘Could the *task* be replicated in practice?’

'Was contamination avoided?' was changed to 'Were *factors affecting typical task performance* avoided?'

'Was co-intervention avoided?' was suppressed.

Given specificities of the UCM method, *a report quality checklist for UCM studies* was developed for this review, inspired by the *STROBE Statement: Guidelines for reporting observational studies* [29]. The checklist contains information items that are desirable for accurate and complete reports of UCM studies, allowing for adequate reproducibility (see Table 1b). The checklist is based on published UCM guidelines [12,13,30], including items that can affect the reliability of the findings and should thus be reported. Specifically, clear identification of, and reasoning for, elemental and performance variables is the first step in ensuring reproducibility (items 1 and 2). The number of trials can affect the reliability of variance estimates and also needs to be reported (item 3). Fatigue due to too many trials can affect coordination and needs to be controlled for (item 4). Changes to initial position and movement speed can increase total movement variability and thus affect UCM estimates. For this reason, initial position and movement time need to be standardized or normalized (item 5 and 6). In UCM analysis, only successful task trials are included in analysis, therefore the number and criteria for unsuccessful trials that are discarded needs to be reported (item 7 and 8). UCM involves the use of task models (geometrical or regression-based) that should be well described (item 9). Finally, increases or decreases in V_{UCM}, V_{ORT}, SI or ASAs should be statistically tested (item 10).

Any disagreements in application of the Critical Review Form or the UCM checklist were resolved by discussion between the three evaluators (V, D.V.; P, V.A. and S, R.R.).

2.4. Data extraction

Data on the population studied, the task, and the main findings of the UCM analyses were extracted, following the consensus of three investigators. The main findings of UCM analyses and their interpretations were classified according suggestions *i* to *iv* (listed in the introduction) for UCM investigations in adults with neurological impairments. Given the definition of a synergy in the UCM approach [12], the results of each study were organized to identify their three main aspects: *the task* served by the synergy, *its elemental variables* and the *performance variables* it stabilized.

3. Results

3.1. Selection of studies

The initial search yielded 549 studies. After removal of duplicates and screening for eligibility, 17 studies, all published in English, were included in this review. The study selection process is shown in Figure 2 in a PRISMA flow diagram [31].

3.2 Description of included studies

Publication dates ranged from 2003 to 2018. There was a total of 174 participants with neurological impairments and 146 healthy controls. All studies were cross-sectional, and only two studies had no control group [32,33]. Mean age of participants was 62.46 (±10.69) years old for the patients with neurological impairments and 61.57 (± 8) for the healthy controls.

The details of all included studies are shown in Table 2. In the 17 selected articles, stroke [34–40] and Parkinson's disease [24,25,32,33,41–43] were most frequently studied. One study was found for each of the following pathologies: multiple sclerosis [44], olivo-ponto-cerebellar atrophy

[45] and spinocerebellar degeneration [46]. With regard motor tasks, seven studies investigated multi-finger pressing tasks [24,32,39,41,43–45], four reaching [34–37], three posture stabilization in quiet standing [25,33,43], one load release while standing [46], one pressing and prehension[42], one wrist and fingers extension [40], and one walking [38]. The most commonly used performance variables were the trajectory of center of pressure in balance tasks [25,33,43,46], total pressing force in finger pressing tasks [32,39,41,44,45] and hand position in reaching tasks [34,35,37]. For these tasks, the most commonly used elemental variables were multi-muscle modes [25,33,36,38,43,46,47], multi-finger modes [32,39,41,42,44,45] and joint angles [34,35,37].

3.3. Quality assessment

The Critical Review Form and the UCM checklist are presented in Tables 1a and 1b, respectively. The two reviewers had no disagreement in any of the items in Table 1a. However, they disagreed on 4 of the items in Table 1b. The disagreements were resolved by consensus between reviewers.

The quality appraisal is shown in Table 1a. In general, the selected studies showed good methodological quality; the scores for the Critical Review Form varied from 10 to 16 out of a maximum of 17 points. Scores varied from 4 to 10 out of a maximum of 10 points for UCM analysis. See Table 1b for details of the UCM checklist. All studies described the task used for UCM analysis in detail, except for Srivastava et al (2016) [38]. This study investigated synergies stabilizing foot trajectory during the swing phase in overground walking. The methods of standardizing initial position, number of steps taken or distance walked were not reported. Thus, it was not possible to define how many repetitions of the swing phase were used during the test session. Also, no information was given on how much data was acquired for variability analysis.

No mention of strategies for avoiding fatigue was made in two studies [38,41]. The performance variables and elemental variables were clearly identified in all studies, but two studies did not justify the choice of elemental variables [24,40].

3.4. Results and overall conclusion of reviewed studies

3.4.1 The relationship between pathology and changes in V_{UCM} and V_{ORT}

Fourteen of the studies in this review investigated V_{UCM} , $V_{ORT,}$ or SI in individuals with specific pathologies compared to healthy controls (fifteen studies). See Table 3 for a summary of results. Eight studies consistently found reduced SI (weaker synergies) for patients with Parkinson's disease [24,25,41–43] olivo-ponto-cerebellar atrophy [45], multiple sclerosis [44], compared to healthy controls. Five studies did not report the specific changes in V_{UCM} or V_{ORT} that led to SI reduction [25,38,41,43,45]. Two studies found V_{UCM} was reduced (less flexibility) in patients with multiple sclerosis [44] and Parkinson's disease [42], one study found unchanged V_{UCM} in Parkinson's disease [24], and one found increased V_{UCM} (more flexibility) in spinocerebellar degeneration [46]. Three studies found increased V_{ORT} (less consistency) in Parkinson's disease [24,42] and spinocerebellar degeneration [46], and one reported unchanged V_{ORT} in multiple sclerosis [44]. Thus, although weaker synergies (lower SI) compared to healthy controls were a consistent finding across all the four pathologies, specific changes in V_{UCM} and V_{ORT} varied.

The reduction of synergy index is not as consistent in the case of patients with stroke (see Table 3). In fact, of the six studies that investigated synergies in patients with stroke compared to controls, three found unchanged synergy index [34,38,39] and one found weaker synergies for reaching ipsilaterally but not contralaterally [35]. In most studies, V_{UCM} was similar [34,36,38]

and in one it was larger than in controls [40]. However, V_{ORT} was also found to be larger than in controls in three studies [35,36,40].

3.4.2 The relationship between synergies index and performance in everyday functional tasks

Most studies that investigated the relationship were restricted to general disease-related clinical scales: The Modified Fugl-Meyer for patients with stroke or the Unified Parkinson's Disease Rating Scale (UPDRS) for patients with Parkinson's disease. Five [32,36,38,39,42] of seven studies found no significant correlations between scale scores and UCM indices. The SI for multi-digit synergies was significantly correlated with movement time in a task involving moving a glass with water by patients with Parkinson's disease [42]. The correlation between multi-digit SI and manual dexterity (Grooved Pegboard test scores) in patients with stroke was inconsistent: it was found to be significant only for the left hand, which was not necessarily the most affected (all 12 patients were right-handed and six had right-hemisphere damage) [39].

3.4.3 The relationship between functional deficits and ASAs

Seven studies investigated ASAs [25,39,41–45]. All of them compared ASAs between individuals with neurological impairment and healthy controls. Consistently, patients with Parkinson's disease, olivo-ponto-cerebellar atrophy, multiple sclerosis and stroke show ASAs that are smaller in magnitude, delayed, or both, when compared to healthy controls. When a person is preparing to release a hand-held load, multi-muscle ASAs have been found to attenuate the stabilization of the center of pressure. One study indicated that these multi-muscle ASAs may be absent in patients with Parkinson's disease [25]. No studies investigated the relationship between deficits in ASAs and scores on standardized tests of functional performance. Only one study found

a significant, moderate and inverse correlation between the magnitude of ASAs and the time to move a glass to target locations [42].

3.4.4 The effects of interventions in pathologically changed synergies

Finally, three studies [32,33,43], investigated the effects of interventions in pathologically changed synergies. Two of them reported stronger synergies (increased SI), either via increase in V_{UCM} [33], or decrease in V_{ORT} [32] after dopaminergic drugs were administered to patients with Parkinson's disease. Another study found no significant changes on SI for patients with Parkinson's disease during deep brain stimulation in comparison with no stimulation. There were, however significant improvements in ASAs (they were larger and occurred earlier) for the patients in the deep brain stimulation on state compared to the off state [43]. No studies investigated the effects of physical therapy treatments on UCM indices.

4. Discussion

This systematic review addressed the specific research questions proposed by Latash and Anson in [4]: *i*) the relationship between pathology and changes in V_{UCM} and $V_{ORT,}$ *ii*) the relationship between strength of synergies and performance in everyday functional tasks, *iii*) the relationship between functional deficits and ASAs, and lastly, *iv*) the effects of interventions in pathologically changed synergies. Seventeen UCM studies investigating alterations in motor synergies of individuals with neurological impairment were reviewed.

Overall, according to the adapted Critical Review Form, the reviewed studies were of fairly good quality, with well-defined objectives, adequate methodological procedures, satisfactory descriptions of experimental tasks, adequate analyses, and pertinent conclusions (most studies

scored between 13 and 15 out of 17). Our checklist, intended as a complementary tool, was designed for assessing reporting quality rather than study quality. The checklist contains information that should be included in an accurate and complete report of an UCM study. The generally high scores (most scored 8 or 9 out of 10) suggest that the steps for UCM analysis are well structured and reporting is uniform. Together, the Critical Review Form and the checklist scores suggest that the reviewed studies produced reliable findings. Nevertheless, it is important to point out that 16 of the 17 reviewed studies were authored by the same two researchers (initial proponents of the UCM method) and this may be a source of bias in results. Replication of the reviewed studies in different laboratories is warranted.

A few considerations for interpreting the results of this review are necessary. Patients with neurological impairments show nonselective recruitment of muscles that lead to stereotyped or mass movement [5–7], or, in other words, altered average coupling patterns between muscles or joints. The UCM method does not prescribe standard procedures to quantify the average sharing or coupling patterns. The focus of UCM analysis is the partitioning of inter-trial variances to quantify stabilization of performance. It is important to point out, therefore, that for a given functional task, even evidently changed motor patterns may coexist with UCM indices that are not significantly altered [13]. If UCM results indicate no differences between patients and controls, it does not mean there are no alterations in kinematics or muscle recruitment patterns. These alterations may be present, but without significant changes in the partitioning of trial-to-trial variance *for the stabilization of a performance variable.*

Results regarding the first question leading to this review, namely the relationship between pathology and changes in V_{UCM} and V_{ORT}, indicate that there may be significant alterations to the synergistic control of movement stability in patients with none or very subtle alterations in overall

movement patterns. Conversely, patients with visibly altered movement patterns may have preserved synergistic control of movement stability.

Reduced SIs and ASAs were a consistent finding for individuals with Parkinson's disease, even when they were asymptomatic [41] or had no clinical symptoms of postural instability [25]. For example, Falaki et al. 2016 [25] found reduced SI for patients with Parkinson's disease that showed no differences in the magnitude and peak rate of forward or backward shift of the center of pressure while standing. Thus, UCM measures may serve as early objective and reliable tests to detect problems in the neural control of movement stability in individuals at risk of Parkinson's disease. Given that diagnosis is usually made only after significant degeneration of the *substantia nigra* [24], early diagnosis is highly desirable because it might change the course of treatment and disease.

In the case of patients with stroke, however, even when there are gross alterations to overall movement patterns, UCM indices may not be changed [34,38,39]. Several studies document altered patterns of joint and muscle couplings (in agreement with clinical observation) leading to a lower number of coordination modes in individuals with stroke when compared to controls [11,34]. There is evidence of decreased muscular independence and co-contraction of large muscle groups [48–50] that reflect disruptions in descending neural pathways and are correlated to deficits in motor function [47,51]. Reisman and Scholz, 2003 [34], for example, report that patients with stroke had longer movement times, greater variance of the hand's path and larger absolute pointing errors compared do controls, but V_{UCM} and V_{ORT} were unaffected. In fact three of six UCM studies included in this review found typical task-specific synergies, indicating that individuals with stroke had preserved ability to combine elemental variables to stabilize task performance.

Together, the results of UCM studies across different pathologies of the nervous system indicate that stability control relates to different functions of the nervous system: overall patterns of movement are more affected by damage to the corticospinal tract, while synergies stabilizing those patterns are more affected by dysfunction of subcortical pathways [17,41,45].

The UCM method investigates stability control and does not aim to quantify overall sharing patterns. Many studies quantify sharing patterns (modes) and then use them in the UCM analysis as elemental variables (variables that the CNS is assumed to manipulate independently). Methods to define modes include, for example, principal component analysis of EMG patterns [25,33,36,46], and correlation matrices for finger forces [24,32,39,41,42,44,45]. This is important because, in typical individuals, separate joint angles are usually treated as elemental variables. In patients with neurological disorders, however, the ability to control joints independently may be impaired. For them, joints would not be appropriate elemental variables, because their motions would co-vary irrespective of particular tasks, in a way not modifiable by the central nervous system. Therefore, such co-variation would not be a task-specific stabilizing control strategy, i.e., a synergy in the UCM sense [4,13]. Thus, for these patients, the appropriate elemental variables would have to be discovered with supplementary investigation methods [4,13].

Most of the reviewed studies quantified and used multi-finger or multi-muscle modes (see Table 3) as elemental variables for UCM analysis. Some studies used individual joint motions [34–36], and individual wrist or finger forces [24,40,45]. As the assumption that individual joints can be treated as elemental variables may be particularly problematic for neurological patients, results of the latter studies must be viewed with caution. Standardization of methods to define appropriate elemental variables for UCM analysis across healthy and clinical populations is desirable.

According to the UCM approach, synergies are task-specific and always serve functional purposes [12,13]. Viewing synergies as functional rather than abstract concepts, the UCM method investigates them with reference to what they do: organize to allow stable and flexible performance of a specific movement task [12]. The tasks in this review involved multi-finger pressing, keeping balance while standing, reaching and walking. This is a special advantage of the UCM method over other methods devoted to quantifying sharing patterns abstractly, independently of functional tasks.

The UCM method would thus be particularly suited to reveal the relationships between synergy indices and performance in everyday functional tasks (question *ii* of this review). However, only a few studies investigated the relationship between V_{UCM}, V_{ORT} and SI to standardized tests of motor performance – Fugl-Meyer and UPDRS – and most found no relationship. There may be three reasons for this pattern of negative results. First, the exigencies of experimental laboratory procedures might have led to constrained and overly simplified tasks and models (for instance, linearization is a prerequisite to UCM calculations), weakening their relationship to everyday motor performance. Two significant challenges for the geometrical models used in UCM analysis, for example, are to allow for the use of 3D angles in whole-body tasks, and to deal with nonlinearities. Second, Fugl-Meyer and UPDRS were designed to capture stages or signs of pathology progression or recovery, and may be too general and not sensitive enough to capture performance in the functional tasks of daily life that are more directly related to the investigated synergies (especially in the case of patients with mild symptoms). Other standardized functional measures of everyday motor function (for example Dynamic Gait Index [52], Functional Gait Assessment [53], Berg Balance Scale [54], Wolf Motor Function Test [55], Action Research Arm Test [56], Freezing of Gait Questionnaire [57], Profile PD [58], Modified

Parkinson Activity Scale [59]) might be more sensitive and appropriate for revealing relations to synergies. The third issue, however, is the ordinal nature of many activity outcome measures used in clinical practice. Their sensitivity for revealing relations to alterations in synergistic control needs to be further investigated.

There were very interesting findings in UCM studies relating to question *iii*), on the relationship between functional deficits and ASAs. ASAs reflect adjustments of the stability of an ongoing action and are seen as a drop in SI 200–300 ms prior to the initiation of a quick action [17]. If synergies stabilize performance, then the absence of synergy attenuation in preparation for a new action means that the nervous system needs to oppose its own synergies [24,25,44]. Thus, deficits in ASAs may be directly related to functional problems common to patients with neurological impairment: loss of agility, difficulty to initiate movement and freezing in Parkinson's disease [13,17,44]. Unfortunately, the relationships between ASAs and functional limitations were not specifically investigated in any of the reviewed studies, except for one that reported longer movement times for individuals with smaller ASAs in a prehension task [42]. Most studies focused on comparing ASAs between patients and controls. The results were consistent with regard to deficits in this feature of stability control for all populations studied: stroke, Parkinson's disease, multiple sclerosis, and olivo-ponto-cerebellar atrophy. ASAs were either reduced in magnitude or delayed in time. In tow studies, they were absent in patients with Parkinson's disease when they were performing a finger-pressing task [22,30]. These findings indicate that ASAs might reflect important deficits behind functional limitations in patients with neurological impairment, and should be further investigated.

Lastly, in relation to question *iv*, about the effects of interventions in pathologically changed synergies, two studies [32,33] on the effects of dopaminergic drugs provide an important

proof of concept for the UCM approach. Dopamine replacement is a widely used drug with proven efficacy for the reduction of motor symptoms in patients with Parkinson's disease. For these patients, SI, V_{UCM}, V_{ORT} and ASA indices were sensitive enough to capture the specific positive effects of drugs on coordination. The drugs led to stronger synergies with more flexibility (higher V_{UCM}) [33] or less performance inconsistency (lower V_{ORT}) [32] in the inter-trial variability of movement in patients with Parkinson's disease. ASAs were stronger and faster in the on-drug state [32,33]. These results lend strong support to the utility of synergy indices for clinical research and practice. Unfortunately, no studies investigated the effects of physical therapy interventions on the synergy indices of patients with neurological impairment.

5. Conclusion

Given the available UCM literature and overall good study quality, this review indicates that UCM indices provide clearly established and sensitive measures of coordination in individuals with neurological impairments. The UCM is a promising method for physical therapy research to quantify progress and adjust the therapeutic process to produce the desired treatment outcome for patients. UCM studies can inform clinical decisions on whether synergies have to be broken, created, rebalanced or strengthened. For example, the results of this review suggest that physical therapists should develop interventions to strengthen synergies of patients with Parkinson's disease, olivo-ponto-cerebellar atrophy, multiple sclerosis and spinocerebellar degeneration. There is some evidence that the strength of multifinger synergies can be improved with specially designed practice [60,61]. For patients with stroke, however, the reviewed studies do not show consistently weaker synergies that need to be strengthened. Patients with stroke may benefit more from interventions designed to rebalance their synergies. There is also some evidence of synergy

rebalancing after specially designed training [62,63]. Finally, ASAs were in general smaller in magnitude, delayed, or both, for all clinical populations studied, indicating the need to develop and test specific training strategies to improve ASAs. Clinical research on physical therapy interventions can adopt UCM methods to quantify how movement practice enhances task-specific movement coordination (SI, V_{UCM}, V_{ORT} and ASAs), and prevents functional and health issues.

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Conflict of interest

None declared.

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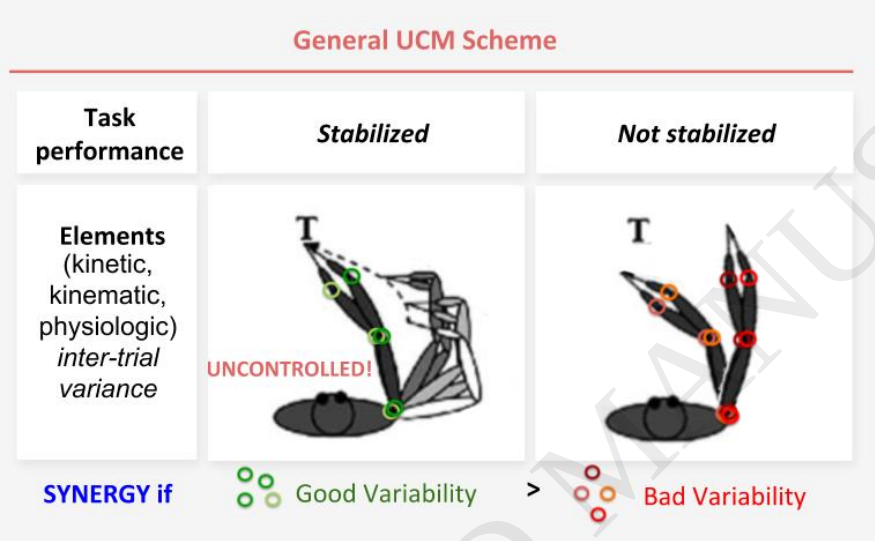
Figure 1. General UCM scheme to identify and quantify synergies. A person seen from above is moving the arm forward to place a pointer at a target T. Several combinations of shoulder, elbow and wrist angles can lead to the same correct pointer position at T. These combinations keep performance stable (middle column). Some other combinations will lead to pointing errors and will not keep performance stable (right column). The UCM method is based on choosing a task, defining a performance measure as well as participating elements (either at the kinetic, kinematic or physiologic levels), and then partitioning inter-trial elemental variance two kinds: V_{UCM} (related to performance stability) and V_{ORT} (not related to performance stability). A synergy exists if there is more variability of the V_{UCM} kind. Greater proportions of V_{UCM} to V_{ORT} variability indicate stronger synergies.



*Dummy figure adapted from *Latash, M. L., Scholz, J. P., & Schöner, G. (2007). Toward a new theory of motor synergies. Motor control, 11(3), 276-308*, permission pending

Figure 2. Prisma Flow Diagram

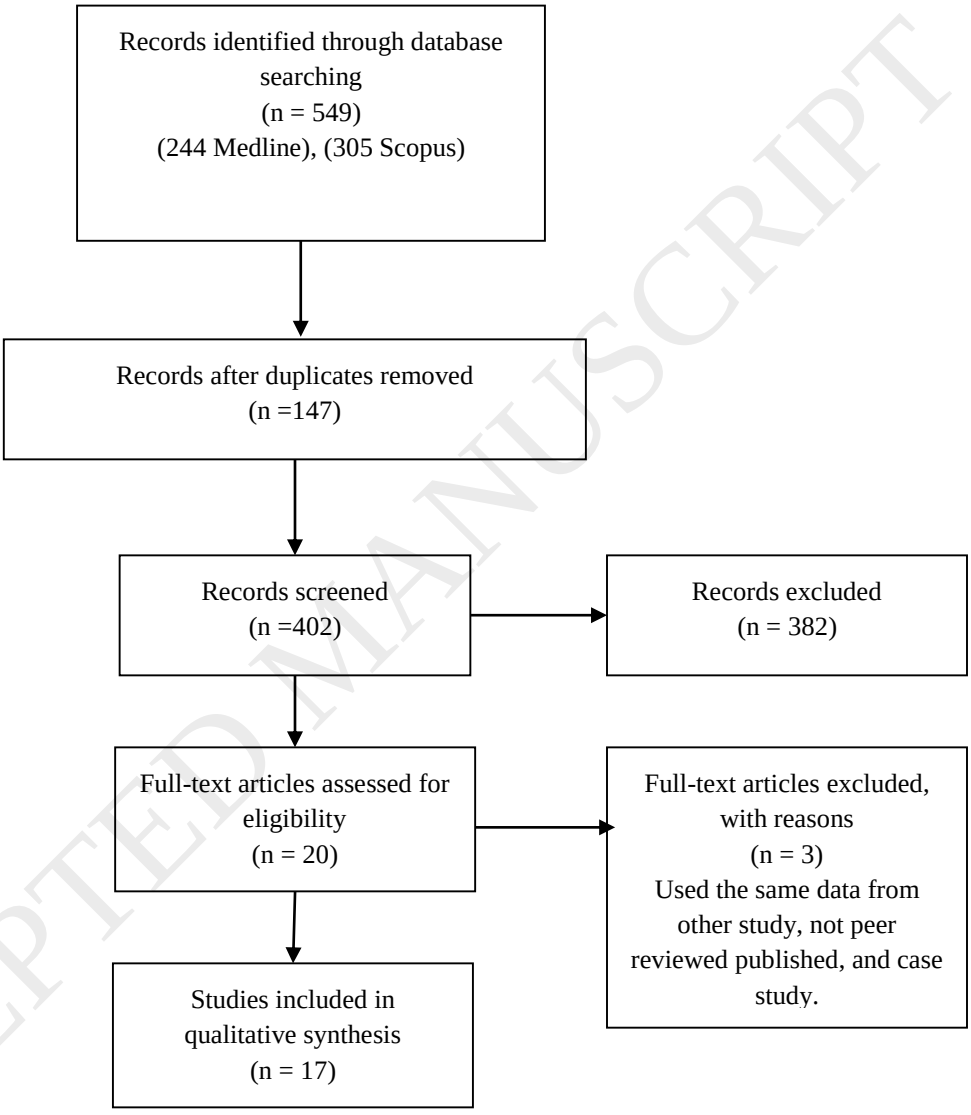


Table 1a. Summary of quality appraisal for individual studies.

Included Studies	Asaka and Wang 2011 [46]	Falaki et al. 2016 [25]	Falaki et al. 2017 [33]	Falaki et al. 2018 [43]	Gera et al. 2016 [36]	Gera et al. 2016 [37]	Jo et al. 2015 [42]	Jo et al. 2016 [39]	Jo et al. 2016 [44]	Kang and Cauraugh 2017 [40]	Park et al. 2012 [41]	Park et al. 2013 [24]	Park et al. 2013 [45]	Park et al. 2014 [32]	Reisman and Scholz 2003 [34]	Reisman and Scholz 2006 [35]	Srivastava et al. 2016 [38]	Number of "Yes" in each question (17 max)
Questions																		
Was the purpose of the study clearly stated?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	17
Was the literature review appropriately presented?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	17
Was the design appropriate for the study purpose?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	17
Was the sample adequately described?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	17
Was the sample size justified?	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	No	0
Was an informed consent obtained?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	17
Were the clinical tools used to characterize functional level of patients reliable?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	17
Were the clinical tools used to characterize functional level of patients valid?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	17
Was the task used for UCM analysis described in detail?	Yes	Yes	YNAes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	16

Could the task be replicated in practice?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	16
Were factors affecting typical performance avoided?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NR	Yes	NA	NA	Yes	Yes	NAd	13
Were the results reported in terms of statistical significance?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	17
Were the analysis method(s) appropriate?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	17
Was clinical importance reported?	No	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	13
Did any participant drop out from the study?	No	No	No	No	Yes	No	No	No	No	No	No	No	No	No	Yes	No	No	2
Were the limitations acknowledged and described?	No	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	No	No	No	Yes	Yes	Yes	No	10
Were the conclusions appropriate, given the study methods?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	17
Total number of "Yes" for each study (17 max.)	13	15	15	14	16	14	15	15	15	13	13	14	13	14	16	15	10	
Legend: NA- Not applicable NAd- Not addressed, NR- not reported																		

Table 1b. Checklist for UCM reporting

Included Studies	Asaka and Wang 2011 [46]	Falaki et al. 2016 [25]	Falaki et al. 2017 [33]	Falaki et al. 2018 [43]	Gera et al. 2016 [36]	Gera et al. 2016 [37]	Jo et al. 2015 [42]	Jo et al. 2016 [39]	Jo et al. 2016 [44]	Kang and Cauraugh 2017 [40]	Park et al. 2012 [41]	Park et al. 2013 [24]	Park et al. 2013 [45]	Park et al. 2014 [32]	Reisman and Scholz 2003 [34]	Reisman and Scholz 2006 [35]	Srivastava et al. 2016 [38]	Number of "Yes" in each question (17max)
Questions																		
1. Were the PVs and EVs clearly identified?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	17
2. Was the choice of PVs and EVs justified?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Yes	15
3. Was the number of trials reported?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	16
4. Was fatigue avoided?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	NR	Yes	Yes	Yes	NR	14
5. Was the initial position standardized?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NA	16
6. Was movement time normalized?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	16
7. Was the number of trials included and excluded from analysis reported*?	No I:50 E:NR	Yes I:17 E:7	Yes I:16 E:8	Yes I:18 E:6	No I:30 E:NR	Yes I:35 E:5	Yes I:20 E:4-10	Yes I:22 E:3-12	Yes I:19 E:6	No I:24 E:NR	Yes I:25-35 E:7-11	No I:20 E:NR	Yes I:25 E:8	Yes I:18 E:5	No I:20 E:NR	No I:20 E:NR	No I:NR E:NR	10
8. Were the criteria to exclude trials reported?	No	No	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	No	No	9
9. a) Task model: was the task model well	NA	NA	NA	NA	No	No	NA	NA	No	Yes	NA	No	NA	NA	Yes	Yes	NA	3

supported/validated ? Or b) Regression-based model: was significance of coefficients reported?	Yes	Yes	Yes	Yes	No	No	Yes	Yes	No	NA	No	No	Yes	No	NA	NA	Yes	8
10. Were statistical comparisons reported?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	17
Total number of "Yes" for each study (10 max.)	8	9	9	10	7	9	10	10	9	8	8	6	9	9	8	8	4	

Legend: NA- Not applicable, NR- not reported, EV: Elemental variables, PV: Performance variables, I: included trials, E: excluded trials, *average number of trials across groups or conditions.

Table 2. Summary of the Selected Studies

Studies	Purpose	Sample	Task
Asaka and Wang 2011 [46]	To investigate muscle modes and multi-muscle (EVs) synergies stabilizing the trajectory of the COP (PV) in patients with SCD compared to controls.	9 patients with SCD 9 healthy controls	Standing (load release task)
Falaki et al. 2016 [25]	To investigate whether multi-muscle (EVs) synergies stabilizing the trajectory of the COP (PV) are weaker, and anticipatory synergy adjustments are smaller, in patients with PD compared to controls.	11 patients with PD 11 healthy controls	Standing (voluntary sway, fast sway, load release task)
Falaki et al. 2017 [33]	To investigate whether multi-muscle (EVs) synergies stabilizing the trajectory of COP (PV) and anticipatory synergy adjustments would be improved on dopaminergic drugs for patients with PD.	10 patients with PD.	Standing (fast body sway, fast sway, load release task)
Falaki et al. 2018 [43]	To investigate whether multi-muscle (EVs) synergies stabilizing the trajectory of the COP (PV) and multi-finger (EVs) synergies stabilizing total pressing force (PV) on finger sensors would be improved with deep brain stimulation for patients with PD.	10 patients with PD 16 healthy controls	Standing (load release task) and multi-finger button-pressing.
Gera et al. 2016 [36]	To investigate whether multi-muscle (EVs) synergies stabilizing the trajectory of trunk (PV) in upward and downward reaching are altered in patients with stroke compared to controls.	10 patients with stroke 9 healthy controls.	Reaching target up and down beyond arm length while sitting
Gera et al. 2016 [37]	To investigate the relative contribution of each of the shoulder, elbow and wrist joints (EVs) to hand path variability (PV) in stroke survivors compared to controls.	22 patients with stroke 10 healthy controls.	Reaching and touching a target within arm length while sitting
Jo et al. 2015 [42]	To quantify multi-finger (EVs) synergies stabilizing forces and moments produced in handled objects (PVs) and explore the relationship to functional scores and task performance in patients with PD and controls.	8 patients with PD 8 healthy controls.	Pressing, prehension, and moving a glass with water.
Jo et al . 2016 [39]	To investigate multi-finger (EVs) synergies stabilizing total pressing force (PV) on finger sensors and anticipatory synergy adjustments in a quick finger force action in patients with stroke compared to controls.	12 patients with stroke 12 healthy controls	Multi-finger button-pressing
Jo et al. 2016 [44]	To explore whether multi-finger (EVs) synergies stabilizing total pressing force (PV) on finger sensors are altered in patients with MS compared to controls.	13 patients with MS, 13 healthy controls.	Multi-finger button-pressing
Kang and Cauraugh 2017 [40]	To investigate bimanual wrist and finger extension force (EVs) synergies stabilizing total isometric force (PV) in patients with stroke compared to controls.	9 patients with stroke 9 healthy controls	Bilateral isometric wrist and fingers extension, at several proportions of maximum voluntary contraction
Park et al. 2012 [41]	To investigate multi-finger (EVs) synergies stabilizing total pressing force (PV) on finger sensors in patients with PD compared to controls.	10 patients with PD 11 healthy controls	Multi-finger button-pressing
Park et al. 2013 [24]	To investigate whether finger (EVs) synergies indices stabilizing total pressing force and moment (PVs) on finger sensors are smaller in patients with PD compared to controls.	8 patients with PD 8 healthy controls	Multi-finger button-pressing
Park et al. 2013 [45]	To quantify changes in multi-finger (EVs) synergies stabilizing total pressing force (PV) on finger sensors and anticipatory synergy adjustments in patients with OPCA compared to controls	7 patients with OPCA 9 healthy controls	Multi-finger button-pressing
Park et al. 2014 [32]	To investigate whether multi-finger (EVs) synergies stabilizing total pressing force (PV) on finger sensors, anticipatory synergy adjustments and finger individuation would be improved on dopaminergic drugs for patients with PD.	8 patients with PD	Multi-finger button-pressing

Reisman and Scholz 2003 [34]	To investigate whether arm joints (EVs) synergies to stabilize the hand position (PV) during reaching are altered in patients with stroke compared to controls.	8 patients with stroke 8 healthy controls	Reaching to a target while sitting
Reisman et al. 2006 [35]	To investigate whether arm joints (EVs) synergies to stabilize the hand position (PV) during reaching are altered in patients with stroke compared to controls.	7 patients with stroke 7 healthy controls.	Reaching to a target while sitting
Srivastava et al. 2016 [38]	To investigate whether leg multi-muscle (EVs) synergies to stabilize footpath (PV) during the swing phase of gait are altered in patients with stroke compared to controls.	12 patients with stroke 12 healthy controls.	Walking over ground at self-selected speed
EV: Elemental variable, PV: Performance variable			

Table 3.Main Findings of UCM Analyses and Conclusions				
I. The relationship between pathology and changes in V_{UCM} and V_{ORT}				
Pathology	**Studies**	**Synergy Results**	**Task Performance Results**	**Interpretation**
Multiple Sclerosis	Jo et al. 2016 [44]	$V_{UCM}\downarrow$ $V_{ORT}=$ SI $\downarrow$	Patients with MS showed significantly lower maximal finger forces, a tendency toward slower force pulses and higher unintended force production (enslaving).	Patients with MS have reduced ability to use mutually compensatory multi-finger forces (modes) to stabilize total pressing force in a finger button-pressing task.
Olivo-Ponto Cerebelllar Atrophy	Park et al. 2013 [45]	SI $\downarrow$	Patients with OPCA showed lower maximal forces and higher unintended force production (enslaving).	Patients with OPCA have reduced ability to use mutually compensatory multi-finger forces (modes) to stabilize total pressing force in a finger button-pressing task
Parkinson's Disease	Falaki et al. 2016 [25]	SI $\downarrow$	Patients with PD showed no differences in the magnitude and peak rate of forward or backward COP shift during fast sway while standing.	Patients with PD have reduced ability to use mutually compensatory multi-muscle activation patterns (modes) to stabilize trajectory of the COP trajectories in a voluntary load-release task in standing, even without clinical manifestations of postural instability.
	Jo et al. 2015 [42]	$V_{UCM}\downarrow$ $V_{ORT}\uparrow$ SI $\downarrow$	Patients with PD showed smaller maximal force values, longer movement times (pressing, prehension and manipulation tasks), larger grip forces at steady states and smaller grip force modulation during the handle motion.	Patients with PD have reduced ability to use mutually compensatory multi-finger forces (modes) to stabilize total force and moment of force in pressing and prehension tasks.
	Park et al. 2012 [41]	SI $\downarrow$	Patients with PD showed significantly lower maximal finger forces and higher unintended force production (enslaving).	Patients with PD have reduced ability to use mutually compensatory multi-finger forces (modes) to stabilize total pressing force in constant and cyclic button-pressing task.
	Park et al. 2013 [24]	$V_{UCM}=$ $V_{ORT}\uparrow$ SI $\downarrow$	Performance comparisons were not reported.	Patients with PD have reduced ability to use mutually compensatory individual finger forces to stabilize total pressing force but not total moment of force in a finger button-pressing task.
	Falaki et al. 2018 [43]	SI = (finger task) SI $\downarrow$ (postural task)	Except for patients showing longer times to reach peak finger forces compared to controls from earlier publications, performance comparisons were not reported.	Patients with PD in chronic use of DBS do not show reduced ability to use mutually compensatory multi-finger forces (modes) to stabilize total pressing force in a button-pressing task, but show reduced ability to use mutually compensatory multi-muscle activation patterns (modes) to stabilize trajectory of the COP in a load release task while standing.
Spinocerebellar Degeneration	Asaka and Wang 2011 [46]	$V_{UCM}\uparrow$ $V_{ORT}\uparrow$ SI $\downarrow$	Performance comparisons were not reported.	Patients with SCD have reduced ability to use mutually compensatory multi-muscle activation patterns (modes) to stabilize the trajectory of the COP in a voluntary load-release task while standing
Stroke	Gera et al. 2016 [36]	$V_{UCM}=$ $V_{ORT}\uparrow$	Patients with stroke showed larger movement times (for reaching) (note that UCM analysis	Patients with stroke have reduced ability to minimize combinations of trunk multi-muscle activation patterns (modes) that destabilize trunk

			normalizes for time)	trajectory, especially when reaching upward while sitting.
	Jo et al. 2016 [39]	SI =	Patients with stroke showed lower maximal finger forces and higher unintended force production (enslaving).	Patients with stroke have unaffected ability to use mutually compensatory multi-finger forces (modes) to stabilize total force in finger button-pressing tasks.
	Kang and Cauraugh 2017 [40]	V_{UCM} ↑ V_{ORT} ↑ SI ↓	Patients with stroke showed higher RMSE at 50% of MVC and less bilateral force accuracy. MVC was not significantly altered.	Patients with stroke have reduced ability to use mutually compensatory bilateral wrist and finger extension forces to stabilize total isometric force at the 50% of maximum voluntary contraction level.
	Reisman and Scholz 2003 [34]	V_{UCM} = V_{ORT} =	Patients with stroke showed longer movement times, greater variance of the hand's path and larger absolute pointing errors.	Patients with stroke have unaffected ability to use mutually compensatory arm joint motions to stabilize hand path during reaching.
	Reisman and Scholz 2006 [35]	V_{ORT} ↑ SI ↓	Patients with stroke had greater variance of hand path extent, of trunk position and of relative hand–trunk position.	Patients with stroke have reduced ability to use mutually compensatory hip, trunk and arm joint motions to stabilize hand movement extent and relative trunk-hand position when reaching ispilaterally of the hemiparetic side.
	Srivastava et al 2016 [38]	V_{UCM} = V_{ORT} = SI =	Performance comparisons were not reported.	Patients with stroke have unaffected ability to use mutually compensatory multi-muscle activation patterns (modes) to stabilize footpath during the swing phase of walking.
II. The relationship between strength of synergies and performance in everyday functional tasks				
Pathology	**Studies**	**Results**	**Interpretation**	
Olivo-Ponto Cerebelllar Atrophy	Park et al. 2013 [45]	SI ↔ UPDRS	Multifinger synergies stabilizing total pressing force in a finger button-pressing task may be related to more general changes in motor behavior.	
Parkinson's Disease	Jo et al. 2015 [42]	SI X UPDRS-III SI ↔ Task time	Multifinger synergies stabilizing total pressing force in a finger button-pressing task did not relate to general changes in motor behavior. Multifinger synergies may be related to changes in performance in object manipulation tasks.	
	Park et al. 2014 [32]	SI X UPDRS-III	Multifinger synergies stabilizing total pressing force in a finger button-pressing task did not relate to general changes in motor behavior.	
Stroke	Gera et al. 2016 [36]	V_{UCM} and V_{ORT} X Modified Fugl-Meyer (upper extremity) V_{UCM} and V_{ORT} X Trunk Impairment Scale (dynamic sitting balance and coordination) V_{ORT} ↔ Trunk Impairment Scale (upward reaching).	Multi-muscle synergies stabilizing trunk trajectory in a reaching task did not relate to severity of upper extremity motor impairment or to trunk impairment. Inconsistency of trunk trajectory while reaching upward may be related to impairments in dynamic sitting balance and trunk coordination.	

	Gera et al. 2016 [37]	V_{ORT} ↔ Modified Fugl-Meyer (upper extremity) *after removing co-variation of the shoulder with other joints	Shoulder coordination in a reaching task may be related to severity of upper extremity motor impairment.
	Jo et al. 2016 [39]	SI X Fugl-Meyer (upper extremity) SI ↔ Grooved Pegboard test	Multi-finger synergies stabilizing total pressing force in a finger button-pressing task did not relate to severity of upper extremity motor impairment and was inconsistently related to manipulative dexterity.
	Srivastava et al 2016 [38]	Normalized sum of V_{UCM} and V_{ORT} X Fugl-Meyer (lower extremity)	Multi-muscle synergies stabilizing footpath during the swing phase of walking did not relate to severity of lower extremity motor impairment.
III. The relationship between pathology or functional deficits and ASA			
Pathology	**Studies**	**Results**	**Interpretation**
Multiple Sclerosis	Jo et al. 2016 [44]	ASA ↓ and <<	Patients with MS have impaired ability to attenuate multi-finger synergies stabilizing total pressing force in preparation to produce a quick change in total force in a finger button-pressing task.
Olivo-Ponto Cerebelllar Atrophy	Park et al. 2013 [45]	ASA ↓ and <<	Patients with OPCA have impaired ability to attenuate multi-finger synergies stabilizing total pressing force in preparation to produce a quick change in total force in a finger button-pressing task.
Parkinson's Disease	Falaki et al. 2016 [25]	ASA Ø	Patients with PD have impaired ability to attenuate multi-muscle synergies stabilizing the position of COP in preparation to releasing a hand-held load while standing.
	Jo et al. 2015 [42]	ASA ↓	Patients with PD have impaired ability to attenuate multi-finger synergies stabilizing total pressing force in preparation to a quick action in pressing and, to a smaller degree, prehension tasks.
	Park et al. 2012 [41]	ASA ↓ and <<	Patients with PD have impaired ability to attenuate multi-finger synergies stabilizing total pressing force in preparation to produce a quick change in total force in a finger button-pressing task.
	Falaki et al. 2018 [43]	ASA ↓ and <<	Patients with PD have impaired ability to attenuate multi-finger synergies stabilizing total pressing force in preparation to produce a quick change in total force in a finger button-pressing task. They also have impaired ability to attenuate multi-muscle synergies stabilizing the position of COP in preparation to releasing a hand-held load while standing.
Stroke	Jo et al. 2016 [39]	ASA <<	Patients with stroke have impaired ability to attenuate multi-finger synergies stabilizing total pressing force in preparation to produce a quick change in total force in a finger button-pressing task.
IV. The effects of interventions in pathologically changed synergies			
Pathology	**Studies**	**Results**	**Interpretation**
Parkinson's Disease	Falaki et al. 2017 [33]	V_{UCM} ↑ V_{ORT} = SI↑	Dopaminergic drugs can increase the ability to use mutually compensatory multi-muscle activation patterns (modes) to stabilize the position of the COP in quiet standing. It can also increase the ability to attenuate multi-muscle synergies stabilizing the COP in preparation to releasing a hand-held load while standing.

		ASA● *on-drug compared to off-drug	
	Falaki et al. 2018 [43]	V_{UCM} = V_{ORT} = SI = ASA↑ *DBS-on compared to DBS-off	DBS did not change indices of synergies stabilizing the position of the COP while releasing a hand-held load, and did not change the indices of synergies stabilizing total pressing force in a finger button-pressing task. DBS increased the ability to attenuate synergies in preparation to a quick change of performance variables in both tasks.
	Park et al. 2014 [32]	V_{UCM} = V_{ORT} ↓ SI ↑ ASA ↑ and >> *on-drug compared off-drug	Dopaminergic drugs can increase the ability to use mutually compensatory multi-digit forces (modes) to stabilize total pressing force in a finger button-pressing task; and the ability to attenuate multifinger synergies stabilizing total pressing force in preparation to produce a quick change in total force in a finger button-pressing task.

Legend: ASA- Anticipatory Synergy Adjustments Synergy, DBS- Deep Brain Stimulation, COP- Center of Pressure, MS- multiple sclerosis OPCA- olivo-ponto-cerebellar atrophy PD- Parkinson's disease SCD- spinocerebellar degeneration, SI-Sinergy Index, RMSE- root mean square error, MVC- maximum voluntary contraction

V_{UCM} ↓: smaller- less flexibility V_{ORT} ↓: smaller- less inconsistency SI ↓: smaller- weaker synergies

V_{UCM} = : similar- same flexibility V_{ORT} = : similar- same consistency SI = : similar -same synergy strength

V_{UCM} ↑: larger- more flexibility V_{ORT} ↑: larger- greater inconsistency SI ↑: larger – stronger synergies

↔: positive correlation ↔: negative correlation X: no correlation

ASA ↓: smaller ASA <<: delayed ASA Ø: absent

ASA↑: larger ASA>>: not delayed ASA● : present