Dynamic interaction of the corticospinal tract with the reticulospinal tract across various phases of stroke

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Abstract

To date, the dynamic mechanisms by which the corticospinal tract (CST) and its alternative tract (i.e. the reticulospinal tract (RST)) interact and evolve after the CST has been damaged by stroke has not been fully explored. To gain insight into the mechanisms, we construct a computational model to reproduce several critical features of subscore distributions of the Fugl-Meyer assessment (FMA) for the upper extremity following stroke. Subscores of the FMA present clues about the working neural substrates affected by stroke, potentially distinguishing preferential uses of the CST and RST. A stochastic gradient descent method is employed to emulate biologically plausible phenomena, including activity- or use-dependent plasticity and the preferred use of more strongly connected neural circuits. The model replicates several segments of empirical evidence presented by imaging and neurophysiological studies. One of the main predictions is that substantial CST recovery is achievable unless the initial degree of residual corticospinal neurons following stroke falls below a certain level. Another prediction is that while the functional capabilities of the CST and RST increase in a harmonic way post-stroke, the degrees of functional capability those tracts reach are in a competitive relationship. We confirm that the neural system prioritizes optimizing a more strongly connected motor tract and uses the other tract in a supplementary manner to enhance overall motor capability. This model presents insights into efficient therapy designs.

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To date, the dynamic mechanisms by which the corticospinal tract (CST) and its alternative tract (i.e. the reticulospinal tract (RST)) interact and evolve after the CST has been damaged by stroke has not been fully explored. To gain insight into the mechanisms, we construct a computational model to reproduce several critical features of subscore distributions of the Fugl-Meyer assessment (FMA) for the upper extremity following stroke. Subscores of the FMA present clues about the working neural substrates affected by stroke, potentially distinguishing preferential uses of the CST and RST. A stochastic gradient descent method is employed to emulate biologically plausible phenomena, including activity- or use-dependent plasticity and the preferred use of more strongly connected neural circuits. The model replicates several segments of empirical evidence presented by imaging and neurophysiological studies. One of the main predictions is that substantial CST recovery is achievable unless the initial degree of residual corticospinal neurons following stroke falls below a certain level. Another prediction is that while the functional capabilities of the CST and RST increase in a harmonic way post-stroke, the degrees of functional capability those tracts reach are in a competitive relationship. We confirm that the neural system prioritizes optimizing a more strongly connected motor tract and uses the other tract in a supplementary manner to enhance overall motor capability. This model presents insights into efficient therapy designs.

Keywords: Stroke, corticospinal tract, reticulospinal tract, Fugl-Meyer assessment, synergy

INTRODUCTION

While corticospinal tract (CST) damage is accompanied by cortical damage, a significant recovery of motor impairment necessitates the restoration of the CST, more than that of the cortical areas, emphasizing the great role of the CST in motor recovery (Cramer, 2008, 2020). In the case that the anatomical function of the CST is not sufficient enough to convey motor commands properly, the neural system searches for alternative pathways to send down motor commands for motor execution (Baker, 2011; Bradnam et al., 2013; Fisher et al., 2012; Murphy & Corbett, 2009). One of the representative tracts in the human is the contralesional reticulospinal tract (RST) (Baker, 2011; Ko et al., 2021).

Clinical observations suggest that the amount of potential motor recovery following a stroke primarily depends on residual CST connectivity after stroke observed in the first few weeks, measured primarily using motor evoked potentials (MEPs) status and fractional anisotropy (FA) asymmetry (Stinear et al., 2012, 2017a). Largely persons having a stroke fall into two groups: one group significantly recovers to the level of mild impairment with substantial arm/hand dexterity and the other group stays at the level of severe

impairment limiting the restoration of arm/hand dexterity. The success or failure to retrieve arm/hand dexterity would depend on whether CST connectivity is resilient during the subacute phase where spontaneous motor recovery occurs. In the case that CST connectivity is not resilient, the RST may alternatively evolve leading to an improvement in gross motor function.

Though motor improvement presumably relying preferentially on the CST or RST during the subacute phase has been studied using neurophysiological methods (e.g., brain stimulation) (Byblow et al., 2015; Schambra et al., 2019), the dynamic mechanisms by which these tracts interact and evolve remain unclear. Some studies suggest that: 1) the anatomical functions of tracts in the neural system recover simultaneously from damage (Cleland & Madhavan, 2021; Duncan et al., 1994; Matsuyama & Drew, 1997; Schepens & Drew, 2006; Wilkins et al., 2017) and 2) the anatomical functions of the CST decreases when that of the RST increases (Hadjiosif et al., 2022; H. Kim et al., 2018). However, those studies present empirical evidence through which it is difficult to capture the overall charateristic of the dynamics of motor tracts during the period of spontaneous recovery.

In this study, we construct a computational model, based on the Hebbian theory which generally describes neural plasticity in the neural system (Whitlock et al., 2006), to reproduce several key features of subscore distributions of the Fugl-Meyer assessment (FMA) for the upper extremity. This allows us to gain insight into the interactive evolution of motor tract dynamics depending on the initial degree of CST connectivity post-stroke. Subscores of the FMA, derived from 27 subtests for in-synergy and out-of-synergy movements, present clues about the working neural substrates, potentially distinguishing uses of the CST and RST. It has been hypothesized that while the type of in-synergy movements (tested using the flexion synergy and extension synergy test items) is mediated by either the CST or RST, the type of out-of-synergy movements (tested using the synergy-mixing and out-of-synergy test items) is solely mediated by the CST. It would be possible to estimate CST functional capability and behavioral restitution by taking a look at interactive evolutions between the out-of-synergy movement capability and in-synergy movement capability assessed with the FMA. A stochastic gradient descent algorithm is incorporated into the Hebbian theory to reflect activity- or use-dependent plasticity (Friel et al., 2013). This algorithm successfully replicated the evolution of the torque generation of the elbow joint during flexion which is indicative of upper extremity functional activity following stroke, as well as, it revealed that more powerfully connected motoneurons are optimized earlier (Reinkensmeyer et al., 2012a).

With this model, we simulate the degree of potential CST recovery, and accordingly motor improvement, depending on the degree of residual corticospinal capability at the onset of a stroke. Our interest is to examine how the CST and RST interact and evolve in the subacute phase, per the hypothesized principle "more strongly connected, earlier optimized". These efforts will provide insights into clinically observed motor improvement during the subacute phase as well as therapy design.

METHODS

Concept description

Throughout this study, tract anatomical capability, typically termed tract connectivity, describes the degree of tract connection to convey motor commands to innervate the target motoneurons. Tract connectivity, perhaps synonymously used with tract integrity, particularly of the CST, has been well studied with imaging (e.g., diffusion tensor imaging (DTI)) and neurophysiological methods (e.g., TMS). Tract accessibility, on the other hand, reflects the nervous system's ability riding on activity- or use-dependent plasticity to volitionally wire the tract for motor execution and is less paid attention. Tract functional capability is linked to the capability of performing the target movement using the tract. An improvement in tract functional capability is accompanied by improvements in anatomical capability and accessibility.

Tract model development

Hebb's model is employed for the functional capabilities of tracts. The model encompasses the features of activity- or use-dependent neural plasticity and its accompanying anatomical capability following a stroke. The following basic equation describes the overall motor capability reflecting the involvements of descending pathways and their corresponding neural activities.

$$C_i = \sum_{i=1}^{N} f_w(w_i) f_x(x_i),$$

where *C, w* and *x* denote the overall motor capability, the weight of a connection and cell firing rate, respectively. *f* denotes a response function and *N* is the number of cells.

Increases in the values of weights are assumed to primarily represent anatomical recovery. The values of firing rates are assumed to primarily represent a will of the volition system that tries to achieve a motor goal (accessibility). Those values are thought to also reflect anatomical recovery through cortical reorganization. We assume that weights and firing rates evolve as motor execution is repeated based on use-dependent neural plasticity (Chakrabarty et al., 2009; Martin et al., 2007). Employing a stochastic gradient descent method that describes reinforcement learning, the weights and firing rates are updated in a way adaptive to the overall motor capability, in the following steps (Reinkensmeyer et al., 2012b):

1. Activate cells with a firing pattern $x_i = x_0 + v_{xi}$ and increase the weight with a pattern $w_i = w_0 + v_{wi}$, where v_{xi}, v_{wi} are random noise, and measure the corresponding C_i.
2. Update the cell activation patterns and weights:
$$x_{i+1} = x_i + g_x(Cn - C_i)v_{xi},$$
$$w_{i+1} = w_i + g_w(Cn - C_i)v_{wi},$$
where g_x and g_w denote learning gains and Cn is the normal overall motor capability before a stroke.
3. Repeat.

Here we assume that the ipsilesional CST and contralesional RST are the primary descending pathways in individuals with stroke. In our computational model, the overall motor capability is determined by the functional capabilities of the CST and RST, each of which is expressed as follows:

$$C_i = C_{\mathbf{CST}i} + C_{\mathbf{RST}i},$$

$$C_{\mathbf{CST}i} = \sum_{i=1}^{N_{\mathbf{CST}}} f_w(w_i) f_x(x_i),$$

$$C_{\mathbf{RST}i} = \sum_{i=N_{\mathbf{CST}}+1}^{N_{\mathbf{CST}}+N_{\mathbf{RST}}} f_w(w_i) f_x(x_i),$$

where $N_{\mathbf{CST}}$ and $N_{\mathbf{RST}}$ denote the numbers of cells connected to the CST and RST, respectively.

Tract model simulation

Relying on the observation that reticulospinal inputs show an amplitude of 20% as great as the corticospinal inputs (Baker, 2011; Riddle et al., 2009), we set the ratio of the numbers of cells connected to the CST and RST before stroke as 5:1 for our model, with an assumption that each cell has the same capability. Five-sixth of the total cells, N, are allocated to the cortex area from which the CST originates (i.e. primary cortex), while one-sixth are allocated to the cortex area from which the RST originates (i.e. premotor cortex,

supplementary motor area) (Baker, 2011). We simulate 120 cells in total (100 CST cells, 20 RST cells). In this simulation, three cases are considered according to the number of dead cells or dead connections (i.e. zero weight). The first case is that less than 20% of the cells connected to the CST are dead, which is hypothesized to simulate populations with strong CST connectivity in the acute phase. Another case is that all cells connected to the CST are dead, which is hypothesized to simulate populations who exhibit strong RST functional capability. The last case is that 20~100% of the cells are dead. From the last case, we could gain insight into the mechanism that FA values in the acute phase determine the potential possible recovery (Byblow et al., 2015; Stinear et al., 2017b). The number of the CST cells with zero weights is determined as a random number chosen from a uniform distribution. The initial values of w and x of the CST for each case are also determined uniformly randomly, within the range of $[\sqrt{\#\ of\ alive\ CST\ cells}/10 - 0.1, \sqrt{\#\ of\ alive\ CST\ cells}/10 + 0.1]$ for both w and x. There is imaging evidence that the contralesional RST is physically damaged in response to stroke (Owen, 2017). We assume that the initial values of the weights for the RST are in a range between 0.5 and 0.7 for the first case and between 0.0 and 0.7 for the second and third cases. The fact that those values are not set as 1 reflects diaschisis which describes remote effects on structurally-functionally connected brain regions due to stroke (Carrera & Tononi, 2014). The values of firing rates are set to a low value (~0.001) for all cases (weak accessibility to the RST network). However, those parameter value selections are not sensitive to the replication of results. The values of the learning gains for w and x are set as 2.0×10^{-4} for the first case, while those for the second and third cases are set randomly between 1.0×10^{-5} and 1.0×10^{-4}. This difference in those values may reflect the differences resulting from the amount of upper-extremity activity according to the severity of impairment (Lang et al., 2007; Noorkõiv et al., 2014), as well as, the degree of CST injury (white matter integrity), FA asymmetry, necrotic tissue, edema, and inflammation, which are known to affect recovery (Furlan et al., 1996; Stinear & Byblow, 2014). C_n in the stochastic gradient descent law is set as 100, with an assumption that the neural system aims to return to the original state where the full capability of the CST is used. The response function f is set as a saturation function that situates values at ±1.

Tract simulation results

A, Case 1 (less than 20% of the cells connected to the CST are dead):

The case may correspond to “fitters” in the proportional recovery rule.

1. The CST generally recovers to 80% of its potential capacity to be recovered.

: Through simulation (see Fig. 1), we observe that the CST recovers to 80% of its potential capacity to be recovered, which agrees with the empirical observation in (Hammerbeck et al., 2021), if the percentage of death cells or entirely disconnected connections is less than 20% of its original cells. The finding presented in (Hammerbeck et al., 2021) may be from populations with strong initial CST connectivity, who can retrieve hand/arm dexterity.

2. The anatomical capabilities of the CST and RST are in a reverse relationship.

: Studies evidenced that the anatomical capabilities of the CST and RST are in a reverse relationship (Hadjiosif et al., 2022; H. Kim et al., 2018). Given that functional capability is nearly proportional to anatomical capability, Fig. 1 implies that the anatomical capabilities of the CST and RST are in a reverse relationship or “competitive” relationship. We observe time evolutions of the CST and RST of 6 subjects (color relevant), suggesting that a greater CST capability leads to a lower RST capability across trials.

3. Recovery of a tract is along with that of another tract.

: Fig. 1 suggests that the capability of the CST increases along with that of the RST as trials advance. This is in agreement with the findings in (Jang & Lee, 2019).

4. The model tends to optimize the activity of more strongly connected cells first.

: The neural system tends to keep using what they have used to use with priority (Reinkensmeyer et al., 2012a). Fig. 2 shows that populations with strong CST connectivity in the acute phase activate CST cells to their maximum first and activate RST cells next to compensate for the dead CST cells.

5. CST connectivity, not motor impairment severity, in the acute phase, is a critical factor for recovery.

: Regardless of the severity of the initial motor impairment, CST connectivity in the acute phase, measured by TMS, predominantly determines the potential spontaneous recovery (Byblow et al., 2015; Schambra et al., 2019). Our results imply that substantial recovery of the CST could be achieved if more than 80% of cells or connections for corticospinal inputs are still alive following a stroke.

B. Case 2 (all cells connected to the CST are dead):

The case that more than 20% of the cells connected to the CST are dead might correspond to "nonfitters" in the proportional recovery rule. Fig. 3 shows the case that cells connected to the CST are all dead. Since it is entirely anatomically damaged, the CST is not usable for motor execution. Use of the RST continues and use-dependent features increase gradually as seen in Fig. 3.

C. Case 3 (20~100% of the cells):

This case is accompanied by the assumption that CST cells or connections are damaged as much as the case that 20% of the original CST cells are dead. This assumption is to check which tract is optimized first. The volition system tends to recruit as many as available motoneurons to achieve motor tasks. Since the corticospinal networks become sparse after stroke, the volition system is assumed to first optimize RST cells which are relatively more strongly connected, and then try to recruit CST cells to achieve the capability to conduct motor tasks. Fig. 4 explains this recruitment mechanism in that RST cells are optimized first, and CST cells are optimized next.

While Case 3 might correspond to "nonfitters" in the proportional recovery rule, it shows the possibility that hand/arm dexterity can be retrieved if the anatomical capability of the CST (i.e. cell death) in the acute phase is above a certain level. This corresponds to the fact that the FA value in the acute phase is a critical factor in predicting the potential recovery (Byblow et al., 2015; Stinear & Byblow, 2014).

Empirical observations

We re-analyzed FMA scores collected in a longitudinal study [20]. A total of 67 participants with unilateral upper-extremity motor deficits following first-ever stroke were assessed at 2, 4, 6, 8, 12, 16, 20, and 24 weeks after stroke. Motor function undergoes phases of recovery that are not notably affected by types of therapeutic intervention over the first 24 weeks (6 months) after stroke [21]. Those data were collected within ±3 days for the assessments at weeks 2–8 and ±1 week for those at weeks 12–24. The percentages of the 67 participants providing data at each time point were as follows: 100% at 2 weeks, 88% at 4 weeks, 82% at 6 weeks, 79% at 8 weeks, 73% at 12 weeks, 67% at 16 weeks, 57% at 20 weeks, and 61% at 24 weeks.

We included participants who completed the last assessment (at 24 weeks) and at least 4 assessments in total in our analysis to trace back their motor recovery trends depending on the severity of impairment assessed in the chronic phase. We grouped participants into two groups based on the total score of the FMA assessed at 24 weeks: CST group (FM≥43) is assumed to preferentially use the CST, and the RST

group (40≥FM) is assumed to preferentially use the RST. It is widely accepted that individuals with mild impairment since stroke exhibit significant recovery within the first 1-2 months, while individuals with moderate or severe impairment throughout the subacute phase (< 6 months) and even the first year [2]. Features of motor functions in those two groups are largely differentiable based on UEFM around 180 days since stroke [6]. It is hypothesized that the CST group preferentially uses the CST while the RST group preferentially uses alternative tracts (i.e. RST), exhibiting apparent abnormal synergies [4,22]. The total score of the FMA differentiates the two groups based on previous studies [23].

Reproduction of Fugl-Meyer subscores

We believe that movements of each type (in-synergy or out-of-synergy) of movements for FM subtests can be conducted if the functional capability of an appropriate tract reaches a certain level. While the type of in-synergy movements is mediated by either the CST or RST, the type of out-of-synergy movements is mediated by only the CST. In this situation, we assume that in individuals with strong initial CST connectivity, the CST is preferentially used to conduct both types of in-synergy and out-of-synergy movements (CST group). In contrast, in individuals with weak initial CST connectivity, the RST is preferentially used to conduct the type of in-synergy movements, and the CST is preferentially used to conduct the type of out-of-synergy movements (RST group).

A total of 100 subjects in each group are simulated to reproduce the time evolutions of the 27 items of the FMA that evaluate motor function. The 27 items include in-synergy items (6 flexor synergy, 3 extensor synergy) and out-of-synergy items (3 mixing synergy, 3 little synergy, 5 wrist, 7 hand items) [24]. Subject allocation does not notably affect the results. The initial functional capability (%Capabilities) of the CST in each subject is determined by the number of dead cells which is chosen which is chosen in a uniformly random way, ranging [1 20] for the CST group and [21 80] for the RST group, respectively.

As for the CST group, Case 1 is applied. We found that the difficulty levels of the 9 in-synergy items are not discriminable, based on empirical data (Fig. 7), and set their thresholds for Score “2” as [0.80 0.81 0.82 0.83 0.84 0.85 0.86 0.87 0.88]. The 9 thresholds are randomly re-ordered and applied to each individual. Referring to the empirical data in Fig. 7, we divide the 18 out-of-synergy items into difficult, medium and easy items, and set their thresholds for Score “2” as [0.75 0.76 (easy); 0.77 0.78 0.79 (medium); 0.80 0.81 0.82 0.83 0.84 0.85 0.86 0.87 0.88 0.89 0.90 0.91 0.92 (difficult)]. The thresholds of each difficulty level are randomly re-ordered and applied to each individual. While the thresholds of out-of-synergy items for Score “1” are set by multiplying the threshold of each item for Score “2” with a uniformly random number [0.5 0.8], the thresholds of in-synergy items for Score “1” are set by multiplying each threshold for Score “2” with a uniformly random number [0.5 0.8].

As for the RST group, we take a similar way, applying Case 3. The thresholds of the in-synergy items for Score “2” are set as [0.10 0.12 0.14 0.16 0.18 0.20 0.22 0.24 0.26]. Note that those thresholds are applied to the RST and its corresponding cortices. The thresholds of in-synergy items for Score “1” are set by multiplying each threshold for Score “2” with a uniformly random number [0.20 0.22]. The thresholds of the out-of-synergy items for Score “2” are the same as those for Score “2” for the CST group. The thresholds of out-of-synergy items for Score “1” are set by multiplying the threshold of each item for Score “2” with a uniformly random number [0.5 0.8].

RESULTS

Tract simulation results

A, Case 1 (less than 20% of the cells connected to the CST are dead):

The case may correspond to “fitters” in the proportional recovery rule.

1. The CST generally recovers to 80% of its potential capacity to be recovered.

: Through simulation (see Fig. 1), we observe that the CST recovers to 80% of its potential capacity to be recovered, which agrees with the empirical observation in a study [25], if the percentage of death cells or entirely disconnected connections is less than 20% of its original cells. The finding presented in a study [25] may be from populations with strong initial CST connectivity, who can retrieve hand/arm dexterity.

2. The anatomical capabilities of the CST and RST are in a reverse relationship.

: Studies evidenced that the anatomical capabilities of the CST and RST are in a reverse relationship [9,10]. Given that functional capability is nearly proportional to anatomical capability, Fig. 1 implies that the anatomical capabilities of the CST and RST are in a reverse relationship or “competitive” relationship. We observe time evolutions of the CST and RST of 6 subjects (color relevant), suggesting that a greater CST capability leads to a lower RST capability across trials.

3. Recovery of a tract is along with that of another tract.

: Fig. 1 suggests that the capability of the CST increases along with that of the RST as trials advance. This is in agreement with the findings in [8].

4. The model tends to optimize the activity of more strongly connected cells first.

: The neural system tends to keep using what they have used to use with priority [12]. Fig. 2 shows that populations with strong CST connectivity in the acute phase activate CST cells to their maximum first and activate RST cells next to compensate for the dead CST cells.

5. CST connectivity, not motor impairment severity, in the acute phase, is a critical factor for recovery.

: Regardless of the severity of the initial motor impairment, CST connectivity in the acute phase, measured by TMS, predominantly determines the potential spontaneous recovery [6,7]. Our results imply that substantial recovery of the CST could be achieved if more than 80% of cells or connections for corticospinal inputs are still alive following a stroke.

B. Case 2 (all cells connected to the CST are dead):

The case that more than 20% of the cells connected to the CST are dead might correspond to “nonfitters” in the proportional recovery rule. Fig. 3 shows the case that cells connected to the CST are all dead. Since it is entirely anatomically damaged, the CST is not usable for motor execution. Use of the RST continues and use-dependent features increase gradually as seen in Fig. 3.

C. Case 3 (20~100% of the cells):

This case is accompanied by the assumption that CST cells or connections are damaged as much as the case that 20% of the original CST cells are dead. This assumption is to check which tract is optimized first. The volition system tends to recruit as many as available motoneurons to achieve motor tasks. Since the corticospinal networks become sparse after stroke, the volition system is assumed to first optimize RST cells which are relatively more strongly connected, and then try to recruit CST cells to achieve the capability to conduct motor tasks. Fig. 4 explains this recruitment mechanism in that RST cells are optimized first, and CST cells are optimized next.

While Case 3 might correspond to "nonfitters" in the proportional recovery rule, it shows the possibility that hand/arm dexterity can be retrieved if the anatomical capability of the CST (i.e. cell death) in the acute phase is above a certain level. This corresponds to the fact that the FA value in the acute phase is a critical factor in predicting the potential recovery [6,19].

Empirical observations

Figs. 5 and 6 show the time evolutions of the total scores of (in-synergy and out-of-synergy), (out-of-synergy), and (in-synergy) test items after stroke. We used linear interpolation about missing assessments by replacing each missing value with the mean of 2 adjacent values. The trends seen in the CST group (n=30) correspond to Case 1 in our model. Regardless of the severity of the initial impairment, substantial recovery is achieved within the first two months. We note that the recovery rates of the types of in-synergy and out-of-synergy movements are not differentiable, suggesting that both types are mediated by the CST.

The RST group (n=8) was further divided into two subgroups. One subgroup (n=3, 16≥FM) was not able to conduct any out-of-synergy movements, corresponding to Case 2. The other subgroup (n=5, 16<FM) may correspond to Case 3. The recovery rates of the types of in-synergy and out-of-synergy movements are differentiable, suggesting that both types are mediated by different neural substrates.

Results of subscores reproduction

Fig. 8 presents the results reproduced by the proposed model.

1. The severity of initial impairment is not relevant to the potential degree of recovery in the CST group [4,6].
2. The CST group reaches the plateau of motor recovery within a shorter period in comparison to the RST group [2].
3. The RST group recovers at a slower rate [1].
4. Improvement in the ability to conduct the type of out-of-synergy movements follows that of in-synergy movements. This is in agreement with the Brunnstrom approach that addresses six recovery stages based on the concept that people with stroke develop the ability to move out of abnormal synergies [26].

DISCUSSION

Replication of biological mechanisms

This modeling study was initiated based on primary observations from the PR rule (Byblow et al., 2015) and the Predicting potential for upper limb recovery 1, 2 (PREP 1, 2) algorithms (Stinear et al., 2012, 2017a), and also by a study (Schambra et al., 2019). The functional recovery post-stroke can be differentiated in a dichotomous manner depending on the connectivity of the ipsilesional corticospinal tract assessed within two weeks after a stroke. The reliance on alternative tracts increases if neural networks along the CST become too sparse or disconnected to convey motor commands to appropriate motoneuron pools. We strived to describe the selective and competitive relationship between two hypothetically primary descending pathways after stroke, employing Hebb's model that is typically used to model use-dependent neural plasticity (Whitlock et al., 2006).

Our model successfully describes a battery of phenomena we commonly observe in individuals affected by stroke. Above all, the model replicates that the degree of the initial anatomical damage to the CST substantially determines the direction of neural recovery (behavioral restitution or compensation). In our model, some cells (i.e. ipsilesional M1 cells) connected to the CST are destructed and even disabled by stroke (their firing rates are 0), as it emulates the real system (Dobkin & Carmichael, 2016; Sekerdag et al., 2018). If those cells cannot function anymore and the amount of such cells is above a certain level, the neural system begins to use relatively more optimized (less damaged) neural pathways. The model assumes that the corticospinal pathways connected to those cells are accordingly disabled by stroke. This is in agreement with the PR rule and PREP algorithms which suggest that the initial structural capacity of the CST, which is measured with DTI, determines the degree of potential recovery categorized into "fitters" versus "non-fitter" (PR rule), or "completed, notable" versus "limited, none" (PREP algorithm). If the cells affected by stroke still rudimentarily function (their firing rates are not 0), that is, they are not entirely dead, the neural system continues to regrowth and enhance them for motor execution (Murphy & Corbett, 2009), and those cells and their corresponding circuits become re-optimized. This can be described as Hebbian-type refinement of neural circuits (Miller et al., 2000). This cascade is analogous to the typical occurrences post-stroke. Indeed, stroke deprives some neurons of their normal metabolic substrates, and eventually their functions in seconds (Murphy et al., 2008). Those neurons are unable to maintain their normal transmembrane ionic gradients, eventually leading to apoptotic and necrotic cell deaths (Hossmann, 2006; Murphy & Corbett, 2009). Surviving neurons in the peri-infarct cortical areas with sufficient blood perfusion undergo active structural and functional remodeling (Miller et al., 2000). Dendritic growth and axonal sprouting occur to rewire damaged connections or form new connections (Murphy & Corbett, 2009). Accordingly, motor function recovers and improves; behavioral restitution can be achieved. Also, our model demonstrates that the initial motor impairment is not correlated with the potential recovery post-stroke (Byblow et al., 2015; Grefkes & Fink, 2014; van der Vliet et al., 2020). This supports that the spontaneous recovery mechanism and use-dependent neural plasticity revive ipsilesional cells or pathways if they are still surviving (Murphy & Corbett, 2009).

Studies reported that persons with more mild impairment show quicker recovery than those with more severe motor impairment (Cramer, 2008). Meanwhile, motor improvement in persons who are assumed to increase their reliance on alternative tracts continues over the first year of stroke. This suggests that it takes more time for more impaired persons to adapt to use of compensatory mechanisms for the damaged CST and achieve functional fractionation of the alternative neural pathways, in comparison to use of the recovered CST and ipsilesional cortex for persons with mild impairment. In the case that CST connectivity is deficient, compensatory strategies occur, including a shift in inter-hemispheric lateralization towards the contralesional hemisphere and a shift in representational maps around the infarcted zone (Murphy & Corbett, 2009). Though the neural circuit used as a substitute is relatively intact or less damaged, time for adaptation is required for activity- or use-dependent plasticity. The amount of fractionation correlates with the time since stroke onset (Casadio et al., 2013). In the model simulation, we described this phenomenon

by assuming that the initial RST accessibility is very low (the firing rates of the RST cells were set near 0). The functional capability of the RST starts from around 0 regardless of the degree of damage by stroke to the CST (refer to Figs. 1-4), so it takes more time for the RST to reach its maximum functional capacity and the motor improvement in individuals who rely on the RST predominantly (i.e. the RST group) tends to be delayed in comparison to those who rely on the CST predominantly (i.e. the CST group).

We decreased and randomly selected values of the learning gains in the model for the RST group to replicate the various recovery rates of individuals in the RST group. The majority of individuals with strong initial CST connectivity generally recover on average 70% to 80% within 1 or 2 months since stroke, regardless of sex, age, race, and the amount of behavioral efforts (Marshall et al., 2009; Winters et al., 2015; Zarahn et al., 2011). However, individuals with weak or no initial CST connectivity relatively show large variability in the recovery rate (Kwakkel et al., 2023; van der Vliet et al., 2020). This large variability possibly originates from factors that influence the rate of neural plasticity, including sex, age, lesion size, degree of CST injury (white matter integrity), FA asymmetry, necrotic tissue, edema, and inflammation, which are known to affect recovery (Furlan et al., 1996; Stinear & Byblow, 2014). The learning gains in the model reflect the difference in individuals' capability for neural recovery and plasticity.

The time evolutions of FMA scores suggest that the ability to conduct the type of out of synergy movements slowly increases in stroke survivors with severe impairment throughout the subacute phase beyond the chronic phase (refer to Figs. 5 and 6). This implies that the functional capabilities of the CST and RST increase in a harmonic way post-stroke. This observation agrees with imaging studies showing that all tracts tend to recover simultaneously after damage (Jang & Lee, 2019). This evidence alludes to the possibility that more impaired individuals can restore hand/arm dexterity, even in the presence of RST functional upregulation which appears around the beginning of the chronic phase (Dewald et al., 1995; Ellis et al., 2009; Hammerbeck et al., 2021). Branches of the CST to even motoneurons for the fingers still function in individuals with severe impairment; those individuals merely show a degraded ability to extend the fingers because of weak CST connectivity or overwhelming abnormal synergies mediated by the RST (Baghi et al., 2023; D. Kim et al., 2023). However, at the same time, there is a priority of optimization between the tracts. The relatively less damaged RST network is optimized to its maximum functional capacity first, and the CST continues to recover in compensation for the residual functional capability, which the RST cannot fulfill solely. This sequence largely agrees with at least up to Stage 4 of the Brunnstrom approach, which addresses six recovery stages based on the concept that stroke survivors (with moderate-to-severe impairment) develop the ability to move out of abnormal synergies (Brunnstrom, 1966; Li, 2017). People with stroke primarily do basic synergistic movements in the first three stages. At Stage 4, patients can do movements that deviate from synergistic movements; at Stage 6, patients can perform a variety of movements without the influence of stroke-caused synergies. It could be interpreted that the Brunnstrom approach encapsulates the general sequence of motor symptoms following stroke, and our model explains the underlying neural principle of the sequence.

Suggestions for therapy design

The constraint-induced movement therapy (CIMT) is known as a promising rehabilitation approach, which aims to promote the recovery of the ipsilesional hemisphere while suppressing the inhibition of the contralesional hemisphere on the activity of the ipsilesional one (Kwakkel et al., 2015). This therapy effectively reduces the possibility that neural reorganization (maladaptation) interferes with regaining the motor function of the affected limb through cortical motor expansion by reducing the reliance on the less affected limb (Sawaki et al., 2008). However, the CIMT could also cause maladaptation, which is made through compensation. Behavioral restitution, a return toward standard motor patterns with the affected limb (Kwakkel et al., 2023), requires the recovery of the ipsilesional hemisphere and CST. However, training certain types of movement, even with the affected limb, can selectively enhance the structural and

functional capabilities of the RST. A study with intact primitives showed that strength training with pulling movement enhances the RST, not the CST (Glover & Baker, 2020). In human subjects, an alternative neural pathway (i.e. the RST) is predominantly used to excite the biceps on the paretic side following stroke (Schambra et al., 2019). Also strength training in grasping promotes the RST (Maitland & Baker, 2021). Our model did not differentiate the types of movements that cause neural refinement or optimization of a particular tract. We assumed that activity- or use-dependent neural plasticity in our model is achieved with repetitive movements with muscles that can be excited via either the CST or RST. Those include shoulder abductor/flexor (Fujiwara et al., 2001; Hammerbeck et al., 2019), elbow flexor (Schambra et al., 2019) and finger flexor (Baker, 2011). Interestingly, a study reported increased contralesional connectivity to the triceps on the paretic side (Hammerbeck et al., 2019). Either the corticospinal network or the reticulospinal network is optimized with priority through use-dependent processes by repeating movements with those muscles, depending on the initial CST connectivity. If the reticulospinal network is optimized with priority, it ultimately facilitates RST upregulation and abnormal synergies.

Abnormal co-activation across muscles may originate from the physical feature of the RST that branches multiple motoneuron pools across the upper extremity and activates them together when a central command descends (Burge et al., 2007; Davidson & Buford, 2006; Davidson & Bufore, 2004; Hirschauer & Buford, 2015; Soteropoulos et al., 2012). Selective muscle activation even in individuals who preferentially use the RST may need to employ the CST to convey motor command, instead of the RST. Naturally, its repetition could promote the structural and functional capabilities of the CST and lead to the preferential use of it. Upper-limb movement away from stereotypical abnormal synergies may be a promising way to achieve behavioral restitution. Through a comparison of the effect of the elbow extension task with shoulder abduction loading with that done without loading, studies revealed that the exercise of elbow extension with shoulder abduction loading significantly increases reaching range of motion (Ellis et al., 2009, 2018). Also, training stroke survivors to simultaneously coordinate and synchronize multiple fingers, alleviating the flexion synergy, is effective in retrieving finger individuation and hand dexterity (Mawase et al., 2020). Note that it leads to a significant improvement in the FMA score, suggesting that the impairment of the upper extremity becomes alleviated.

In our model, the functional capability of the CST is limited by the number of the cells on the ipsilesional hemisphere that survive after stroke. However, we believe that cortical representations can be reconstituted in the peri-infarct tissue through repetitions of out-of-synergy movement, like in the CIMT (Sawaki et al., 2008). It would be worth investigating the effect of inducing the corticospinal network to be optimized first in individuals with weak or no initial CST connectivity after stroke through conducting out-of-synergy movements and blocking activities that enhance the reticulospinal network.

Limitations

Reproduction of the time evolutions of FMA scores using the model involves the following assumptions:

Assumption 1--- The out-of-synergy movements instructed in the FMA are mediated predominantly via the CST.

Assumption 2--- The in-synergy movements instructed in the FM assessment are predominantly mediated via the CST in individuals with strong initial CST connectivity while being predominantly mediated via the RST in individuals with weak or no initial CST connectivity throughout all phases of stroke.

Assumption 3--- The amounts of behavioral efforts are the same across subjects and phases of stroke.

Assumption 4--- Accessibility to the RST is low, while accessibility to the CST is high in the acute phase, regardless of the degree of impairment.

All these assumptions are difficult to verify with the model, and FMA scores themselves. For the first assumption, it would be possible that the type of out-of-synergy movements is mediated even via the RST.

We cannot rule out the possibility of functional fragmentation (remodeling) of the alternative neural substrates (contralesional cortices and RST). Several studies demonstrated that structural reorganization of the contralesional cortices undergoes following stroke and contributes to motor improvement, possibly promoting joint individuation (Buetefisch, 2015; Cai et al., 2016; Reitmeir et al., 2011). Reversely, no studies have clarified that individuals who achieve substantial recovery in the subacute phase with strong initial CST connectivity still exhibit abnormal synergy expressions to conduct the in-synergy movements instructed in the FMA. It is required to investigate whether the in-synergy movements instructed in the FMA are mediated via the CST, RST or both across individuals with different degrees of impairment to increase the rigor of our model. This will justify the second assumption.

For the third assumption, the central nervous system tends to keep using the original tract that had been used for motor execution before stroke and searches for an alternative tract if the original tract fails to descend motor command to execute the target movement (Murphy & Corbett, 2009). Tract accessibility may be evaluated by investigating cortical activation where motor command is generated. This assumption could be justified by confirming that cortical activation is apparent in the ipsilesional hemisphere, not in the contralesional hemisphere in the acute phase, regardless of the degree of damage to the CST.

For the last assumption, the model does not reflect variability in the extent of daily-life activities of the individuals with stroke which substantially affects neural plasticity, and eventually motor function recovery. Several studies reported that the amounts of upper-extremity activity in daily life vary depending on subjects (Grefkes et al., 2020; Lang et al., 2021; Lum et al., 2020; Shim et al., 2014). Tract connectivity and accessibility both rely largely on activity- or use-dependent plasticity (Chakrabarty et al., 2009; Martin et al., 2007; Murphy & Corbett, 2009; Reinkensmeyer et al., 2012a). The effect of behavioral efforts was reflected in our model by updating the weight of a connection and cell firing rate. However, in this study, we assumed that the amounts of behavioral efforts are the same across all phases of stroke as well as the subjects to focus on characterizing competition between the tracts as neural reorganization advances. Indeed studies show that motor function undergoes phases of recovery over the first 6 months after stroke regardless of types of therapeutic intervention (Kwakkel et al., 2004, 2023).

Data availability

Data will be available on reasonable request.

Competing interests

The authors declare no competing financial and/or non-financial interests in relation to the work described. Kim declares the ownership of EpicWide, LLC.

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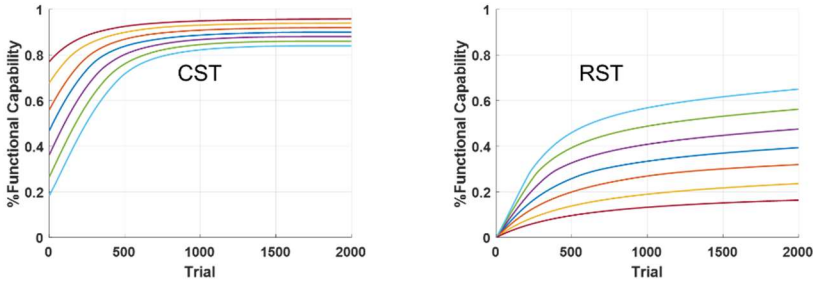


Fig. 1*: Functional capabilities of the CST (left) and RST (right) of 7 subjects (color corresponding) across trials.*

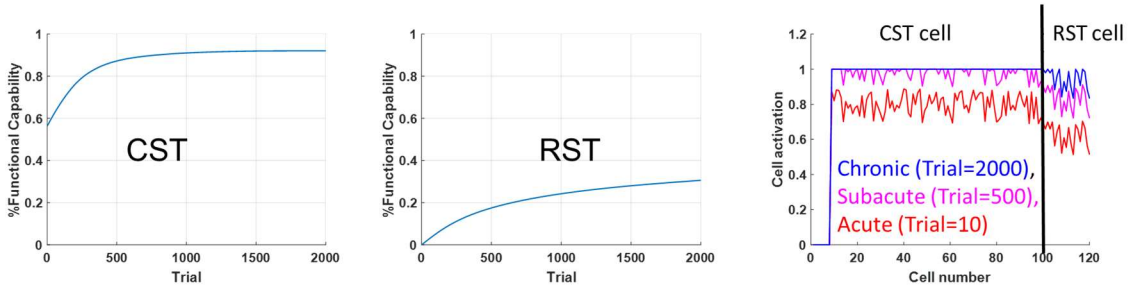


Fig. 2*: Functional capabilities of the CST and RST and cell activations of an individual with strong initial CST connectivity across trials.*

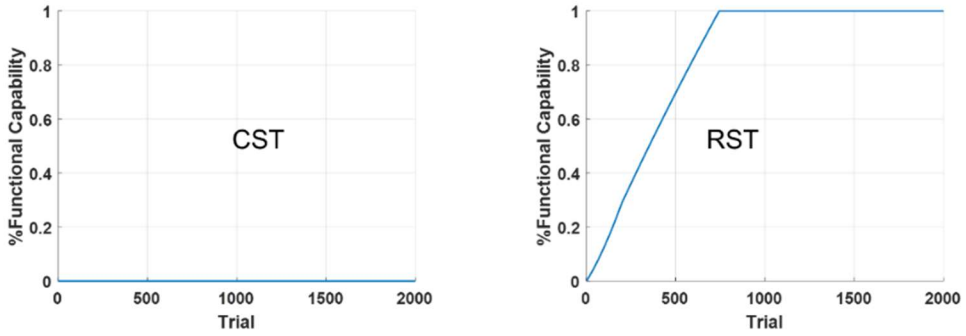


Fig. 3: Functional capabilities of the CST and RST and cell activations of an individual with no initial CST connectivity across trials.

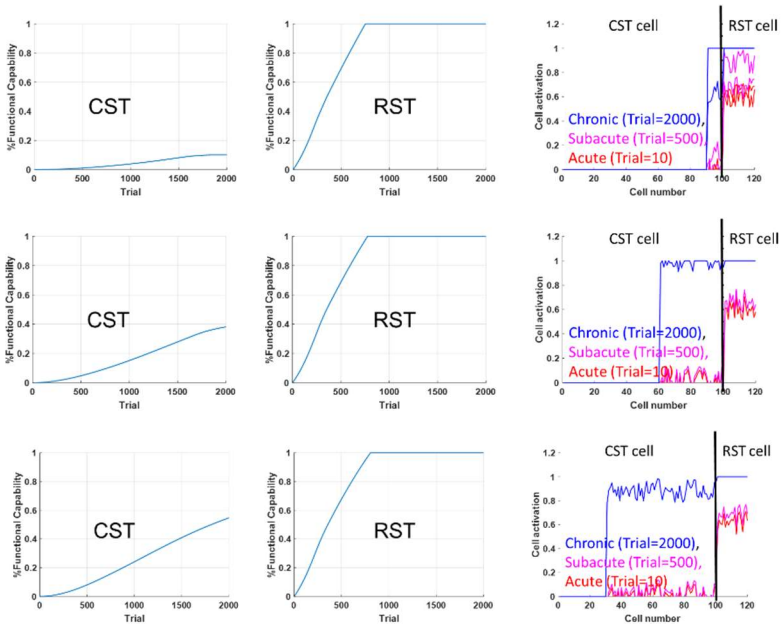


Fig. 4: Functional capabilities of the CST and RST and cell activations of an individual with different numbers of dead CST cells or connections across trials.

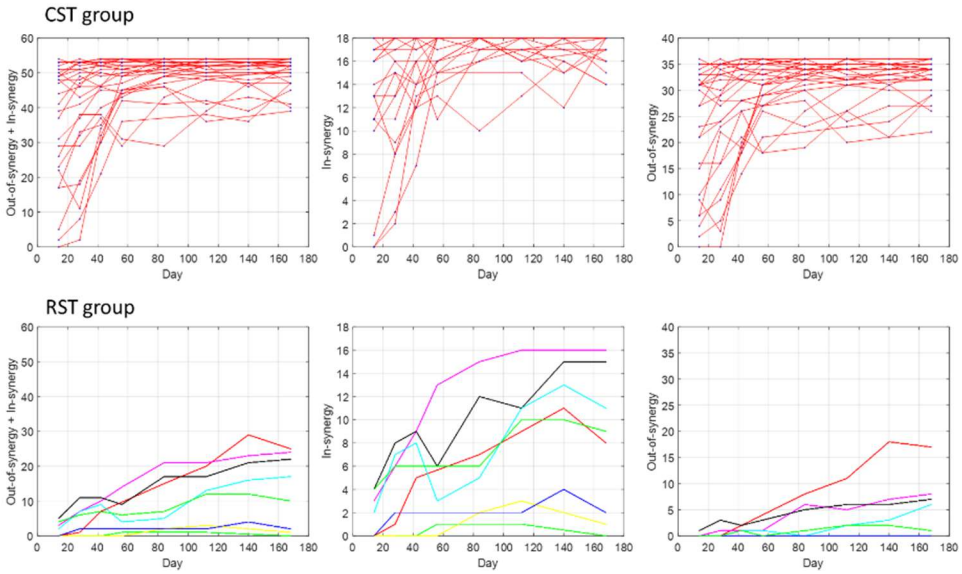


Fig. 5. Time evolutions of the total scores of (in-synergy and out-of-synergy), (out-of-synergy), and (in-synergy) test items after stroke. The same colors correspond to the same subjects for the RST group).

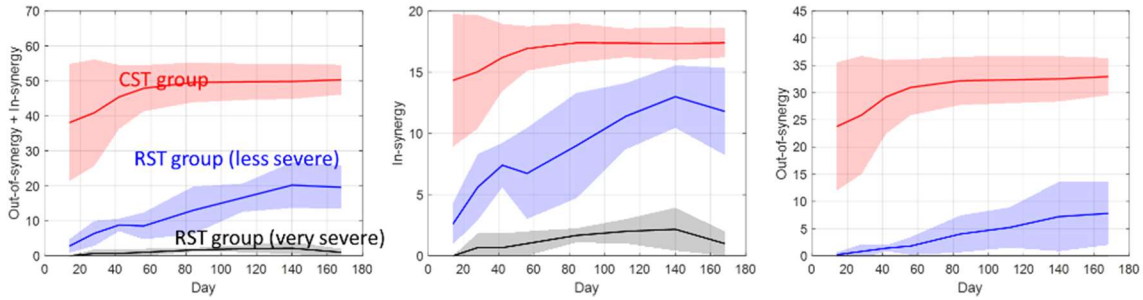


Fig. 6. Time evolutions of the total scores of (in-synergy and out-of-synergy), (out-of-synergy), and (in-synergy) test items averaged across participants in each group. The RST group is further divided into two subgroups about FM=16. Cloud: 1SD.

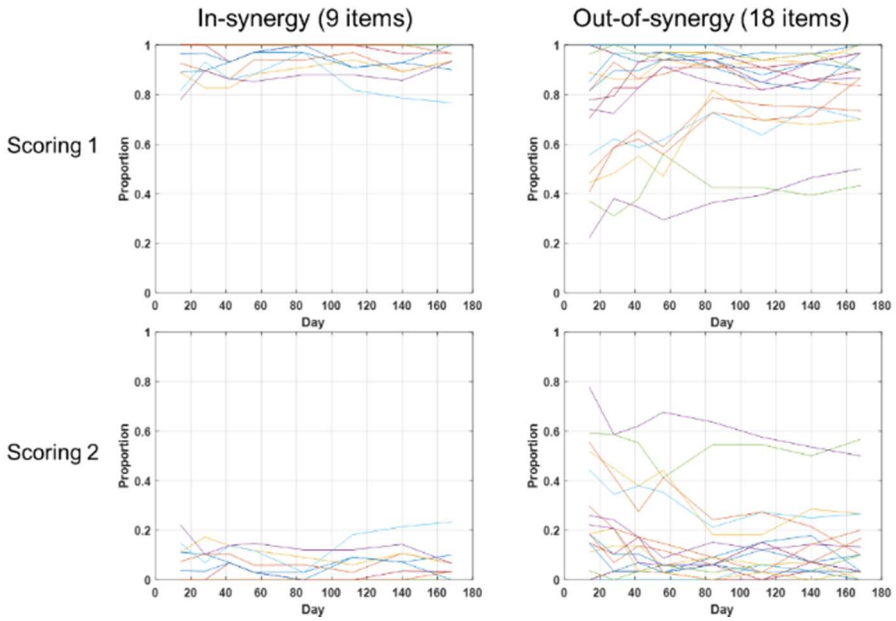
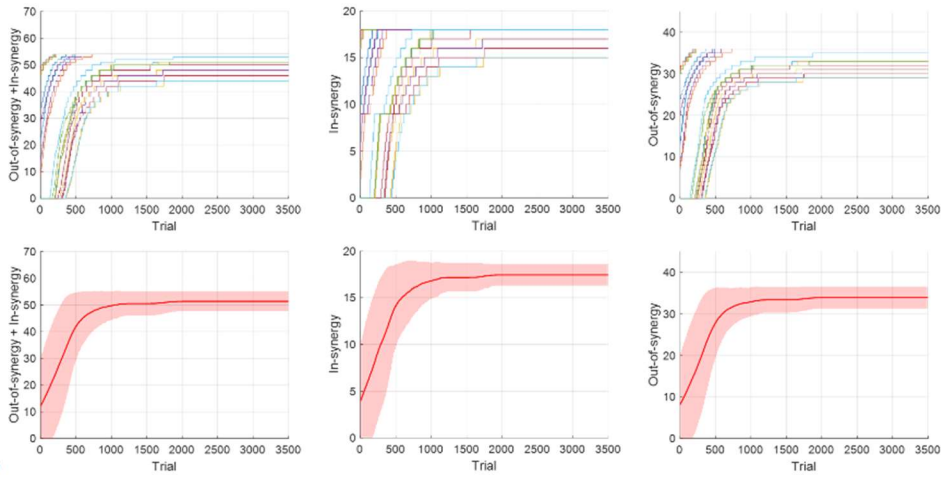
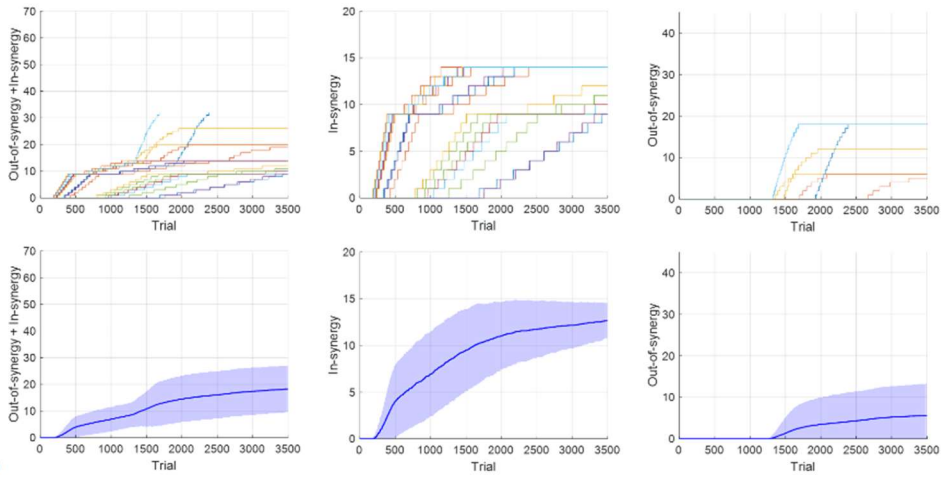


Fig. 7. Time evolutions of the proportions of the participants in the CST group who score 1 or score 2 in each test item.



(a)



(b)

Fig. 8. Time evolutions of the total scores of (in-synergy and out-of-synergy), (out-of-synergy) and (in-synergy) test items since the stroke, in simulated individuals (n=20 randomly selected) with (a) strong CST connectivity (Case 1) and (b) weak CST connectivity (Case 3). The same colors correspond to the same subjects for each group). The bottom plots show total scores averaged across individuals (n=100). Cloud: 1SD.