

Tau analysis of arm movements in early infancy as a detection method for cerebral palsy

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Abstract

Cerebral palsy is the most common motor disability seen in children. Physicians agree that early detection and intervention for affected children is desirable, yet current diagnostic measures rely heavily upon a child's failure to meet normal developmental milestones, causing significant delays for diagnosis and treatment. This study set out to investigate the feasibility of using the principles of general tau theory to identify movement dysfunction in very young infants with cerebral palsy. Three potential tau-related markers were investigated in a sample of 20 infants with withheld diagnoses, 10 infants with cerebral palsy and 10 healthy control infants. Analyses focussing on one of these markers, the standard deviation of the coupling constant k , was found to distinguish between infants with and without cerebral palsy for 18 out of the 20 infants included in this study. It was also found that a threshold standard deviation of k equal to 0.30 differentiated between infants with and without cerebral palsy with a specificity of 0.80 and a sensitivity of 0.90. Furthermore, particular classifications of cerebral palsy appeared to be associated with different patterns of values across the infants' two limbs. It was therefore concluded that analyses based in tau theory show potential to be able to quantitatively predict with high sensitivity and specificity both the presence and subtype of cerebral palsy.

INTRODUCTION

Cerebral Palsy: Background

Cerebral palsy (CP) is defined as a group of permanent disorders of the development of movement and posture, causing activity limitation, that are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain (Rosenbaum et al., 2007). It is a disorder that encompasses an extensive, heterogeneous range of neurological conditions that primarily involve the motor and posture systems (Sewell, Eastwood, & Wimalasundera, 2014), and which are caused by an event or series of events no longer active at the time of diagnosis (Rosenbaum et al., 2007). Thus the range of functional presentations for children and adults with cerebral palsy can be extremely broad. Some individuals with cerebral palsy are close to functionally unaffected by their condition, with only very mild motor impairments. Others are deeply affected both physically and intellectually, and require life-long care. Cerebral palsy is delineated from other neurological conditions by the specification that the neurological insult must occur between the perinatal period and, in spite of no explicit upper age limit, an approximate age of 2 years (Ashwal et al., 2004; Rosenbaum et al., 2007). Diagnosis of cerebral palsy rests largely upon an infant's delay or failure to reach normal developmental milestones, and as a consequence most children receive a diagnosis at an age of 1 to 2 years (Ashwal et al., 2004). In today's society cerebral palsy is considered to be a permanent condition without cure.

Worldwide, cerebral palsy is by far the most common form of motor disability in children. Studies have reported a variety of incidences for cerebral palsy, ranging mostly between around 1.5 and 3 cases per 1000 live births (Sewell et al., 2014). The most recent systematic review at the time of writing (Oskoui, Coutinho, Dykeman, Jette, & Pringsheim, 2013) gave a worldwide aggregate figure of 2.11 instances per 1000 live births. The relationships seen between the prevalence of CP and birth weight, and the prevalence of CP and gestational age, are of particular importance. Significantly higher incidences of cerebral palsy are seen in infants born very low birth weight (VLBW) and low birth weight (LBW). In birth weights $\geq 2500\text{g}$ the prevalence of cerebral palsy is just 1.3 per 1000 live births. This rises to 10.2 in birthweights 1500-2499g, 59.2 in birthweights 1000-1499g and 56.6 in birthweights $<1000\text{g}$. A similar relationship can be seen between prevalence of CP and gestational age at birth, where prevalence is just 1.4 per 1000 live births in infants born >36 weeks gestation, 6.8 in those born at 32-36 weeks, 43.2 in infants born at 28-31 weeks and as high as 82.3 in infants

born before 28 weeks (Oskoui et al., 2013). These prevalence rates serve to assist parents and doctors of infants in high-risk populations to be prepared for an eventual diagnosis, as well as be attentive to potential early warning signs and missed milestones.

Several different focuses exist for classification of cerebral palsy, which are usually combined to give an overall indication of the severity of a person's cerebral palsy. The three main classification focuses are: according to the anatomical distribution of affected limbs (where terms such as hemiplegia and diplegia are used), according to the presentation of a movement abnormality (where terms such as spastic, hypertonic, dyskinetic or ataxic are used), or based on the individual's level of independent motor function (most commonly measured using a therapist-scored scale called the Gross Motor Function Classification System (GMFCS)). Each focus has its benefits and its drawbacks. It is important to know which of a person's limbs are affected by their CP, but anatomical classifications in particular often paint an inaccurate picture. Individuals can have a classification of unilateral (one-sided) cerebral palsy, yet have some degree of involvement on the opposite side. Others can have a classification of bilateral cerebral palsy, yet have clear asymmetries between each side (Rosenbaum et al., 2007). The preferred treatment methods for spastic cerebral palsy, meanwhile, can be very different than the preferred treatment methods for ataxic cerebral palsy.

Early diagnosis of cerebral palsy

It is a common misconception that rates of cerebral palsy are on the rise due to an increase in the survival rate of pre-term infants, and as such that better diagnosis and treatment methods are needed to prevent healthcare systems from becoming overwhelmed. However, the prevalence rate of cerebral palsy has in fact remained relatively steady since the late 1980s (Surman et al., 2009; Winter, Autry, Boyle, & Yeargin-Allsopp, 2002). Survival rates for preterm infants have indeed increased from 44% in 1971 to approximately 85% in 1998 (Volpe, 1998), but the increased incidence of CP due to this has been offset by improvements medical interventions for other conditions causing cerebral palsy (Oskoui et al., 2013).

A combination of two particular medical practices is believed to be responsible for much of the decrease in incidence of cerebral palsy amongst preterm populations. This is the administration of antenatal corticosteroids to in-utero infants to stimulate development of the lungs before birth and avoid surfactant deficiency, combined with the administration of

magnesium sulphate to delay labour for long enough that the corticosteroids will be effective (Engle, 2008; Oskoui et al., 2013). In addition, improved treatments in other non-prematurity related illnesses causing cerebral palsy, such as infantine jaundice, meningitis and rubella, have also contributed to the maintenance of a steady prevalence rate for cerebral palsy (Oskoui et al., 2013).

There appears to be little evidence to indicate that the burden of disease from cerebral palsy is threatening to increase significantly in the near future. However, the potential for vastly increased personal outcomes in individuals with CP is nonetheless a very strong motivating factor in the promotion of early diagnostic methods for cerebral palsy. Nowadays many clinicians are reluctant to mention to parents their suspicions of a child having cerebral palsy before a clear diagnosis can be made, partly due to avoid unnecessarily burdening them if this suspicion is unfounded, and partly because health services in most countries require an official diagnosis before treatment can be commenced. However, the resulting delay in receiving therapeutic intervention for those children who do in fact have cerebral palsy is feared to be responsible for the entrenchment of many mal-adaptive motor patterns that then become compounded by pathological soft tissue adaptations (Shepherd, 2014).

That normal development is disrupted by the neurological insult that causes CP is integral to the definition of cerebral palsy. The timing of the original injury during this period of high development has highly negative circular consequences for the infant. The initial functional limitations caused by neurological injury cause developmental delays, and these developmental delays result in further functional limitations, eventually in the form of permanent soft-tissue changes. It is hypothesised that in cerebral palsy, the main issue limiting functional recovery after an initial neurological insult is that the brain has been compromised while it is still being “calibrated”. In early infancy the brain is at its most neuroplastic and is more responsive to its experiences than it is during later life (Kolb, Mychasiuk, Muhammad, & Gibb, 2013). In this way, it is possible that the outcomes seen in children and adults with cerebral palsy could be compared to the well-documented effects of sensory deprivation during those senses’ critical and sensitive periods (Berardi, Pizzorusso, & Maffei, 2000).

Early therapeutic interventions in cerebral palsy

The obvious benefit of diagnosing cerebral palsy as early as possible is the subsequent ability to implement very early therapeutic interventions. There is, however, a distinct lack of literature regarding early interventions in human infants with cerebral palsy under 12-18 months of age; simply due to the current inability to diagnose CP early enough to study the potential effects (Shepherd, 2014). Instead, as is often the case in medical research, current hypotheses have been reached via the cautious application of principles discovered in animal studies onto humans.

Behavioural therapy studies investigating the effect of a stimulating environment (Comeau, Gibb, Hastings, Cioe, & Kolb, 2008; Kolb & Elliott, 1987) and regular tactile stimulation (Kolb & Gibb, 2010) on rats¹ have demonstrated that there may exist an opportunity for increasing functional improvement following perinatal cortical lesions. Cortically lesioned rat pups who received tactile stimulation in the form of gentle stroking had significantly improved spatial learning and skilled motor function as compared to the otherwise matched animals that did not receive tactile stimulation. Additionally, rats with perinatally-inflicted bilateral cortical lesions benefited greatly from being placed in a highly stimulating environment as soon as they were weaned, while rats with perinatally-inflicted bilateral cortical lesions that were not placed in a stimulating environment until adulthood experienced no benefit from the environment.

The studies mentioned above, if proven to be applicable to humans, may indicate the presence of a finite motor critical- or sensitive period during early life, as is seen in vision, audition, language and more (Kandel et al., 2013). Such a case would explain why current treatment options for cerebral palsy are mostly limited to symptom management (Shepherd, 2014) and, in the event that cerebral palsy were diagnosed early enough, could provide an exciting avenue for improving functional outcomes in individuals with cerebral palsy.

¹ In terms of neuronal migration and synaptogenesis, a rat at birth is equivalent to a 5-month-old preterm human foetus, and a human at birth is equivalent to a 5-day-old postnatal rat (1995 Kolb). Thus, any cross-species comparisons are made based on these ratios rather than absolute age ((10-05-15) 2003 Luciana)).

Tau Theory

The aim of the present study is to explore the possibility of tau theory being used to diagnose cerebral palsy at the young age of 3 months post-term. Tau theory is a theory of ecological psychology that posits that all purposeful movement occurs as the transition between a current state and an envisioned goal state, where the difference between these two states is described as a “motion gap” (Lee, 2009). Tau (τ) is the name given to the function describing the duration of time until this goal state is reached, given the current rate of closure. Tau theory posits that in order to control a self-generated, purposeful movement, the only parameter that needs to be perceptually monitored is τ (and by extension its derivative $\dot{\tau}$ - the way that τ changes over time).

Tau theory was first envisaged by Professor David Lee, and was used to explain the braking strategies used by experienced drivers (Lee, 1976). This study described the way that drivers use knowledge of τ to prospectively control ongoing braking, where $\dot{\tau}(t) = b$. If $b \leq 0.5$ then the vehicle would stop either at or before the obstacle, but if $b > 0.5$ then the vehicle would crash into the obstacle. The theory was expanded on a short time later by introducing the concept of tau-coupling, where it was hypothesized that movement may also be prospectively controlled by keeping the τ of one’s own bodily movement in a constant ratio with the τ of an external object’s movement. Examples of prospective control using external τ coupling can be seen in (Kayed & van der Meer, 2009; van der Weel, van der Meer, & Lee, 1996), both of which studied children’s tau-coupling of self-generated reaching movements onto moving toys.

A more recent expansion of tau theory hypothesises that internally driven movements without clear external goals can also be described in terms of tau coupling, where the tau to which the body movement is coupled onto an internally generated “plan” for the movement, known as a tau guide (τ_G) (Lee, 2009). The tau guide is hypothesised to be expressed in the brain in the pattern of flow of electrical energy through ensembles of neurons, existing as a template for movement control upon which proprioceptive feedback can be compared. An example of prospective control using internal τ coupling (τ_G coupling) can be seen in (Craig & Lee, 1999), which found that the pressure used by newborn infants during nutritive sucking follows the pressure curve that would be predicted for a tau-coupled movement. Spencer and van der Meer (2012) also found that when initiating gait, the centre of pressure of the weight shift in adult humans was internally τ_G coupled.

K-values

The value “k” is a coupling constant that describes the relationship between two coupled tau functions. In practice, the k-value of a tau-coupled movement determines the kinematics of that movement, in particular the shapes of the movement’s velocity and acceleration profiles. K is a useful value to use when considering tau theory, as it represents the simplest available parameter that, if simply kept constant, can dictate both the quality and the velocity profile of a movement. A k-value between 0 and 0.5 results in a movement for which velocity peaks in the first half of the movement, and has a longer deceleration period. A k-value between 0.5 and 1.0, on the other hand, results in a movement where velocity peaks in the second half of the movement, and has a shorter deceleration period. It is also possible to produce k values above 1.0, where this results in a movement where velocity is still increasing when the goal state is reached. Velocity profiles for different values of k are given in Figure 1.

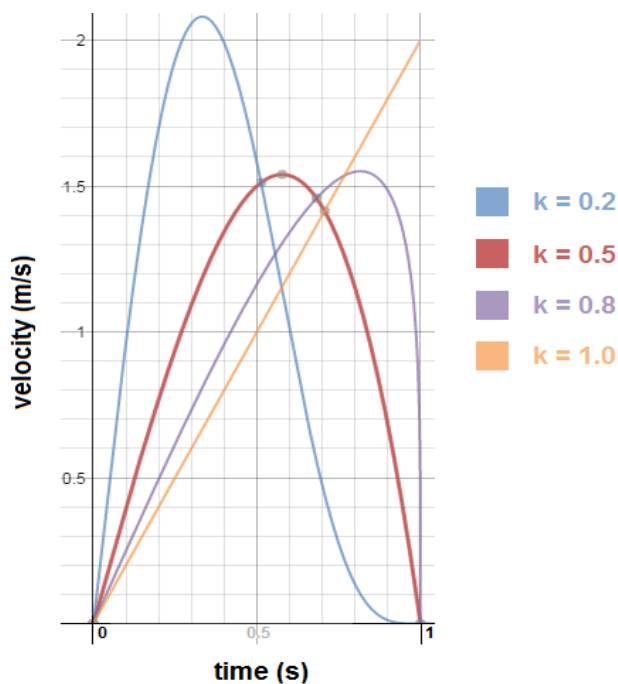


Figure 1: Lower k values see earlier peak velocities and longer deceleration periods. Higher k values see later peak velocities and shorter deceleration periods (or for $k \geq 1.0$, no deceleration period).

In the case of $0.5 < k < 1.0$ braking must theoretically reach infinity at the exact moment of motion-gap-closure in order to stop precisely at the goal state. Due to the practical impossibility of this, k values in this range instead see a “controlled collision”, wherein movement has not yet come to a complete stop by the time the goal state has been reached. This form of motion-gap closure can be useful, such as when a baseball bat hits an incoming ball, or a somersaulter lands from a jump, the latter of which has been demonstrated to be tightly tau-coupled (Lee, Young, & Rewt, 1992).

The particular value taken by k has furthermore been demonstrated to be chosen based on the goal of the task (Craig & Lee, 1999; Lee, Simmons, Saillant, & Bouffard, 1995), and to be a potential predictor of different levels of motor control (Austad & van der Meer, 2007; Spencer & van der Meer, 2012).

The coefficient of determination and percentage tau coupling

The assumption that a movement is controlled using tau-coupling is modelled using a regression analysis. A recursive linear regression analysis produces two outputs of particular interest: a coefficient of determination (r^2), giving an indication of the degree of linearity between τ_G and tau of the actual movement; and a percentage coupling (%-coupling) value measuring the percentage of the movement that fits the shape of a τ_G -coupled movement after a recursive linear regression (a more comprehensive description of this process can be found in the methods section). Kayed and van der Meer (2009) implicated this parameter as an indicator of control in infants, where higher percentage coupling values were associated with a time-to-closure perceptual strategy and then higher levels of motor control.

Could tau theory be used to predict cerebral palsy in high-risk infants?

That voluntary movement is controlled by prospective regulation of motion-gap closure rates is a well-respected theory within ecological psychology. Proof of this fact, however, will likely not come about until evidence of an internally generated tau guide is discovered. However, the large quantity of research with findings that are consistent with tau theory is a promising start. Indeed, if tau theory has predictive powers for detecting motor control dysfunction that are not possible under other theories of movement control, then this too is strong evidence to support tau theory.

David Lee himself has explicitly described his own belief that tau theory could perhaps be used to diagnose neuro-developmental disorders in infants (Lee, 2009). Other researchers within the field of tau theory support this view (Craig, Grealy, & Lee, 2000), and have postulated that analysis of the temporal control and kinematics of an infant's early-developing motor skills may reveal neurological abnormalities. Furthermore, the developers of the highly regarded General Movements Assessment (GMA) diagnostic method for cerebral palsy

strongly advocate that the *quality* of infants' movements is the most important indicator of infants' neurological outcome (Ferrari, Cioni, & Prechtl, 1990; Prechtl et al., 1997).

The present study aimed to investigate whether differences could be observed in the tau coupling of spontaneous arm movements of infants with and without cerebral palsy. The arm movements of twenty infants were recorded at a corrected age of 10-15 weeks and the quality of tau-coupling for these movements was analysed. Based on previous results of tau analyses in this population group (Craig et al., 2000; Lee, Daniel, Turnbull, & Cook, 1990; van der Meer, Wee, Lee, Laing, & Lin, 1995; van der Weel et al., 1996), it was hypothesised that a lack of motor control in infants with cerebral palsy would be detectable as high k values, low percentage coupling values and/or high standard deviations of k.

METHODS

Subjects

Infant recruitment and data collection occurred between 2000 and 2002 through St Olav's hospital in Trondheim by then PhD candidate and physiotherapist Lars Adde. Preterm infants and infants with a high risk of developing cerebral palsy were recruited from St Olavs hospital's neo-natal intensive care unit (NICU). Healthy term infants were recruited from the maternity ward. Infants were then assigned anonymous identification numbers and had measurements and characteristics pertinent to the study recorded as seen in Table 1. A parent or carer of each infant gave informed consent and was advised of their right to withdraw their child from the study at any time.

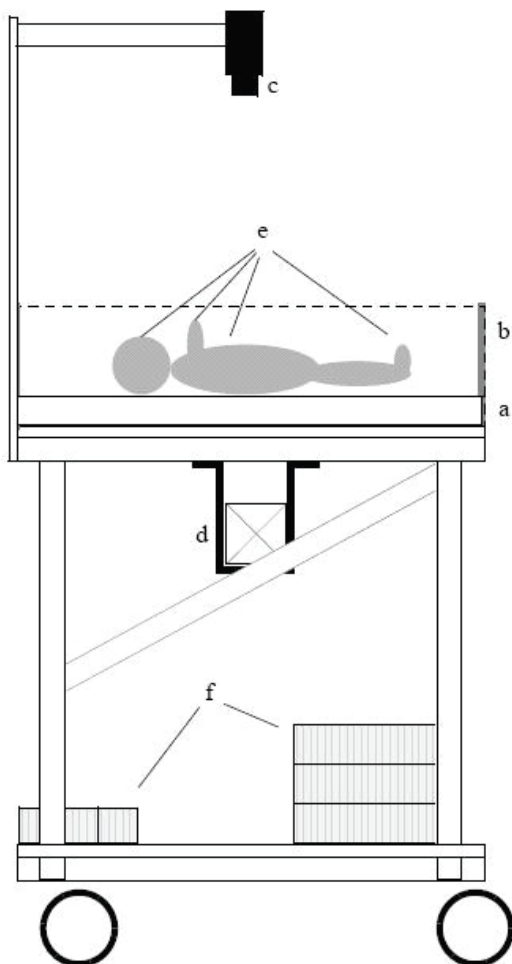


Figure 2: The data acquisition setup. The infant was placed on the mattress (a) surrounded by transparent walls (b), with a magnetic tracking system (d) mounted on the mattress undersurface and sensors (e) attached to wrists, ankles, sternum and forehead. The power supply for the motion tracking system (f) was mounted at the base of the setup, and a video camera (c) was mounted overhead but not used in the present study. (Courtesy of L. Adde and Ø. Stavadahl, 2010)

Infant ID	Premenstrual age at birth (weeks)	Birth weight (grams)	Age at recording (weeks)	CP status	Subtype of CP	GMFCS (5 yrs)
P040	34	1985	15	Yes	Spastic quadriplegia	5
P044	24	695	12	Yes	Spastic hemiplegia (left)	Did not survive
P045	24	720	13	Yes	Spastic hemiplegia (right)	2
P054	40	3580	14	Yes	Spastic hemiplegia (left)	3
P071	41	3456	12	Yes	Spastic quadriplegia	5
P096	29	920	15	Yes	Spastic hemiplegia (right)	1
P101	28	1080	11	Yes	Spastic diplegia	1
P103	40	3470	11	Yes	Spastic hemiplegia (right)	1
P108	33	2465	13	Yes	Spastic quadriplegia	5
P112	23	470	12	Yes	Spastic hemiplegia (left)	4
P002	40	3540	11	No	-	-
P003	40	3800	15	No	-	-
P010	39	3200	14	No	-	-
P011	39	3200	14	No	-	-
P012	42	4725	12	No	-	-
P015	40	3020	14	No	-	-
P032	39	3580	11	No	-	-
P074	40	3820	14	No	-	-
P075	39	3560	10	No	-	-
P081		1238		No	-	-

Table 1: Pertinent measurements recorded for each of the twenty infants included in the study.

Use of subjects in this study

The movement data for these infants were provided for analysis in two distinct stages, designated as phase 1 and phase 2. Phase 1 comprised an initial sample of just two infants (P040 and P081), where it was known that one infant was later diagnosed with cerebral palsy and one was not, but it was not known which infant was which. Phase 2 comprised an additional sample of 18 infants, where it was known that 9 infants were later diagnosed with cerebral palsy and 9 infants were not, but it was again not known which infants belonged to which classification.

During phase 1 the arm movements of the selected two infants were analysed using tau theory by calculating mean k-values, mean percentage-coupling values and standard deviations of k for each of the infants' two arms. These values were evaluated and a prediction as to the infants' later diagnoses was made. This prediction was then checked against the infants' true outcomes and confirmed to be either correct or incorrect. During phase 2 an identical process was undertaken using the further sample of 18 infants. The k-values, percentage-coupling values and standard deviations of k calculated for these 18 infants were evaluated. Based on the results of this evaluation a prediction was made as to the infants' later diagnoses. These predictions were then checked against the infants' true outcomes and confirmed to be either correct or incorrect. Finally, observations of possible correlations between the values calculated for infants with cerebral palsy and their respective subtypes of cerebral palsy were made.

Data collection and preparation

Movement data from each infant were captured using a MiniBIRD 3D electromagnetic motion tracking system mounted beneath the infant and sensors attached to the forearms, lower legs, sternum and forehead (see Fig. 2). All recordings were performed at least 30 minutes after the infant had been fed, and were acquired at 25Hz with a spatial resolution of 1/250 inch. This procedure was in accordance with the requirements of the relevant institutions' ethical committees.

Each infant's data set was cropped to a length of eight minutes so as to optimise consistency, where the original lengths of recording differed considerably between infants (mean 13.1

minutes; sd. 4.3). The 8 minute length was available to all infants with the exception of infant P045, whose recording was only long enough to contribute 4.3 minutes of data.

The procedure for cropping the data files was undertaken in the following order until such time as an 8 minute length was achieved, at which time the procedure was stopped.

1. Non-endogenous movements were removed, specifically the period of time before recording began (flat-line data) and the period at the end of recording when the infant was lifted by an adult
2. Areas with little or no arm movement (close-to-flat-line areas) were removed
3. Any data points still present after the 8 minute mark were removed

The cropped data were then smoothed using a Gaussian filter so as to reduce noise. A sigma value of 2 was used, representing a whole-number approximation to the standard deviation of infants' mean movement durations (180ms).

Movement determination

Local positional minima and maxima were identified for the entire duration of the data set, and were used to identify each change in movement direction of the arm. For the purposes of the calculations to follow, each set of data points between a positional minimum and maximum was defined to be one individual movement (where the "goal position" for the movement was the data point corresponding to this minimum/maximum). The beginning and end of each movement were then cropped to remove data whose velocity was less than 10% of the movement's maximum velocity. This was in line with previous tau analysis research (Lee, Craig, & Grealy, 1999) which indicated that limb movements' slow initial and terminal velocities are inherently noisy, and as such that these sections of the movement are neither representative nor helpful to be included in analysis. Each resulting set of data points was henceforth referred to the "individual movement" and was analysed as described below.

Calculations

The following abbreviations are used in this section:

Overarching parameters (unchanged for entire recording period)

x_{initial}	= the anchor point; the location of the wrist at the beginning of the movement.
x_{goal}	= the final distance that the wrist has travelled at the end of each arm movement
t_{initial}	= 0; the time at which x_{initial} occurs
r^2	= the coefficient of determination; indicating the strength of linear association between two variables

Movement parameters (different for each individual movement)

T	= movement duration; the time at which x_{goal} is reached
t_0	= a point in time infinitesimally soon after $t=0$ (used because $t=0$ would cause $\tau_G = \infty$)
x_{t_0}	= the distance of the wrist from the goal position at $t=t_0$
x_n	= the distance of the wrist from the anchor point at $t=n$
\dot{x}_{t_0}	= the velocity of the wrist at $t=t_0$
\dot{x}_n	= the velocity of the wrist at $t=n$
X_n, Y_n, Z_n	= the wrist's X, Y or Z coordinate at $t = n$
$\tau(t)$	= the time until closure function of a given motion gap given its current rate of closure
τ_G	= the putative "guide" for the closure of a motion gap, representing the brain's internal plan for the movement

Recorded data were obtained in the form of Cartesian X, Y and Z coordinates. A simple trigonometric method was employed in order to unite these coordinates into a single distance value; first the values of X_n , Y_n and Z_n were translated for the entire recording period such that $X_{t_0} = Y_{t_0} = Z_{t_0} = 0$. Then each sampling point then reformulated as the distance value (x_n) using Eq. (2).

$$x_n = \sqrt{X_n^2 + Y_n^2 + Z_n^2} \quad (2)$$

Eq. (3) was then used to calculate the mathematical function representing the brain's putative internal plan for each movement (τ_G).

$$\tau_G(t) = \frac{1}{2} \left(t - \frac{t^2}{t} \right) \quad (3)$$

In order to calculate the mathematical function representing the infant's actual arm movement a 25Hz distance-time-series comprised of a series of values for x_n every 40ms was created from the prepared movement data. A 25Hz velocity-time-series was then calculated based upon the distance-time-series using the finite difference differentiation method (Mitchell, 1980; Nayroles, Touzot, & Villon, 1992). Each datum from these time-series was then plugged into Eq. (4) so as to create a 25Hz τ_{wrist} -time-series.

$$\tau_{wrist}(t) = \frac{x(t)}{\dot{x}(t)} \quad (4)$$

A regression analysis was then performed comparing τ_{wrist} and τ_G so as to identify the strength of tau coupling found between τ_{wrist} and τ_G . This was done by plotting the τ_{wrist} -time-series against the mathematical function $\tau_G(t)$. The resulting plot then underwent a recursive linear regression analysis, whereby the left-most points in the plot were removed one by one until such time as the coefficient of determination (r^2) exceeded the threshold level of $r^2 > 0.95$. This threshold value was considered proof that those data it was valid for, was tau coupled. The ratio of the original number of data points compared to those remaining once $r^2 > 0.95$ was reached, multiplied by 100, was defined as the percentage coupling value of the movement. Finally, the constant k was defined as the gradient of the regression line, where $\tau_{wrist} = k \times \tau_G$. This process was completed once for each individual arm movement.

Movement data from each of the infants' arms were analysed according to the above procedure, producing k values and %-coupling values for each individual movement of each arm. So as to best assure that only deliberate movements were included in the analysis, a lower movement amplitude threshold of 1 inch was set. From the movements fulfilling this criterion a mean k value, mean %-coupling value and standard deviation of k were calculated for the infants' arms. Thus, all ensuing references to "k values", "%-coupling values" and "standard deviations of k" in the remainder of this study should henceforth, unless otherwise specified, be considered to refer to these means.

Diagnosis prediction

These means and standard deviations were then evaluated based on the principles of tau theory, where high k values, low %-coupling values and high standard deviations of k are associated with the lower levels of control seen in cerebral palsy, and low k values, high %-coupling values and low standard deviations of k are associated with higher levels of control (Austad & van der Meer, 2007; Craig & Lee, 1999; Kaye & van der Meer, 2009; Lee, 2009; van der Weel et al., 1996).

During phase 1 evaluation and prediction was undertaken based on the absolute values obtained during analysis for each of the infants. During phase 2 evaluation and prediction was undertaken based on the values obtained during analysis for each infant relative to the others. During phase 2 the values for the infants in phase 1 whose diagnoses had become known was also used for evaluation and prediction. The phase 2 prediction was made based on a two-step cluster analysis completed in SPSS (version 21) that included the two infants whose diagnoses had become known. This cluster analysis is a method of classification used for identifying subgroups within a group of subjects, by identifying and weighting patterns. This method was chosen due to its ability to withstand non-independent data, for the user to choose the number of output clusters, and due to it not being sensitive to outliers (Norušis, 2012).

Cluster Analysis

It was hypothesised that a computational algorithm would have a more comprehensive and time-efficient ability to differentiate the infants into two distinct groups than a single person. For this reason, the SPSS software package's two-stage clustering analysis was employed to evaluate the potential tau-related variables.

Thus, a number of cluster analyses were performed with the intention of determining which variables or combinations of variables could form the basis for splitting the 16 infants into two equal-sized groups, where these groups could logically / conceivably also be a group of infants with cerebral palsy and a group of healthy infants. When cluster analyses produced unequal cluster sizes, enough infants were selected from the larger cluster so as to produce equal cluster sizes. This selection was based primarily on three cluster analyses that used σ_k

values; an analysis based solely upon average σ_k values, an analysis based solely upon $\Delta \sigma_k$ values and an analysis combining both parameters. The selection secondarily included a number of infants who had high average σ_k values.

RESULTS

On average around 350 arm movements, 175 per arm, were identified for each of the 20 infants included in this study. Figure 3 gives an indication of the type of results obtained when analysing an infant's single arm movement, which were in turn used to calculate k -values, % coupling values and values for the standard deviation of k (σ_k).

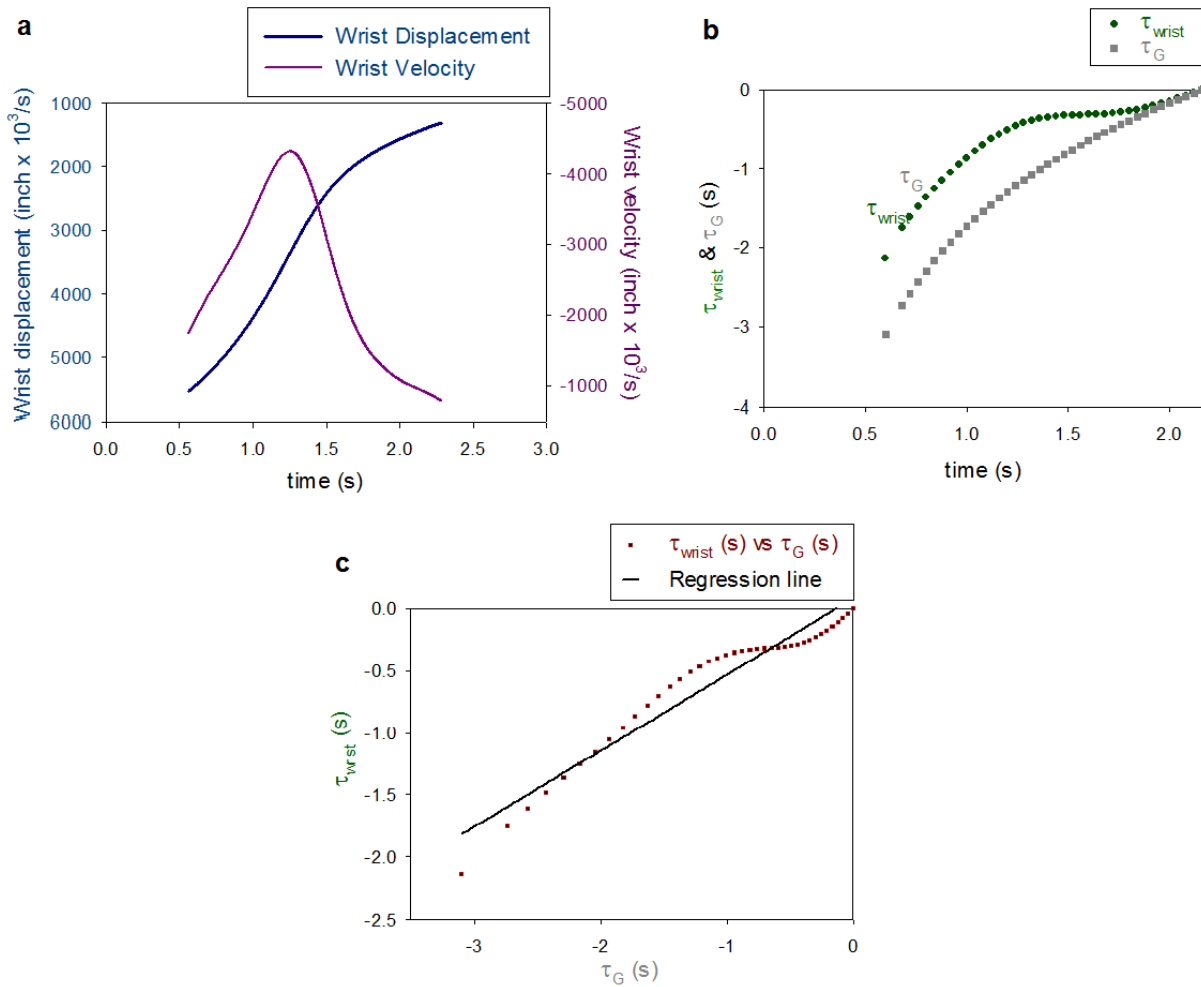


Figure 3: Illustration for an infant's single arm movement of the measurements used in calculations, including displacement and velocity of movement (a), τ_{wrist} and putative τ_G guides for the movement (b), and regression of τ_{wrist} vs τ_G .

Phase 1: Analysis of two infants

K values, %-coupling values and values for the standard deviation of k were calculated for the two infants included in this first phase of analysis. These values were the means of values for all individual arm movements with amplitudes greater than 1 inch, and are summarised in Table 2.

Infant P040 was found to have higher k values and lower %-coupling values than infant P081. The average k value across infant P040's two arms was 0.559, while the average k value across infant P081's two arms was 0.478. An independent t-test analysis comparing these data confirmed the two infants' averaged k values to be significantly different from each other; $t(558) = 4.42$, $p = 0.00001$. A one-sample t-test found that the average k-value of infant P040 was significantly greater than 0.50; $t(344) = 3.15$, $p = 0.002$, while another one-sample t-test did not find the average k-value of infant P081 to be significantly different than 0.50; $t(613) = 1.77$, $p = 0.077$. The average %-coupling value across P040's two arms was 72.1%, while the average %-coupling value across P081's two arms was 78.4%. An independent t-test analysis comparing these data confirmed that P040 had significantly lower %-coupling values than P081; $t(558) = 4.35$, $p = 0.00001$.

Based on these results, in the context of previous tau theory findings regarding markers for poor motor control, it was predicted that P040 was the infant with cerebral palsy and that P081 was the healthy infant. This prediction was confirmed to be correct by the infants' confirmed later diagnoses.

Phase 2: Analysis of 18 infants

K values, %-coupling values and values for the standard deviation of k (σ_k) were calculated for the 18 infants included in phase 2 of analysis. These values were the means of values for all individual arm movements with amplitudes greater than 1 inch, and are summarised in Table 3. Cluster analyses and t-tests were then performed, the cluster analyses using all 20 infants from both phases. The inclusion of the two phase 1 infants with known diagnoses during phase 2 analyses was to exploit all possible available information regarding which values could be used as markers for cerebral palsy. In this way, cluster analyses that failed to differentiate between the two infants with known diagnoses could therefore also be considered to be unlikely to be useful in differentiating the other 18 infants.

	k values		% coupling		σ_k	
	Left	Right	Left	Right	Left	Right
P040	0.546646	0.571975	74.0659	71.231	0.369561	0.290293
P081	0.472585	0.483599	78.5451	78.3222	0.292575	0.293415

Table 2: Mean k-values and %-coupling values, and k standard deviations for all arm movements with amplitudes greater than 1 inch for the two phase 2 infants.

	k values		% coupling		σ_k	
	Left	Right	Left	Right	Left	Right
P002	0.5531	0.5245	74.41	74.67	0.2857	0.2976
P003	0.6026	0.5637	74.12	74.20	0.3962	0.3271
P010	0.5862	0.6075	69.51	61.14	0.3166	0.2887
P011	0.5141	0.4950	75.16	76.92	0.2792	0.2783
P012	0.5062	0.4836	79.22	76.67	0.3087	0.2819
P015	0.5526	0.5297	71.08	66.65	0.2972	0.2577
P032	0.4864	0.4944	81.93	77.65	0.3166	0.2664
P044	0.5086	0.5450	75.30	75.95	0.2771	0.3461
P045	0.5460	0.5117	79.45	71.94	0.3797	0.2810
P054	0.5305	0.5450	75.41	75.13	0.2900	0.3183
P071	0.5238	0.5085	76.54	76.55	0.2775	0.3100
P074	0.5101	0.5572	80.01	71.63	0.2836	0.3052
P075	0.5509	0.5812	73.80	70.00	0.2814	0.2882
P096	0.5389	0.6043	74.87	74.40	0.3284	0.3982
P101	0.5212	0.5470	78.14	78.55	0.2984	0.3262
P103	0.5353	0.6059	71.76	72.61	0.2662	0.3713
P108	0.4930	0.5294	75.59	79.34	0.2360	0.3664
P112	0.4780	0.5676	80.50	76.76	0.2898	0.3222

Table 3: Mean k-values and %-coupling values, and k standard deviations for all arm movements with amplitudes greater than 1 inch for the 18 phase 2 infants.

Neither the significant differences seen between the k-values of infant P040 and P081 nor the differences seen between infants and a k value of 0.5 were seen in the phase 2 analysis. Table 4 illustrates the results of the one-sample t-tests completed for each of the 18 infants in phase 2, as well as two infants previously reported in phase 1. It can be seen that only 10 infants were correctly classified; no different from the result that could be expected purely due to chance. A cluster analysis using k-values, as well as the scatter plot seen in Fig. 4a, highlighted 6 infants with significantly high average k-values, however the sample of infants was known to include 10 infants with cerebral palsy. Based on these analyses the infants' k-values were deemed unlikely to be an indicator of cerebral palsy.

	Significantly different than 0.5?	t(DF)	p
P002	Yes	t(294) = 2.19	p = 0.030
P003	Yes	t(322) = 4.02	p = 0.00007
P010	Yes	t(217) = 4.62	p = 0.000007
P011	No	t(377) = 0.256	p = 0.798
P012	No	t(670) = 0.486	p = 0.627
P015	Yes	t(176) = 1.993	p = 0.048
P032	No	t(463) = 0.707	p = 0.480
P044	No	t(283) = 1.394	p = 0.164
P045	No	t(142) = 1.057	p = 0.292
P054	Yes	t(407) = 2.457	p = 0.014
P071	No	t(400) = 1.122	p = 0.263
P074	No	t(246) = 1.721	p = 0.087
P075	Yes	t(254) = 3.822	p = 0.0002
P096	Yes	t(303) = 3.357	p = 0.001
P101	Yes	t(355) = 2.071	p = 0.039
P103	Yes	t(240) = 3.699	p = 0.0003
P108	No	t(91) = 0.349	p = 0.728
P112	No	t(305) = 0.372	p = 0.710

Table 4: Results of one-sample t-tests completed for the average k values of each of the 18 infants in phase 2. Included is whether the result was significantly different than 0.5, the t-value (t), the number of degrees of freedom (DF), and the p-value (p) for each infant.

Similarly, the %-coupling values generated during phase 2 analysis were found to have a relatively even spread. A cluster analysis using % coupling values, as well as the Fig. 4b scatter plot, highlighted only 2 infants with significantly low % coupling values, though again the sample of infants was known to include 10 infants with cerebral palsy. This result,

coupled with the lack of a predetermined critical % coupling value (similar to the k value of 0.5) resulted in the conclusion that % coupling values were unlikely to be an indicator of cerebral palsy.

Cluster analyses and scatter plots of the difference between left arm and right arm k values (Δk values) for each infant showed similarly low differentiation of infants as was seen for average k values. Cluster analyses and scatter plots of the difference between left arm and right arm % coupling values (Δ % coupling values) also showed low differentiation of infants. These results are presented in Figure 4c-d.

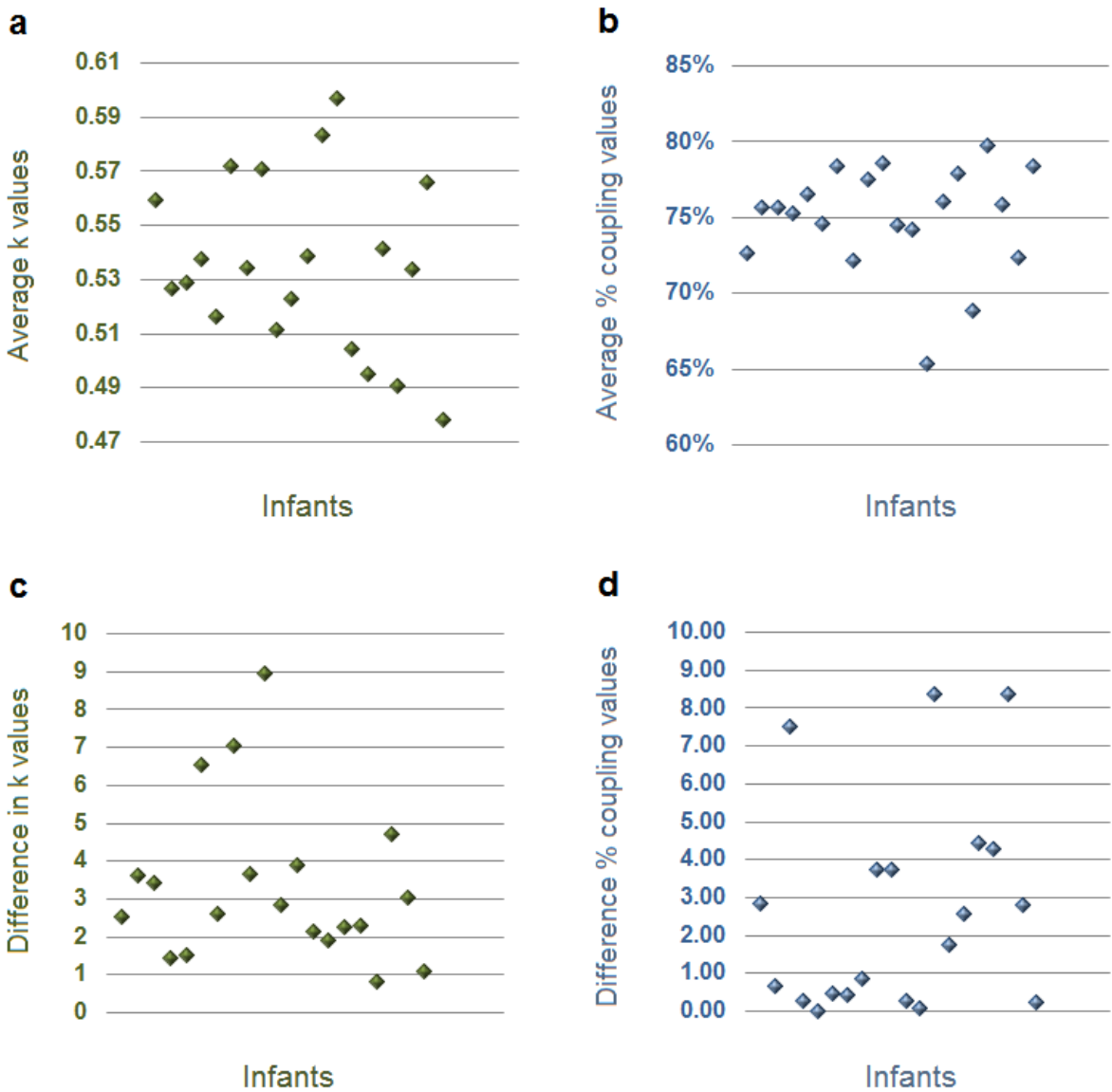


Figure 4: Scatterplots of infants' average k-values (a), average %-coupling values (b), Δk values (c) and Δ % coupling values (d).

Further scatter plots (Fig. 5) and cluster analyses using average and difference in σ_k values were then completed and analysed. The cluster analysis based solely on average σ_k values showed low differentiation between infants, with separation into clusters of 4 and 16 infants. The remaining two cluster analyses returned clusters identical to each other, of 7 and 13 infants each. The two infants with known outcomes (P040 who had CP and P081 who did not) were clustered into separate groups, and thus it was predicted that the infants who shared a cluster with P040 would also have cerebral palsy, and the infants who shared a cluster with P081 would not. This meant that 7 infants were clustered into the CP group and 13 infants were clustered into the non-CP group. Thus 3 infants needed to be selected from the non-CP group to be moved to the CP group. This was done by selecting the three infants in the non-CP group with the three highest σ_k values (infants P054, P101 and P112).

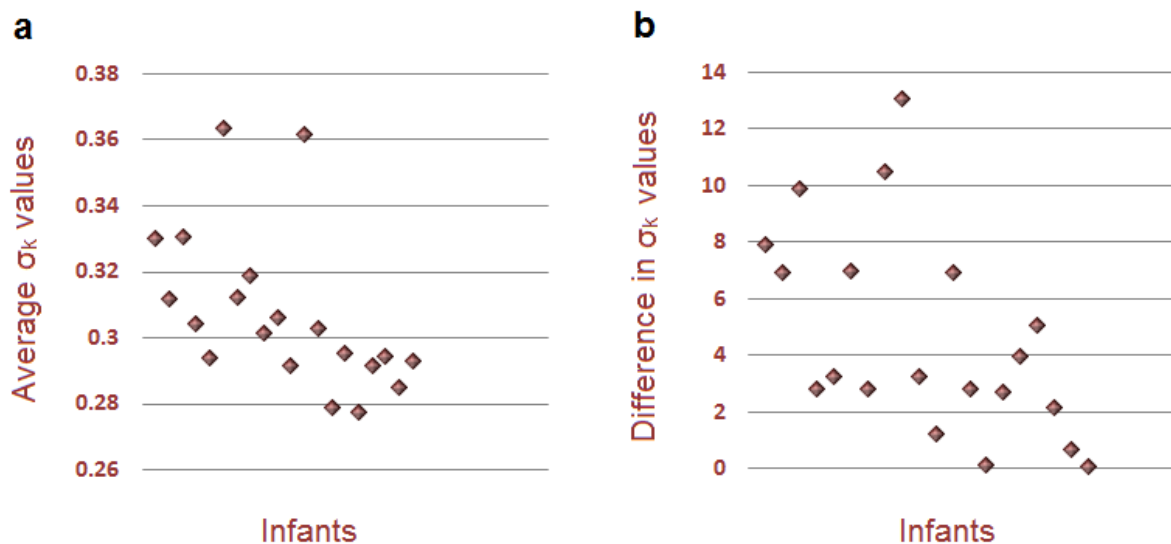


Figure 5: Scatterplots of infants' average σ_k values (a) and $\Delta \sigma_k$ values (b).

Thus, the final prediction made was: CP group: P003, P040, P044, P045, P054, P096, P103, P108 and P112; non-CP group – P002, P010, P011, P015, P032, P074, P075, P081, P101. Sixteen out of eighteen predictions were determined to be correct. Thus, across both phases, 18 out of 20 infants were correctly classified either as having or as not having cerebral palsy.

Prediction: Infants with CP	Actual: Infants with CP	Prediction: Infants without CP	Actual: Infants without CP
P003	P044	P002	P002
P044	P045	P010	P003
P045	P054	P011	P010
P054	P071	P012	P011
P096	P096	P015	P015
P101	P101	P032	P032
P103	P103	P071	P074
P108	P108	P074	P075
P112	P112	P075	P081

Table 5: Fourteen out of the sixteen unknown infants were correctly characterised. Infant P101 was in fact originally characterised as having cerebral palsy, and was only moved to the non-cerebral palsy group so that group sizes would be equal.

Observations

Once the diagnoses of the infants had been revealed, patterns could be observed in the data. In particular an association was observed between subtype of cerebral palsy and the distribution of k values and σ_k values across the two limbs. Of the five infants with hemiplegic cerebral palsy and known GMFCS scores, two infants had higher k values and k standard deviations in their affected arm than their non-affected arm, and three infants had higher k values and k standard deviations in their non-affected arm than their affected arm. The infants that had higher values in their affected arm both had GMFCS scores of 1, indicating the mildest level of motor dysfunction. The infants with higher values in their non-affected arms had GMFCS scores of 2, 3 and 4 respectively, indicating more disabling levels of motor dysfunction.

It was also observed that a threshold average σ_k value of 0.30 could be used to accurately differentiate between infants with cerebral palsy and healthy control infants, with a specificity of 0.80 and a sensitivity of 0.90. All infants with cerebral palsy with the exception of infant P071 had σ_k values above 0.30, while all healthy control infants with the exception of infants P003 and P010 had σ_k values below 0.30.

DISCUSSION

This study set out to investigate the feasibility of using the principles of general tau theory to identify movement dysfunction in very young infants with cerebral palsy. To do so, the arm movements of 20 infants deemed to be at high risk of having cerebral palsy were recorded and analysed under the principles of tau theory. The results indicate that the values of the standard deviation of k can be used to correctly classify all except two infants in this sample group, but that k values and % coupling values cannot. Correlations were also observed between the distribution of σ_k values seen in hemiplegic infants' arms and the anatomical distribution of their cerebral palsy, and a σ_k value of 0.30 was observed to distinguish between infants with cerebral palsy and infants without with good sensitivity and specificity.

After the success seen using k values to differentiate between the two infants during phase 1 of analysis, it was somewhat unexpected that k values did not have the highest prediction success rate of the three hypothesised tau-related markers of cerebral palsy. A large body of research within the field of tau theory has shown that high k values, particularly k values below 0.5, are associated with higher levels of control, while low k values, particularly k values below 0.5, are associated with lower levels of control (Austad & van der Meer, 2007; Craig & Lee, 1999; Lee, 2009; Lee et al., 1995).

Similarly, superior tau coupling indicated by higher % tau coupling values has also been associated with higher levels of control (Austad & van der Meer, 2007; Kaye & van der Meer, 2009). Furthermore, some studies in tau theory (Craig et al., 2000; Lee, Davies, & Green, 1993) employed a non-recursive linear regression method; such that higher r^2 values represent the strength of tau coupling in the same way that % tau coupling values do in this study. This lends additional support to the hypothesis that % coupling values would be correlated with infants with cerebral palsy. It was thus somewhat unexpected that % coupling values did not have a high success rate for predicting cerebral palsy in this sample of infants.

The use of σ_k values is however not a well-established measure of movement control in tau theory research. However, one highly relevant study using tau theory to investigate movement control in children with cerebral palsy (van der Weel et al., 1996) did observe differences in the variability of τ in children with CP as compared to healthy controls. In this study it was observed that children with cerebral palsy had higher variability of τ_{hand} at movement initiation than was seen in control children. This study was performed prior to the

generalisation of tau theory to include internal tau coupling, yet it appears feasible that if τ_{hand} were hypothesised to be coupled onto the internal guide τ_G , then the resulting k values would thus also have high variability. One hopes that it is more than simple serendipity that the only study uncovered by the author that implicates, albeit indirectly, the variability of k as a marker of poor coordination was in a study of children with cerebral palsy.

Once the diagnoses of the infants included in this study were revealed, observations could be made as to true correlations between potential tau-related markers of cerebral palsy and the infants that did have cerebral palsy. The first of these observations was that different classifications of cerebral palsy appeared to be associated with different limb distribution patterns of k values and σ_k values. This is a particularly interesting observation as there are even fewer predictive methods for anatomical distribution of cerebral palsy than there are predictive methods for a general diagnosis of cerebral palsy (Guzzetta et al., 2010; Shepherd, 2014). However, due to the small sample size of ten infants in this study no conclusions should be drawn about broader diagnostic ability of this method until such time as the findings can be corroborated in a larger sample size.

It is nonetheless plausible to suggest that infants with more severe cerebral palsy are aware of their limitations and so are more cautious with the use of their affected arm, resulting in lower σ_k values for the affected arm than the unaffected arm. However, the observations in the present study only relate to correlation and not causation. Thus, it could equally be postulated that infants who are reluctant to use their affected arm fail to learn proper control of this arm and so in fact *develop* a more severe cerebral palsy. This hypothesis is consistent with the principles of constraint-induced movement therapy (CIMT), a treatment approach seeing increased interest in the cerebral palsy community (Basu, Pearse, Kelly, Wisher, & Kisler, 2014; Eliasson et al., 2014; Huang, Fetters, Hale, & McBride, 2009), in which the non-affected limb is constrained so as to force use of the affected limb.

The final observation obtained from the present study was that a threshold average σ_k value of 0.30 could be used to predict cerebral palsy in this sample of infants with a specificity of 0.80 and a sensitivity of 0.90. Though at first glance it may be natural to question why this approach was not applied in lieu of the cluster analyses used, the answer to this question can be elucidated from Figure 5a. The average σ_k values seen in this figure are present as a single large scattering with two potential outliers, but with no indication that the σ_k value of 0.30 is

any more important than any other σ_k value. Thus, while the high sensitivity and specificity of using a σ_k value of 0.30 as a diagnostic measure is attractive, the use of a σ_k value being above 0.30 as an indicator of cerebral palsy should be taken with a rather large grain of salt.

Suggestions for methodological improvements

Tau analysis of these infants' movement data was somewhat hampered by the low (25Hz) sampling frequency of the motion capture technology used in this study. The recording of movements at a higher frequency would be a simple way to ensure a more accurate representation of the infants' arm movements, particularly in arm movements of short durations. The analysis of only infants' arm movements when leg data were also available is another area in which extra information is readily available, where in addition it can be seen that 22% of all cases of cerebral palsy are diplegic, affecting only the legs. Some measure of consolation can, however be found in the knowledge that a single infant with diplegic cerebral palsy was included in this study, and that this infant's cerebral palsy was still correctly predicted, despite the analysis of arm movements only.

The calculation of motion gaps based on the scalar distance of the infants' arms from their starting positions represents another aspect of this study that could be improved. Using a scalar quantity, without any representation of the vector direction of the movement, is a substantial simplification of the recorded movement data. A better way of calculating tau would be to calculate the size of the motion gap using trigonometric methods, but to calculate the point-velocity of the gap closure from the original (directional) movement data. Unfortunately this proved prohibitively difficult due to the rigidity of the software used for analysing the infants' data. To write computer code to achieve this end would likely be a viable option, however it was outside the scope of this project. Thus the simplified scalar quantity and its velocity were used to calculate tau for each arm movement.

Arm movements with % coupling values of all sizes were included in this analysis. Yet it seems unlikely to suggest that a movement that is calculated as being tau-coupled for only 10% of its duration should in fact be considered to be tau coupled. Because k values are calculated as the slope of the linear regression line, there is also reason to question whether k values and k standard deviations calculated for movements with low percentage coupling can be accurate descriptors for these movements. For this reason, when analysing the first two infants in phase 1 several analyses were attempted wherein any movements that were

calculated as having a % coupling below 30%, 50% and 70% were removed, to be excluded when calculating the infants' mean % coupling value. The result of this measure, however, was to remove all differences between the two infants, rendering a prediction as to which one had cerebral palsy impossible. For this reason arm movements with low % coupling values were retained.

The large k standard deviations relative to the k values themselves is also a topic of discussion. In contrast to low percentage coupling values, high k standard deviations do not indicate a lack of reliability of their corresponding k value. Instead, the high k standard deviations that are seen in all infants analysed in this study are a representation of the actual variability in the data, a variability that should perhaps not be surprising given the infants' very young age.

Though scepticism toward especially low % coupling values is healthy, it is difficult to distinguish between a movement that is tau coupled and one that is not, based purely upon the % coupling value. Several studies, including Lee et al. (1999) have suggested that for some tasks it may take some time before τ coupling can be established. This is hypothesised to be because of the time needed by nervous system to acquire and process the proprioceptive information relating to the movement, then compare this information to the brain's prospective plan for the movement. Though the hypothesis made in this study was made in relation to adult participants placing a grape between their lips, it should only be more applicable to infants, whose perceptive and proprioceptive systems are still under development. From a developmental perspective it is also important to keep in mind that there is no immediate shift where infants suddenly acquire the ability to skilfully control their movements. Rather, that newborns have some rudimentary control over their arms (van der Meer, van der Weel, & Lee, 1995; A. L. van der Meer, 1997), and that the level control of that they have over their own movements improves steadily during the first few months of life (Piek, 2005). Perhaps then the variability encapsulated by the large standard deviations in these infants' arm movements will see a steady improvement over time, and the results in figure 5 serve as an indication of how far along in this developmental process the infants have come at the time of recording. Thus, if the arm movements of healthy infants' were measured monthly, then a steady decrease in variability would be seen. Evidence to support this theory can be found in one of the few studies investigating movement control using tau in infants under one year of age (Kayed & van der Meer, 2009), where improvements in the use of tau-

coupling to control movement can be seen in infants between the ages of 22 and 48 weeks. In such a case it would be of particular interest to investigate whether these improvements would also be observable in the same way in infants with cerebral palsy.

Suggestions for future work

During the design phase of the present study two approaches were considered for the determination of which, if any, tau related parameters could successfully predict cerebral palsy in very young infants. The first approach was to analyse infants' movement data without knowledge of their diagnoses, testing an abundance of parameters so as to determine which tau-related markers might be associated with infants with cerebral palsy but not healthy controls. This was the approach that was employed in the present study. The second approach considered was to be informed of the infants' outcomes (CP or no CP) at the same time as the movement data was acquired, and to use neural network modelling to determine which parameter(s) could be associated with infants with cerebral palsy but not healthy controls. It was reflected that while testing the first approach first would not affect the ability to test the second approach later, the reverse was not true. It was therefore decided that the present study would follow the first approach. While the results of this study were indeed promising, it would be pertinent, with the infants' known outcomes, to reanalyse their movements using neural network modelling. This approach may then be able to shed more light onto the observations found in the present study.

In conclusion, it has been found that under the circumstances used in the present study, a tau-related marker of cerebral palsy may be identifiable as early as the 3rd month of age. If the results from this sample of infants prove able to be generalised to the broader population then analyses based in tau theory may be able to quantitatively predict with high sensitivity and specificity both the presence and subtype of cerebral palsy. This provides a promising avenue for improving the diagnosis age of children with cerebral palsy, an achievement that could allow the previously impossible investigations into early intervention treatments for infants with cerebral palsy to be undertaken. Further investigation into how well these results can be generalised is, however, needed. A significantly larger sample size of infants, as well as further optimisation of the analysis methods employed, will allow better knowledge of whether the use of the tau-related markers identified in the present study can indeed change the manner and timeframe in which cerebral palsy is clinically diagnosed.

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