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A Systems Biology Approach to Studying Tai Chi, Physiological Complexity and Healthy Aging: Design and Rationale of a Pragmatic Randomized Controlled Trial

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Abstract

Introduction—Aging is typically associated with progressive multi-system impairment that leads to decreased physical and cognitive function and reduced adaptability to stress. Due to its capacity to characterize complex dynamics within and between physiological systems, the emerging field of complex systems biology and its array of quantitative tools show great promise for improving our understanding of aging, monitoring senescence, and providing biomarkers for evaluating novel interventions, including promising mind-body exercises, that treat age-related disease and promote healthy aging.

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Material and Methods—An ongoing, two-arm randomized clinical trial is evaluating the potential of Tai Chi mind-body exercise to attenuate age-related loss of complexity. A total of 60 Tai Chi–naïve healthy older adults (aged 50–79) are being randomized to either six months of Tai Chi training (n=30), or to a waitlist control receiving unaltered usual medical care (n=30). Our primary outcomes are complexity-based measures of heart rate, standing postural sway and gait stride interval dynamics assessed at 3 and 6 months. Multiscale entropy and detrended fluctuation analysis are used as entropy- and fractal-based measures of complexity, respectively. Secondary outcomes include measures of physical and psychological function and tests of physiological adaptability also assessed at 3 and 6 months.

Discussion—Results of this study may lead to novel biomarkers that help us monitor and understand the physiological processes of aging and explore the potential benefits of Tai Chi and related mind-body exercises for healthy aging.

Keywords

cardiovascular health; postural control; gait; mind-body exercise; senescence; prevention

1. Introduction

With our rapidly expanding elderly population, the questions ‘what is healthy aging?’ and ‘how do we promote it’ are increasingly relevant. While modern biomedicine has made great strides in defining and understanding disease, the objective characterization of healthy aging remains elusive. Health requires the integration—across multiple time and spatial scales—of control systems, feedback loops, and regulatory processes that enable an organism to function and adapt to the demands of everyday life. Aging is typically associated with progressive multi-system impairment, leading to decreased physical and cognitive function and reduced adaptability to stress.[1, 2] Because of the complex nature of aging processes, present reductionistic methods may not be adequate for defining good health or healthy aging. Due to its capacity to characterize complex dynamics within and between physiological systems, the emerging field of complex systems biology and its array of quantitative tools show great promise for improving our understanding of aging, monitoring senescence, and providing biomarkers for evaluating novel interventions, including traditional mind-body exercises, that treat age-related disease and promote healthy aging.[3, 4]

Tai Chi is a multi-component mind-body exercise that is grounded in the holistic model of traditional Chinese medicine. The explicit goals of targeting multiple physiological and cognitive processes and integrating their dynamics make Tai Chi particularly well-suited for evaluating the effects on an intervention designed to enhance healthy aging within a systems biology framework. Tai Chi is reported to improve symptoms and systems that typically are associated with age-related decline including cardiovascular function,[5–7] balance,[8, 9] gait,[10] cognitive function,[11, 12] self-efficacy,[13] and quality of life.[14] However, to date, few studies have attempted to study Tai Chi’s impact on age-related physiological processes using complexity measures and to relate such measures to traditional measures of function.

This paper describes the rationale and design of a two-arm randomized clinical trial to evaluate Tai Chi’s effect on age-related loss of complexity and to understand the relationship between complexity, function and adaptability or resilience. This phase II study is designed to inform a future more definitive trial by providing information on preliminary estimates of effect size, and optimal biomarkers for characterizing the impact of Tai Chi on physiological complexity, function, and adaptive capacity. A unique feature of this trial is its use of pragmatically delivered interventions, allowing participants randomized to Tai Chi to choose their training site from within a pre-screened network of long-standing community-based Tai Chi schools.

2. Materials and Methods

2.1. Use of complexity-based metrics of physiological dynamics to study aging

Aging results from gradual changes in the underlying mechanisms of physiological control. The breakdown of nonlinear feedback loops acting across multiple scales of time generally results in a loss of physiological complexity.[1] Physiologic complexity is typically estimated using a number of techniques derived from the fields of nonlinear dynamics and statistical physics that quantify the moment-to-moment quality, scaling, and/or correlation properties of dynamic signals.[4, 15] The two most common sets of metrics are based on the concepts of entropy and fractals. Entropy-based complexity measures relate to the information content of a signal by quantifying the degree of regularity or predictability over one or more scales of time.[16] Growing evidence suggests that signals derived from healthy systems are more entropic (i.e., less regularity) across multiple scales of time, and therefore, are more complex.[17–20] Fractal-based complexity metrics quantify the degree of “self-similarity” in physiologic output over multiple measurement scales.[21] For example, physiologic signals with high complexity like the heart rate of a healthy young individual are statistically self-similar when observed over seconds, minutes, or hours.[22] As with entropy measures, increased fractality within certain ranges has been associated with better health. In this clinical trial, we evaluate whether two widely utilized complexity-based metrics, multiscale entropy (MSE)[23, 24] and detrended fluctuation analysis (DFA)[21, 25] are sensitive and informative metrics for characterizing the impact of Tai Chi on complexity in cardiovascular, locomotor, and balance systems in older adults. Below we briefly summarize studies to date that support the value of complexity-based biomarkers in characterizing age-related decline in cardiovascular, postural control, and gait dynamics.

2.1.1. Cardiovascular dynamics—Several studies support the idea that heart beat dynamics exhibit features of complex systems with fractal-like, long-range correlation properties, and that the degree of complexity of dynamics decreases with age. This observation is supported by both entropy and fractal-based complexity metrics. For example, systematic age-related decline in complexity of heart rate (HR) dynamics above the age of 40 years were observed in two large cross-sectional samples of healthy adults, assessed using both Approximate Entropy (a measure of the amount of regularity and the unpredictability of fluctuations over time-series) and DFA.[26, 27] Additional smaller studies employing a variety of complexity based measures support these findings;[28–30] however, some studies suggest that things may not always be so simple.[31]

Age-related loss in HR beat-to-beat dynamics also appears to be accelerated in populations with heart murmur[32] and heart failure.[16, 33, 34] Of clinical relevance, loss of complexity in HR dynamics has been associated with cardiovascular disease and risks, and in some cases, complexity measures related to HR dynamics are stronger predictors of mortality in the elderly and post-myocardial infarction[35, 36] than linear spectral measures of heart rate variability[19, 20]. Non-linear measures of HR dynamics also are independent predictors of survival in patients with depressed left ventricular function[37] and heart failure;[34, 38] are predictors of vulnerability to life threatening arrhythmia;[39] and can distinguish subjects with coronary artery disease from healthy controls.[40] Finally, there is also some evidence that the complex dynamics of other cardiovascular and cardiorespiratory processes including resting blood pressure and inter-breath intervals decline with age.[28, 41–43]

2.1.2. Postural control during quiet standing—A growing number of studies have confirmed that under resting conditions, postural sway of the body, as commonly assessed by studying center of pressure (COP) displacements recorded with a force platform, exhibits complex variability over a broad range of time scales.[17, 44–46] A few smaller studies in healthy adults support a trend towards age-related loss of complexity of COP dynamics as assessed with MSE, DFA, and related methods[17, 44, 45, 47, 48] but these observations have not yet been confirmed in larger cohorts. Further support for the COP complexity measures come from large cross-sectional studies of older adults that found lower postural sway complexity during quiet standing is associated with frailty.[49] In this same population, decreased complexity was also associated with decreased visual and somatosensory input.[50]

2.1.3. Gait dynamics—Multiple studies support the idea that stride-to-stride variation exhibits long-range self-similar correlations extending over hundreds of steps and that fractal-like gait fluctuations vary with activities such as walking or running on treadmills.[51–54] However, the evidence of gait complexity systematically declining with age in healthy adults is limited to one study. Hausdorff and colleagues evaluated dynamics of healthy older (avg. 76 y) vs. younger (avg. 25 y) adults found that DFA significantly declined with age.[55] For older adults, DFA approached .5, a value that indicates white noise, randomness, and lack of internal long-range structure. Interestingly, in these older adults, other measures of lower extremity function (e.g., 'Timed Up-and-Go' and average stride times) were almost identical to those observed in young adults. Apparently, fractal measures of gait dynamics are sensitive to subtle changes in physiology that are not detected in others gait measures. Further evidence of the utility of complexity based markers of gait variability include studies showing associations between long-range fractal patterns in stride intervals and fall risk,[56] and associations between loss of gait complexity and presence of neuromuscular disorders such as Huntington's, Parkinson's disease, and ALS.[55, 57–59]

2.1.4 Complexity and adaptability—It has been hypothesized that the complexity of physiologic control systems serves an important purpose; it enables the organism to mount a focused adaptive response in order to perform a specific task or overcome an external stress.[1, 2] However, experimental evidence to support this hypothesis is limited. In one large population-based sample of older adults, Manor and colleagues[50] demonstrated that the degree of complexity contained within the postural sway (i.e., COP) dynamics of quiet standing (i.e., baseline) is associated with the capacity to maintain balance while challenged by a cognitive dual task (i.e., counting backwards by 3's from 500). Additional support for this hypothesis is summarized by Manor and Lipsitz.[60]

2.1.5. Restoration of complexity—Despite the association of loss of complexity with aging and disease, surprisingly few studies have prospectively evaluated the impact of therapeutic interventions on restoration of complexity. A handful of smaller studies have demonstrated that exercise training programs can increase fractal-like correlations in HR data.[61–63] Other studies have demonstrated that subsensory mechanical noise applied to the feet via vibrating insoles can restore COP complexity in elderly subjects and those with diabetic neuropathy or stroke.[17, 64]

In summary, complexity based measures of physiological dynamics show promise as meaningful and sensitive biomarkers for age-related decline in healthy adults. Within the context of a randomized clinical trial of older adults, our comprehensive evaluation of age-related decline in complexity in multiple physiological systems and our experimental evaluation of the ability of a promising multi-component mind-body intervention to restore physiological complexity have the potential to make significant contributions to the field of healthy aging. In particular, we anticipate gaining important new insights into the mechanisms underlying three systems (cardiovascular, postural control, and gait) that play a key role to healthy aging, the interactions among these systems, and the potential to reduce age-associated declines.

2.2. Overview of trial design and specific aims

This pilot study is a two-arm randomized clinical trial to evaluate the potential of Tai Chi to attenuate age-related loss of complexity. A total of 60 Tai Chi–naïve healthy older adults (aged 50–79) are being randomized to either six months of Tai Chi training (n=30), or to a waitlist control group receiving unaltered usual medical care (n=30) (Figure 1). Our primary outcomes are complexity-based measures of cardiovascular (heart rate, HR), postural control (center of pressure, COP) and gait (stride interval) dynamics assessed at 3 and 6 months. Multiscale entropy and detrended fluctuation analysis are used as entropy and fractal-based measures of complexity, respectively. Secondary outcomes include measures of physical and psychological function and tests of physiological adaptability also assessed at 3 and 6 months. This study is designed to inform a future more definitive trial by providing information on preliminary estimates of effect size and the most informative biomarkers of complexity, function, and adaptive capacity. This trial is funded by the National Center for Complementary and Alternative Medicine (NCCAM), National Institutes of Health. All clinical research is performed in Boston, MA at the Beth Israel Deaconess Medical Center (BIDMC). Tai Chi is administered in the community as described below. The Institutional Review Board at BIDMC approved this study. The study is registered at Clinical Trials.gov (NCT01340365). At the time of submitting this manuscript, all study aspects are ongoing.

This study addresses two specific aims. Aim 1 is to determine if 6 months of Tai Chi training can increase complexity, function, and adaptive capacity of multiple physiological systems in older healthy adults and will test four hypotheses: *H.1.a) Those who participate in Tai Chi will exhibit higher levels of complexity across all measured physiological systems, compared to baseline values and compared to controls; H.1.b) Those who participate in Tai Chi will exhibit higher levels of physical and cognitive function; H.1.c) Those who participate in Tai Chi will exhibit higher levels of adaptive capacity; and H.1.d) The magnitude of the effects of Tai Chi on physiological complexity, function and adaptive capacity in healthy older adults will be positively correlated with age.* Aim 2 is to determine the relationships between biomarkers of physiological complexity, conventional measures of function and adaptive capacity, and tests four additional hypotheses: *H.2.a) Measures of complexity will be positively correlated with physical and cognitive function; H.2.b) Measures of complexity will be positively correlated with adaptive capacity.* And over time: *H.2.c) Changes in complexity will be positively correlated with changes in physical and cognitive function; and H.2.d) Changes in complexity will be positively correlated with changes in adaptive capacity.*

2.3. Study population and enrollment procedures

Study population: A total of 60 healthy older adults (50–79 years old) are being recruited for our study. Recruitment targets community dwellers living within the Greater Boston area. Inclusion criteria are: 1) Ages 50–79; 2) Living or working within the Greater Boston area; and 3) Willing to adhere to 6 month Tai Chi training protocol. Exclusion criteria are: 1) Diagnosis of a chronic medical condition e.g., cardiovascular disease (myocardial infarction, angina, atrial fibrillation or presence of a pacemaker), stroke, respiratory disease requiring daily use of an inhaler, diabetes mellitus, active cancer (diagnosis < 5 years ago and requiring ongoing chemotherapy or use of cytotoxic agents), or neurological conditions (e.g., seizure disorder, Parkinson's, peripheral neuropathy); or significant neuromuscular or musculoskeletal requiring chronic use of pain medication; 2) Acute medical condition requiring hospitalization within the past 6 months; 3) Self-reported (current) smoking or alcohol/drug abuse; 4) Unmanaged hypertension (resting SBP > 140 or DBP > 90mm Hg); 5) Abnormal heart rate (resting HR > 100 bpm; <50bpm); Abnormal ECG (supraventricular tachyarrhythmia, atrial fibrillation, significant ST wave abnormality, 2nd and 3rd degree heart block); 6) Pregnancy; 7) Current use of prescription medications that affect autonomic function including cardio- or vaso-active drugs and medications; 8) Self-reported inability to walk continuously for 15 min unassisted; 9) Regular Tai Chi practice within past 3 years; 10) Regular participation in structured physical exercise on average, more than 5 hrs/wk.

2.3.1. Recruitment, screening and enrollment procedures—Potential participants are targeted with advertisements in local newspapers, and hospital based clinics and research volunteer databases. Interested individuals contact the study coordinator who conducts an initial eligibility screen by telephone. Individuals who meet initial eligibility criteria are then required to visit, by appointment, at least one of our four prescreened community-based Tai Chi schools to: a) gain a preliminary understanding of Tai Chi (they can observe but not participate in a class); and b) to experience firsthand the logistical requirements of traveling to and from local Tai Chi schools. This run-in, pre-study visit was introduced as a means to screen out individuals that are less likely to be compliant with Tai Chi class attendance and other study protocols. Individuals completing this run-in phase are then scheduled for an in-person screening visit at the BIDMC Clinic Research Center (CRC). The screening visit begins with obtaining informed consent, followed by assessment of vital signs and an EKG to confirm cardiovascular health criteria, and the Mini-Mental State Examination to confirm appropriate cognitive function (subjects with an MMSE score < 24 are excluded). Individuals who meet all screening criteria undergo baseline testing followed by randomization.

2.3.2. Randomization procedures—Study participants are randomly assigned to Tai Chi or wait list control. Randomization assignments are stratified by participant age (50–59, 60– 69, 70–79) and were generated using a permuted-blocks randomization scheme with randomly varying block sizes. Treatment assignments are sealed in opaque, sequentially numbered envelopes by stratum. All randomization materials are stored in a locked file, with access limited to non-blinded study personnel.

2.4. Interventions

2.4.1. Tai Chi

Rationale for Tai Chi Intervention: Tai Chi, also referred to as Taiji, Tai Chi Chuan or Taijiquan, is a mind-body exercise that originated in China, and that is growing in popularity in the West. Tai Chi is based on slow intentional movements, often coordinated with breathing and imagery, that aims to strengthen and relax the physical body and mind, enhance the natural flow of ‘qi’ (or life energy), and improve health, personal development, and in some systems, self defense.[65] Recent surveys suggest that approximately 5 million Americans have practiced Tai Chi, and this number is increasing.[66, 67] Tai Chi shows great potential for becoming widely integrated into initiatives related to healthy aging. Tai Chi appears to be safe, even for the elderly and deconditioned, and clinical and community based studies report high adherence and enjoyment. Moreover, Tai Chi may be cost-effective, requiring no special equipment or facilities. For these reasons, a growing body of clinical research has begun to evaluate the efficacy of Tai Chi as a therapy for a variety of age-related health issues; this research has been critically evaluated in recent reviews.[8, 9, 68–70] Tai Chi has shown to have a positive impact on cardiovascular,[71–80] postural control,[81–91] and locomotor systems,[92–101] as well as cognitive function, psychological well being and quality of life.[11, 14, 102, 103]

It has been argued that Tai Chi itself is inherently a complex intervention, composed of multiple components each of which has potentially independent and synergistic therapeutic value.[65, 104] As such, the study of Tai Chi may best be viewed as a form of whole-systems research rather than the study of a single active ingredient. This multi-component nature of Tai Chi is depicted in Figure 2 and key components are summarized in Table 1. This complexity poses challenges to simple, single-factor, cause-and-effect reductionist models. For example, the reported improvements in balance referenced above likely result from multiple mechanisms including increased leg strength and flexibility, changes in neuromuscular patterning/control, reduced fear of falling, improved body awareness and concentration, and a number of cognitive strategies.[9] Moreover, these factors are likely to interact with one another in non-linear ways, change in relative importance over time, and differ for different practitioners. Consequently, the fundamental premises and tools afforded by complexity theory and systems biology provide an excellent framework for evaluating and monitoring the therapeutic effects of Tai Chi.

Pragmatic Structure of Tai Chi Intervention: All Tai Chi instruction takes place at one of five community-based Tai Chi schools within an already established network used in prior research studies. Tai Chi school characteristics, eligibility and screening procedures are described in detail elsewhere.[105, 106] Briefly, schools were chosen to meet specific criteria ensuring they provide valid, stable Tai Chi programs led by experienced teachers. Importantly, since participants are being asked to make a six-month commitment to Tai Chi training, allowing them to receive training at a school they choose within their local community increases the likelihood of protocol adherence. Administering the intervention through community Tai Chi schools also affords a high level of ecological validity, as participants will be exposed to a number of traditional components of Tai Chi training that are often absent in fixed protocols provided in medical settings. Finally, because of the inclusion of multiple Tai Chi instructors and well-defined but slightly varying protocols, the results of this study will have good generalizability—applying not only to a single protocol of Tai Chi taught by one teacher, but to a range of approaches that share a common, well-defined set of criteria described elsewhere.[105107]

Participants randomized to Tai Chi are required to attend, on average, two classes per week over the six months of the intervention. They are also asked to practice a minimum of 30 minutes, two additional days per week. All of the schools in our network provide DVDs or printed materials to facilitate home practice.

2.4.2. Usual Care—Participants randomized to Usual Care are instructed to continue their medical care as normal and to not begin Tai Chi instruction during the 6 months of the study.

2.5. Participant remuneration

All costs associated with participation in Tai Chi classes, including practice DVDs, are paid for by the study. Participants randomized to the control group are offered a free 3 month course of Tai Chi following the completion of their participation in the trial. Additionally, all participants receive $50 for each outcome assessment they complete (maximum total of $150) and parking expenses associated with outcomes testing visits are covered by the study.

2.6. Outcome measures

Our measurement protocol includes acquisition of 1) steady-state dynamics of the cardiovascular, locomotor and postural control systems, 2) measures of the ability of these systems to respond to imposed stressors, and 3) more traditional measures of function and health related QOL. Additionally, traditional linear outcome measures for heart rate variability, gait, and postural sway will be assessed for comparison with complexity measures. All measurements will be assessed at baseline, 3 and 6-months. All outcome assessors will remain blinded with respect to treatment allocation (Table 2).

All testing takes place in the Syncope and Falls in the Elderly (SAFE) laboratory, located within the BIDMC Clinical Research Center (CRC), and begins at approximately 9:00 a.m. to minimize diurnal variability in physiological outcomes. Study staff first obtain participant informed consent, and then administer screening procedures which include a health history questionnaire, the Mini Mental State Exam, assessment of vital signs (resting heart blood, blood pressure and ECGs), and a pregnancy test (for pre-menopausal women) to confirm eligibility. Eligible participants then undergo all other study related measurements. The testing protocol was designed to minimize fatigue and patient burden and maximize the validity of the data collected; the protocol follows others used in prior SAFE lab studies.[107, 108] The total time for completion of measurements is approximately four hours, with interspersed resting periods and a mid-point snack provided by the CRC.

2.6.1. Cardiovascular measures—HR dynamics are assessed in multiple ways. Steady-state HR dynamics are assessed during seated rest with spontaneous breathing. To collect the sufficient number of heartbeat cycles for complexity measures, HR dynamics are assessed for 30 minutes. Additionally, two 5-minute periods of HR dynamics are assessed during paced breathing (15 and 6 breaths per minute); paced breathing enables the assessment of cardiovascular dynamics and linear measures of HR variability while controlling for the potentially confounding effects of respiration.[109] The effects of perturbation to the cardiovascular system are evaluated from the well-validated sit-to-stand test.[110] Standing following prolonged sitting (≥5 min) results in an immediate elevation in HR, with relative greater change in HR response reflective of impaired cardiovascular regulation. The maximum change in HR (ΔHR) will be quantified by subtracting the minimum HR during sitting from the maximum HR during the subsequent bout of 1 min standing.

2.6.2. Postural control measures—Steady-state postural control dynamics are assessed during quiet standing with eyes open. With arms at the side and bare feet shoulder width apart, subjects are asked to stand as still as possible on standard force plate (AMTI, Watertown, MA), and to visually fixate on an “X” drawn on a wall approximately 3m away at eye-level. Postural sway of the body is quantified by recording COP displacements. To collect sufficient COP data for complexity analysis, 1 min of continuous standing is obtained. The effects of visual and cognitive perturbations are also evaluated. For the visual perturbation, subjects stand similar to above, except with eyes-closed. For the cognitive perturbation, subjects perform the dual task of counting backwards, out loud, in multiples of three, while attempting to repeat the steady-state protocol. This cognitive dual-task is commonly used to challenge standing balance in both healthy and movement disordered populations.[111] To avoid potential effects of learning, subjects begin each trial from 500, 499, or 498, in random order. To account for potential trial-to-trial variability, three one-minute trials are completed for each condition (steady-state, eyes-closed, dual task). Trials are randomized and at least one minute rest is given between each trial. During the first trial, the subject’s feet are outlined with chalk to ensure consistent foot placement.

2.6.3. Gait measures—Steady-state gait dynamics are assessed during over ground walking at preferred speed. Subjects walk along a long corridor (~75m) that is wide enough (~5m) to enable smooth turning. To record consecutive stride-to-stride durations, subjects have foot-switches inserted into their shoes and a data acquisition monitor (Noraxon Inc, Scottsdale, AZ) attached to their waist. To collect the sufficient number of steps required for complexity measures, 10 min of continuous walking is obtained. The effects of a locomotor perturbation on gait speed, an indicator of gait health and overall function,[112] is assessed during continuous over ground walking while performing the same cognitive dual task as in postural control testing. Subjects complete three 1 min trials while counting backwards, out loud, in multiples of three.[113, 114]. Dual tasking decreases walking speed.[111]. The distance walked during each trial will be recorded and used to calculate average speed.

2.6.4. Assessment of function and health-related quality of life—Multiple clinical tests of physical and mental function are obtained to further characterize the sample, evaluate correlations between complexity measures and function, and assess the impact of Tai Chi and age on these outcomes.

Maximum walking speed is assessed by asking subjects to walk in a straight line as fast as possible, without running, on a premeasured 11m course. The time taken to walk 5m, from the 3m to 8m mark is recorded and used to calculate maximal walking speed (m/s). Performance in this clinical test is associated with functional decline.[115] One-legged standing balance on the subject's preferred leg is assessed according to Vereeck et al.[116] Three 30 sec trials are completed for eyes-open and eyes-closed conditions, and the greatest duration (sec) for each condition is used for analysis. This test is correlated with fall risk in older adults.[117] Maximal power output of the lower extremities is estimated by assessing maximum vertical jump height (m). After a standard warm-up consisting of five sub-maximal jumps, subjects complete three countermovement jumps on a stationary Kistler force plate (Kistler Instruments Corp, Amherst, NY). The "flight-time" for each jump, determined from the force plate reading, is used to determine the maximum height reached by the subject's center of mass using the Bosco method.[118] This test has been shown to be safe for community-dwelling older adults, and test scores correlate with mortality rate, fall-risk and overall physical function.[119, 120] Maximum grip strength of the dominant hand is measured using a handgrip dynamometer Grip D (Takei Scientific Instruments, Tokyo, Japan). Measurements are recorded to the nearest 0.5 kg, repeated three times and averaged. Grip strength is correlated with mortality, and disability, and overall function in middle-aged and older adults.[121] Finally, bilateral hip, knee, and ankle joint passive range of motion (degrees) is measured by a trained investigator using a goniometer and standard procedures.[122] Lower body flexibility is assessed using the validated Chair Sit and Reach test.[123]

The amount and intensity of non-Tai Chi exercise is recorded using the Physical Activity Status Scale (PASS). Subjects are asked to estimate their general physical activity during the previous week using an 11-point scale (i.e., 0–10). The scale quantifies physical activity duration by a combination of the minutes of exercise per week and the intensity of this exercise (heavy, modest, or none). The validity of the scale has been documented in both men and women and scores correlate with maximal oxygen consumption in younger and older adults.[124, 125]

Health related quality of life is assessed using the SF-36. The SF-36 has been validated in a variety of populations including older healthy individuals, and has good test-retest reliability.[126, 127]

Cognitive function is assessed with validated measures of executive function, working and short-term memory. The Trail Making Test (TMT) is a widely used instrument that is administered in two parts.[128] TMTa is a visual-scanning task; the time required to draw lines sequentially connecting numbered circles from 1 to 25 is recorded. TMTb assesses time required to connect the same number of circles in an alternating sequence of numbers and letters. TMTb is considered to evaluate executive control, and is correlated with other executive function measures.[129] TMT is a sensitive indicator of overall neurological impairment,[128] and has good reliability.[130] The Controlled Oral Word Association Test (COWAT) examines working memory span.[131] COWAT requires the participant to produce as many words as possible that begin with a given letter of the alphabet (F, A, S). There is 1 minute allowed for each of the three letters. The score is the sum of all acceptable words produced in the three trials. COWAT has good reliability and validity.[132, 133] The Backwards Digit Span Test (BDS) is a widely used measure of short-term memory, i.e. the number of digits a person can absorb and recall in correct serial order. Two trials of eight number sequences are read aloud. Scores are based on the number of sequences correctly recalled (i.e., until the participant consecutively fails two trials of the same digit span length). BDS has good reliability and validity.[131] All three measures have been employed in studies evaluating the impact of exercise on cognitive function in elders.[134]

The Mini-Mental State Examination (MMSE) is employed for screening purposes, and individuals scoring less than 24 are not eligible for the study. MMSE is used widely in primary care and in community based research settings, and has good inter-rater reliability.[135–137]

Mood is assessed using the 30-item Profile of Mood States (POMS-30). This well-validated instrument assesses emotional states that are transient and expected to respond to clinical intervention.[138] Prior studies of Tai Chi have reported improvement in mood, decrease in anxiety, and enhancement in vigor as measured by the POMS scale.[139]

The degree to which participants believe that Tai Chi will be beneficial to their health is assessed using an instrument used in a number of prior complementary and alternative medical intervention studies. Participants are asked to rate how helpful they believe Tai Chi will be for their general health on a 0 to 10 scale. [140]

2.6.5. Compliance with Tai Chi protocol—Compliance with the required training schedule is monitored using a combination of class attendance cards that are signed by Tai Chi instructors following each visit, and participant-completed home practice logs. Participants are asked to send class attendance and home practice logs to study staff monthly using prepaid envelopes provided at the beginning of the study. If attendance and/or practice logs are not submitted on time, the study coordinator calls the participant within 3 days of the due date. Every possible effort is made to keep subjects actively engaged in the protocol following attendance and practice guidelines.

2.7. Computation of complexity measures

Two principal complexity metrics—Multiscale Entropy (MSE) and Detrended Fluctuation Analysis (DFA)—are employed in this study.[21, 25, 141] Multiscale Entropy quantifies the information content of a signal over multiple temporal or spatial scales. Compared to other entropy-based methods, MSE uniquely accounts for dynamical information encoded in physiologic signals over multiple scales and therefore is able to distinguish between highly irregular random (uncorrelated) signals and truly complex ones.[18, 23, 53] DFA quantifies long-range correlation properties (i.e., fractality) of a signal. Unlike alternative approaches (e.g., Fourier spectral analysis and Hurst analysis), DFA permits the detection of intrinsic self-similarity embedded in a seemingly nonstationary time series. DFA has been successfully applied to a wide range of simulated and physiologic time series in recent years.[15, 27, 111] Computations of these indices are briefly summarized below. Extensive information on these measures, including details of algorithms, tutorials, and examples of their application is provided at Research Resource for Complex Physiologic Signals (www.physionet.org).

2.7.1. Multiscale Entropy (MSE)—The MSE algorithm comprises two steps: (1) a coarse-graining procedure that allows us to look at representations of the system's dynamics at different time scales, and (2) the quantification of the degree of irregularity of each coarse-grained time series, which can be accomplished using sample entropy (SampEn), a statistic introduced by Moorman.[142] The coarse-grained time series are constructed as follows. For scale 1, the coarse-grained time series is the same as the original signal. For scale n, we divide the data into consecutive non-overlapping blocks with n data points each and calculate the mean inside each block. The sequence of average values is the coarse-grained time series for scale n.

Sample entropy is the negative natural logarithm of the conditional probability that two patterns of length m, $x_m(i) = \{x_i,\ldots, x_{i+m-1}\}$ and $x_m(j) = \{x_j,\ldots, x_{j+m-1}\}$ will still be considered similar to each other when points, x_{i+m} and x_{j+m} are added to patterns $x_m(i)$ and $x_m(j)$, respectively. The two patterns, $x_m(i)$ and $x_m(j)$, are separate samples within a time series and are selected based on the level of similarity between them. A threshold tolerance level of r is used – i.e. $d[x_m(i), x_m(j)] \leq r$, where d is a function that measures the distance between vectors. The complexity index is the summation of the sample entropy values for each coarse-grained time series for a pre-selected range of time scales. A higher MSE score implies greater complexity.

2.7.2. Detrended Fluctuation Analysis (DFA)—To estimate a fractal scaling index for long-range correlation properties using DFA, time series (with N data) are first integrated using the following algorithm: $y(k)= \Sigma_{i=1}{}^{k}.[B(i)-B_{ave}]$, where $B(i)$ is the i-th data point of the time series and B_{ave} is the average value of the data points. Next the integrated time series is divided into boxes of equal length, n. In each box of length n, a least squares line is fit to the data (representing the trend in that box). The y coordinate of the straight line segments is denoted by $y_n(k)$. Next we detrend the integrated time series, y(k), by subtracting the local trend, $y_n(k)$, in each box. The root-mean-square fluctuation of this integrated and detrended time series is calculated by: $F(n)=\sqrt{1/N\sum_{k=1}^{N}[y(k)-y_n(k)]^2}$ This computation is repeated over all time scales (box sizes) to provide a relationship between F(n), the average fluctuation, as a function of box size. Typically, F(n) will increase with box size n. A linear relationship on a double log graph indicates the presence of power law (fractal) scaling. Under such conditions, the fluctuations can be characterized by a scaling exponent a, the slope relating log F(n) to log n. Since an exponent of 1 represents fractal scaling and smaller deviations from 1 are more complex, we can quantify complexity as the absolute value of 1-a complex.

2.8. Statistical analysis

2.8.1. Analytic plan

Aim 1: Our goals is to compare the change over time in the Tai Chi students versus the controls. The primary analysis will use an intention-to-treat paradigm, i.e., participants will be evaluated on the basis of group assigned by randomization without regard to subsequent adherence. Since this is a pilot study, we will not impute values for missing data; however, the statistical models we are using will include all available data. We recognize that some participants may drop out before the follow-up evaluation and that some outcome measures may not be evaluable for some participants. We will make no adjustment for multiple testing. A secondary 'per-protocol' analysis will be limited to participants who were compliant (attended 70% of classes and completed at least 70% of home sessions). Our primary analysis will employ linear mixed effects regression models that examine change over time (i.e., slope) for each outcome measure (i.e., the complexity measures, MSE and detrended fluctuation analysis) for each of the systems (i.e., heart rate, postural control and gait). The models will incorporate a random intercept and a random slope for each participant.

We will also conduct sensitivity analyses that incorporate additional covariates into the models, including age, gender, baseline physical and mental health, BMI, and exercise behavior. We are particularly interested in examining age with a focus on assessing whether age substantially reduces the variability of the random effects, i.e., whether it explains a substantial proportion of between-person variability in baseline complexity and slope. Analyses of secondary outcomes will follow the same general analytic approach. We will use mixed effects models to examine the effects of Tai Chi training over time on physical and cognitive function (exercise capacity, balance, upper and lower extremity strength, cognitive function, and quality of life) and adaptive capacity (change in heart rate, change in COP displacement, change in stride variability).

Aim 2: We hypothesize that function and adaptive capacity are associated with complexity. We will first examine the association between complexity measures and function/adaptive capacity at baseline. We will calculate Pearson correlation coefficients between the complexity measures (MSE and detrended fluctuation analysis) and the measures of function/adaptive capacity. To examine the independent association between complexity and function/adaptive capacity, we will fit ordinary least squares regression models using the function/adaptive capacity measures as the dependent variable. Independent variables will include age and sex as well as any other baseline characteristics associated with the function variable. We will add the complexity measure to this model and evaluate the Wald test and the change in R2. We will also investigate whether changes in complexity are associated with changes in function and adaptive capacity. We will fit linear regression models with change in function and adaptive capacity as the dependent variable and change in complexity as the independent variable of interest. Since we will have 2 observations per participant (change at 3 months and change at 6 months), we will use generalized estimating equations methods (GEE) to account for the within-person correlation. Independent variables will include the measure of function and adaptive capacity at baseline, age, sex, treatment group and time (3 vs. 6 month). Further, we hypothesize that complexity is the primary mediator of the association between Tai Chi and improvements in adaptive capacity. We will examine this using the approach recommended by Judd and Kenny.[143] For example, to examine whether multi-scale entropy of postural sway (i.e., COP) during quiet standing mediates the effect of Tai Chi on the postural adaptation to a dual cognitive task among the older participants, we will fit 3 regression models: regress MSE on Tai Chi use; regress COP response on Tai Chi; and regress COP response on MSE and Tai Chi use. The associations seen in these models determine the existence and strength of mediation. Despite the implicit directionality of our hypotheses, all tests will be two-sided. We recognize that we are examining a moderate number of outcomes in this study. Since it is a pilot study and has limited power, we do not intend to adjust for multiple testing.

2.8.2. Sample size and statistical power—Our analysis will be based on a longitudinal regression analysis in which we do not have an estimate of the within-participant correlations. In the worst case, the two follow-up measures provide no more information than a single follow-up, and the power calculation is equivalent to that for a simple t-test.

With 30 participants in each group, we will have 50% power to detect an effect size of 0.52 (i.e., the sample size provides 50% sensitivity to detect a difference between groups .52 times the standard deviation of the outcome measure) and 80% power to detect an effect size of 0.74 for each of the main effects. Our primary hypothesis, however, is an interaction effect. Our sample size provides at least 50% power to detect an interaction effect size of 1.03, under this worst case scenario. At the other extreme, if the two follow-up observations are independent, we will have 50% power to detect an interaction effect size of 0.72 and 80% power to detect an effect size of 1.03. The use of regression models further increases power by accounting for additional sources of variability. Unpublished data from a trial of heart failure patients found that the mean difference in MSE change between Tai Chi and control was 2.26, which translates to an effect size of 1.2. Therefore, changes of this magnitude will likely be present in our current study and thus our sample will provide adequate power.

2.9. Adverse Events

Adverse events are monitored through participant feedback, reports from Tai Chi schools, and study team observations during testing visits and monthly follow-up calls to participants. Tai Chi schools received information on potential Tai Chi-related side effects and adverse events as well as the protocol, and are instructed to call the study PI if any participant is experiencing any symptoms of concern. Participants are provided with information on safety policy and adverse event forms, and are instructed on their use by study personnel at the conclusion of the baseline testing visit. Adverse events that take place during testing are also reported to the PI by the SAFE laboratory assessor. All adverse events are reported to the IRB as prespecified in a data and safety monitoring plan.

3. Discussion

Understanding the biology of aging and evaluating interventions that promote healthy aging are becoming increasingly important priorities. As summarized in this paper, a growing body of research supports the idea that aging is associated with loss of complexity in multiple physiological systems.. However, a number of outstanding questions remain that limit our ability to evaluate complexity-based physiological metrics as biomarkers for monitoring healthy aging, as well as their value for quantifying the impact of therapeutic interventions such as Tai Chi on age-related disease prevention and rehabilitation. Using mathematical tools drawn from the emerging field of complexity and systems biology, this study will characterize how Tai Chi—a multi component mind-body exercise—impacts moment-to-moment variations in heart beat, gait, and postural control, as well as the relationship of these patterns to more traditional measures of physical and mental function. This study will advance our understanding by systematically characterizing age-related decline in multiple physiological systems in a well-defined cohort of adults, and the relationship of these complexity metrics to more traditional measures of physical and cognitive function; and by evaluating and comparing two separate metrics for characterizing physiological complexity.

There are a number of limitations inherent in this study that are important to note. First, we are only considering two of many metrics available to characterizing the complexity of physiological dynamics. Different metrics may provide insight into unique aspects of complex dynamics.[144] Which metrics prove to be optimal will require more extensive comparisons in future larger studies with diverse populations, and may also vary with the specific biological questions being explored.

Second, and related to this first limitation is the paucity of experimental research available to inform a mechanistic interpretation of complexity metrics. Our goal in the current study is to characterize the impact of Tai Chi training on complexity outcomes, and the relationship of these outcomes with multiple validated markers of age-related function. However, to better interpret how and why Tai Chi may impact physiological complexity, mechanistic studies that experimentally alter complex physiological processes will be needed. Taking postural control as an example, experimental studies that systematically perturb various combinations of processes known of contribute to postural control (e.g. plantar proprioception, vision, vestibular function, executive function) and quantify the impact of these perturbations on complexity signals (e.g. COP), will better inform the meaning and value of these metrics, and help us understand how interventions like Tai Chi may impact complexity and resilience.

Third, the duration of this study is relatively short for understanding the longer-term impact of Tai Chi in healthy aging. While many studies, especially those evaluating older adults or population with significant health impairments, have reported functional changes in periods of three to six months, the six month duration of this study will only evaluate the potential of Tai Chi to impact age-related decline. Tai Chi is traditionally considered a life-long learning tool, and it is believed that with time, both proficiency and health benefits improve. Long-term interventional studies as well as well-designed observational studies comparing long-term Tai Chi practitioners (e.g. > 10 years) to matched controls will be needs to fully evaluate the long-term impact of Tai Chi on healthy aging.

Finally, in our attempt to comprehensively evaluate multiple physiological systems and outcomes, it is possible that the large battery of tests we utilize could overly burden participants and impact the quality of the data collected. To minimize this potential limitation the following strategies were integrated into all protocol to minimize fatigue and bias. 1) Short breaks are placed between all physical activities and replications of specific physical tasks, and mid-way through the overall protocol participants are provided with a light lunch and 20 minute break. 2) Cognitive and seated tasks are interspersed with physical ones. 3) The exact same sequence of tests are used at all three evaluations, so if there is any systematic fatigue near the end of the protocol, this would be consistent between baseline and follow-up tests. However, to date we have completed more than 100 testing visits, and at no visit has anyone been incapable of completing the entire battery of tests. Moreover, in our final test which involves 10 minutes of continuous walking, we explicitly ask if participants are experiencing fatigue or pain, and to date, no one has responded with a yes.

In conclusion, limitation withstanding, results of this study may lead to novel measures that help us monitor and understand the physiological processes of aging, and explore the potential benefits of Tai Chi and related mind-body exercises for healthy aging.

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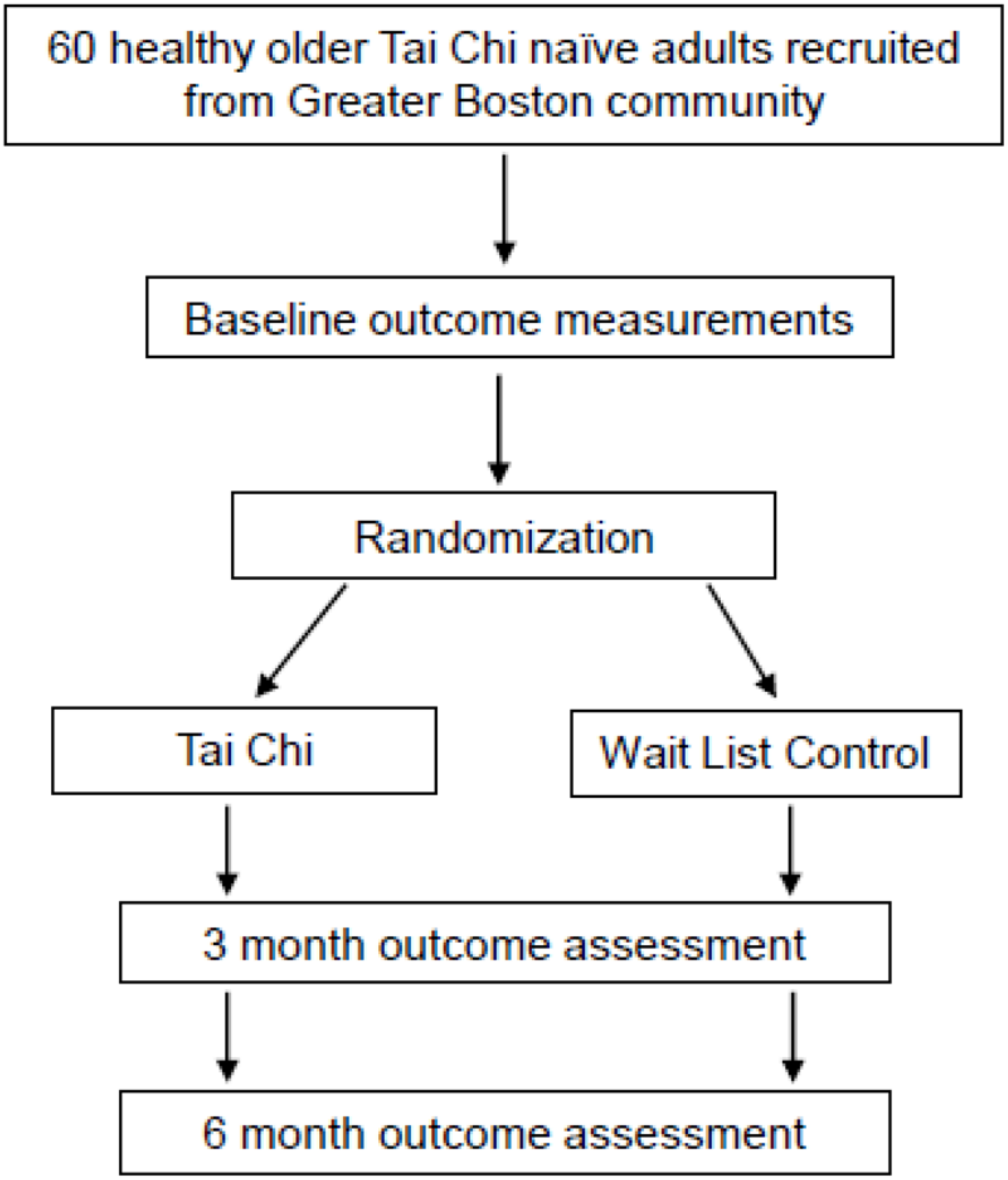

Figure 1.
Study design

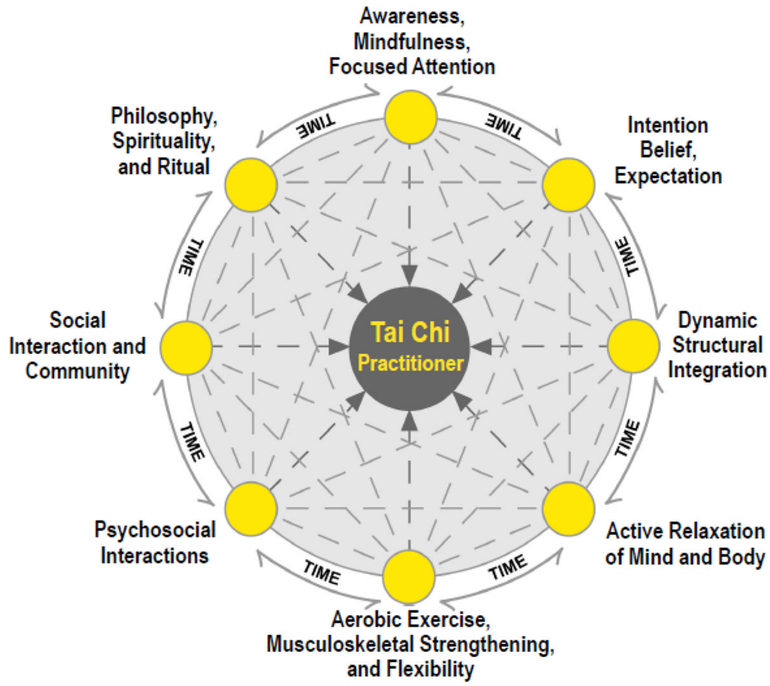

Figure 2.
Schema characterizing the multicomponent nature of Tai Chi, depicting eight classes of therapeutic components or 'active ingredients'. Arrows connecting each element acknowledges interdependence of these factors, and 'time' emphasizes that relevance of each component may change as practitioners skills develop. (Modified from Wayne and Kaptchuk 2008; Wayne and Fuerst 2013).[145]

Table 1

A summary of purported therapeutic components or ‘active ingredients’ of Tai Chi. (modified from Wayne and Fuerst 2013)[145]

Therapeutic component or ‘active ingredient	Brief description
Awareness, Mindfulness, and Focused Attention	Perhaps the most fundamental ingredient underlying Tai Chi, the slow, deliberate movements and attention to breathe, body positions, and sensations fosters acute self-awareness. The emphasis on moment-to- moment awareness may result in enhanced mindfulness and improved focus.[146–149]
Intention, Belief and Expectation	Imagery, visualization, and related cognitive tools alter intention, belief, and expectation and may contribute significantly to the therapeutic and physiological effects of Tai Chi.[150–152]
Structural Integration; Dynamic Form and Function	Enhanced integration within and between multiple structural and physiological systems is another key active ingredient that may underlie Tai Chi’s therapeutic effect. Biomechanically efficient shapes and patterns of movement may have functional consequences across many systems.[10, 92, 101]
Active Relaxation	Tai Chi’s circular, flowing motion helps shift the body and mind into deeper levels of relaxation, and is believed to be a form of meditation in motion.
Strengthening and Flexibility	Tai Chi provides moderate aerobic training equal to levels obtained in walking at a moderate pace.[153] The integrated movements may result in less strain, greater power with less effort, and better balance. The slowness of the Tai Chi movements, in combination with slightly flexed stances and placing weight on one leg at a time for sustained periods of time, lead to significant lower extremity strength training and increased loading on the skeleton.[105, 154] In addition, slow, continuous, relaxed and repetitive movement also results in dynamic stretching, which enhances overall flexibility.[92, 155, 156]
Natural, Freer Breathing	More efficient breathing improves gas exchange,[157] massages body tissues,[158] including internal organs, helps regulate the nervous system,[159] improves mood,[160] and is believed to balance and move qi within the body and between the body and the environment.
Social Support, Interaction and Community	Being part of a group has therapeutic value for a variety of medical conditions, including cancer, heart disease, depression, and anxiety.[161–163] In ongoing Tai Chi classes, students develop a strong sense of community, with rich interactions and support from teachers and peers.
Embodied Spirituality, Philosophy and Ritual	Tai Chi creates a practical framework for practicing living with a more holistic, Eastern philosophy that integrates body, mind, and spirit.

Table 2

Summary of outcome measures and associated variables

Temporal dynamics during steady-state conditions	**Physiological measure**	**Testing methods**	**Outcome variable**
	Heart rate (HR)	Beat-to-beat variation measured using ECG for a 30 minute during seated quiet resting	HR complexity*
	Standing balance	Center of pressure dynamics during quiet standing with eyes open	COP complexity
	Gait	Stride–to-stride interval at preferred speed during a 20 minute period	Stride complexity
Adaptive capacity	Heart rate	Sit to stand test	Max change in heart rate
	Standing balance	Eyes closed Cognitive dual task	Change in COP complexity Change in magnitude of COP displacement
	Gait	Cognitive dual task	Change in average stride variability
Function and HRQOL	Exercise capacity	Max walking speed	m/sec
	Musculoskeletal strength/power	**a.** Lower extremity power (Jump test) **b.** Grip strength (dynamometer)	**a.** Maximum height of jump(cm) **b.** kg
	Clinical balance	Single leg balance with eyes open and closed	Maximum time on balance
	Range of motion	**a.** Goniometry of lower extremity (hips, knees, ankles bilaterally) **b.** Sit and reach test (back and leg flexibility)	**a.** Degrees of motion **b.** cm
	Mood	Profile of Mood States	Indices of 6 domains of mood
	Cognitive function	Trail Making Test A and B Controlled Oral Word Association Test Backwards Digit Span Test	Time to complete test (sec) Number of words recalled/min Number of digit sequences correctly repeated
	HRQOL	SF-36	Indices of physical and mental health in 8 domains
	Physical activity	Physical Activity Status Scale	Index of physical activity during prior week
Protocol adherence	Tai Chi training	Teacher reported class attendance records Self-reported home practice logs	Numbers of classes/month Hours of home practice/month
Additional screening instruments	Cognitive function	Mini-mental state exam	Index reflecting 5 domains of cognitive health