研究成果の刊行に関する一覧表

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
住谷昌彦, 宮内哲, 山田芳嗣	神経リハビリテーションとニューロモデュレーション治療の併用	ペインクリニック別冊「ニューロモデュレーション技術の進展と疼痛治療への応用」	33 別冊春号	S209-19	2012
Ogawa T, Kawashima N, Ogata T, Nakazawa K.	Limited Transfer of Newly Acquired Movement Patterns across Walking and Running in Humans	PLoS One	7(9)	e46349	2012
Yamauchi J, Miyamoto Y, Torii T, Takashima S, Kondo K, Kawahara K, Nemoto N, Jonah R. Chan, Tsujimoto G, Tanoue A.	Phosphorylation of cytohesin-1 by Fyn is required for initiation of myelination and the extent of myelination during development	ScienceSignaling	5	ra69	2012
Nakazawa K, Obata H, Sasagawa S.	Neural control of human gait and posture	Japanese Journal of Physical Fitness Sports Medicine	1(2)	p. 263-269	2012
Chikuda H, Yasunaga H, Takeshita K, Horiguchi H, Kawaguchi H, Ohe K, Fushimi K, Tanaka S.	Mortality and morbidity after high-dose methylprednisolone treatment in patients with acute cervical spinal cord injury: a propensity-matched analysis using a nationwide administrative database	Emergency Medicine Journal	Epub ahead of print		2013

研究成果の刊行物

Ⅲ．必要な検査と併用療法

4．神経リハビリテーションとニューロモデュレーション治療の併用

住谷昌彦[1]

宮内　哲[2]　山田芳嗣[1]

[1]東京大学医学部附属病院麻酔科・痛みセンター
[2]情報通信研究機構未来 ICT 研究センター神戸研究所

要　旨
　神経障害性疼痛の発症機序については，末梢神経系と脊髄での神経可塑性に関する分子生物学的な基礎研究が進む一方，ヒト神経障害性疼痛患者を対象とした脳機能画像研究からは大脳を中心とした中枢神経系の機能異常が明らかになっている．特に大脳メカニズムとして一次体性感覚野や運動野における体部位再現地図の機能再構築が疼痛発症と密接に関連している．本稿では，体部位再現地図の機能再構築に対する神経リハビリテーションと脊髄刺激療法を代表とするニューロモデュレーション治療の相乗的な効果について概説する．

(ペインクリニック 33：S209-S219. 2012)
　キーワード：神経障害性疼痛，神経リハビリテーション，脊髄刺激療法

はじめに

　神経障害性疼痛の発症機序としては，末梢神経の損傷によってできた神経腫由来の異常インパルスや脊髄レベルでの神経細胞の易興奮性とグリアとの相互作用，脊髄上位中枢レベルでの易興奮性が様々な要因によって誘発されることが動物実験から示されていたが，ヒト神経障害性疼痛患者を対象とした脳機能画像研究からは，主に大脳を中心とする脊髄上位中枢神経系レベルでの機能再構築（reorganization）が神経障害性疼痛の発症基盤として中心的な役割をしていると考えられている．具体的には，一次

体性感覚野（S1）には身体部位に応じた脳領域が存在することが知られ，これらを体部位再現地図（somatotopy）と呼ぶ（図1上右）が，上肢神経傷害後患者では患側上肢に相当する脳領域が縮小し，上肢の隣に位置する口/顔面の領域が拡大してくる機能再構築がS1で起こっている（図1上左）[1]．このような神経傷害後に現れるS1の機能再構築は，傷害神経の支配領域の触覚弁別を訓練することによって上肢の領域が拡大（口/顔面の領域が縮小）する機能再構築が再び起こり，それと同時に神経障害性疼痛が軽減することが報告されている[1]．さらに，一次運動野（M1）にも体部位再現地図があり，上肢末梢神経傷害後の神経障害性疼痛患
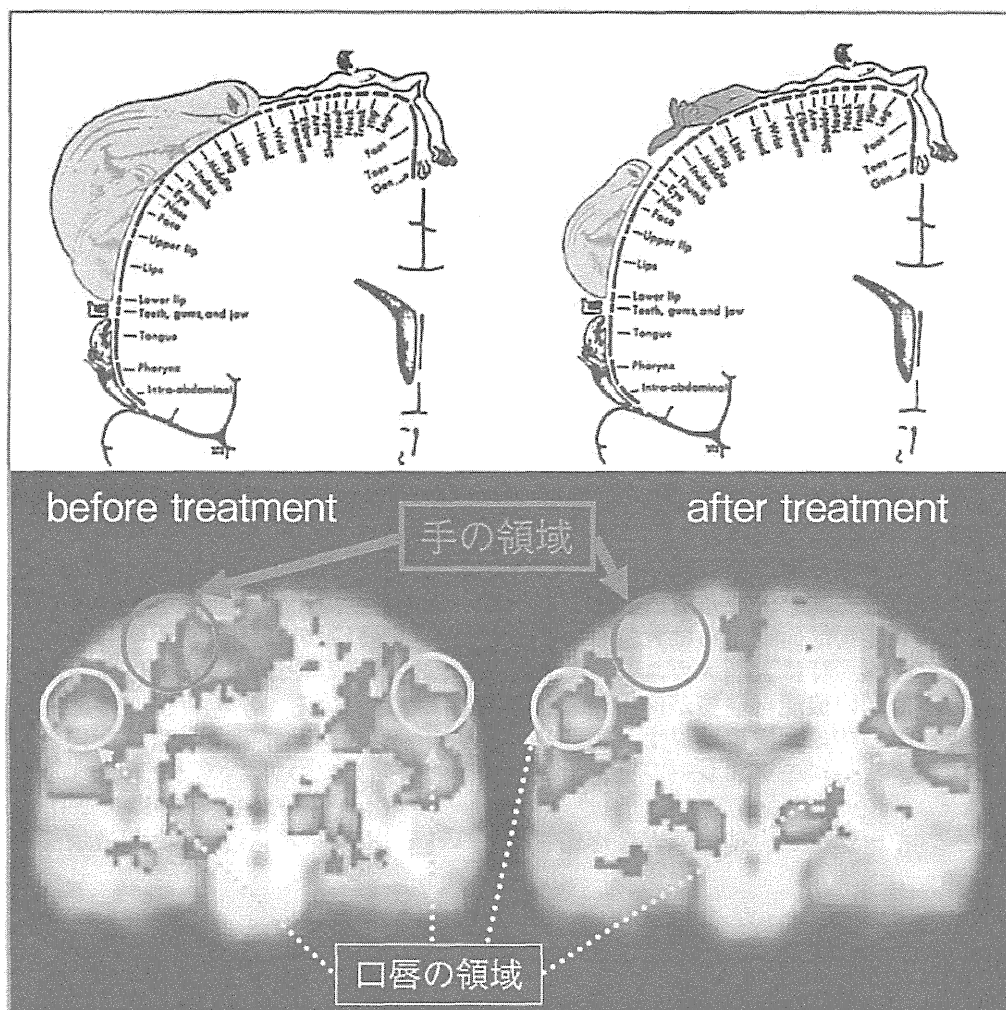
図1　幻肢の随意運動感覚獲得前後の口唇運動時の脳活性化の違い
（文献2より転載）

下段は口唇運動時の一次運動野（M1）冠状断面の活性化を示す．幻肢の随意運動感覚の獲得前（左下図）には口唇の運動によってM1の外側部（黄円）だけでなく頭頂付近にも活性化が認められるが，幻肢随意運動感覚の獲得後（右下図）には口唇運動に伴うM1活性化部位は外側部だけに限局している．このことはM1の体部位再現地図における手の領域（緑円）が回復したことを示す．上段に，幻肢の随意運動感覚獲得前（左上図）と獲得後（右上図）の体部位再現地図の模式図を示す

者では，M1でも上肢領域の縮小と口/顔面領域の拡大が認められ，M1の上肢領域に存在する神経細胞の興奮性が高まっている．このような感覚運動皮質（S1/M1）の機能再構築は，神経損傷後に疼痛を知覚しない患者には観察されず[3]．M1への磁気刺激や電気刺激が神経障害性疼痛をはじめとする難治性疼痛に有用なことも報告[4,5]されていることから，M1と神経障害性疼痛の発症は密接に関連している．

1. 神経傷害罹患肢の運動と感覚の脳内表象

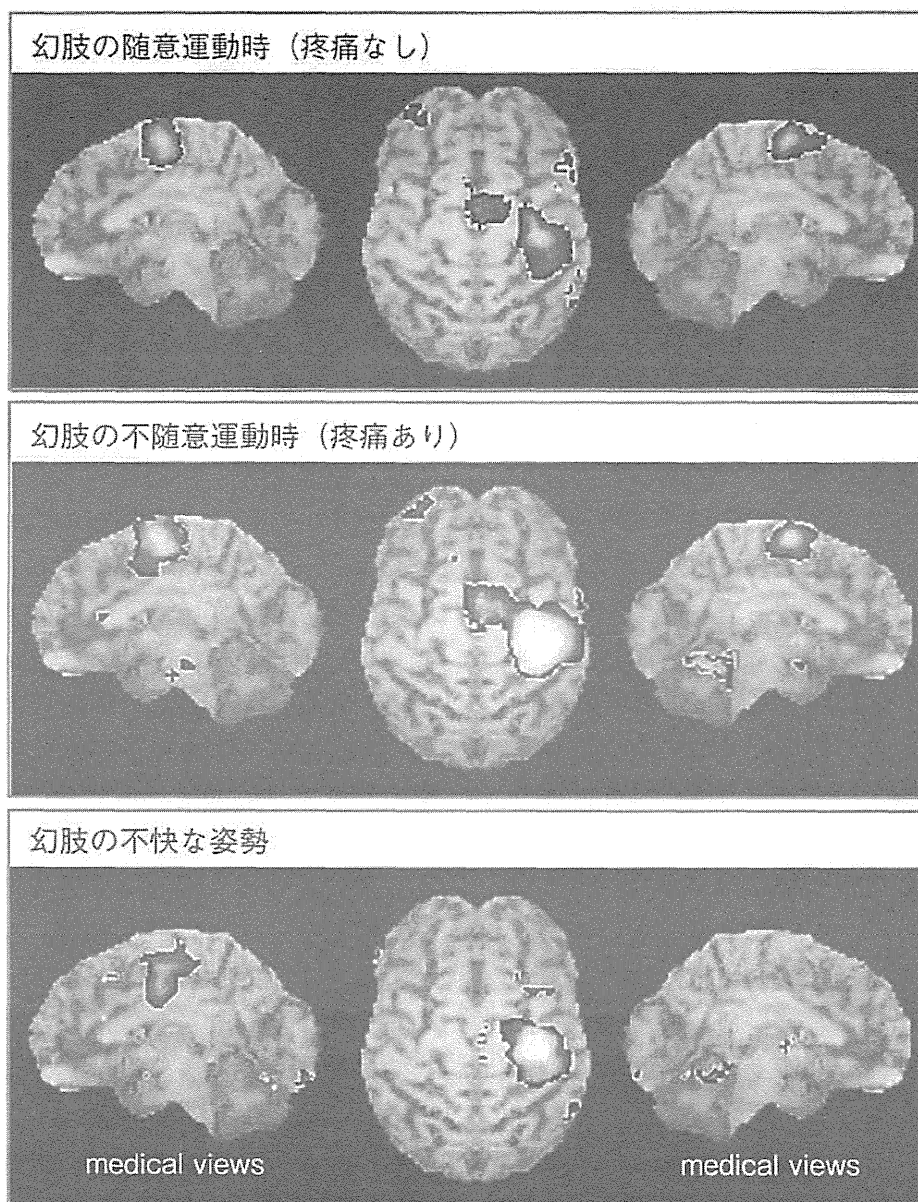神経傷害後に現れる神経障害性疼痛の中でも，大脳機能との関連が詳細に明らかにされている幻肢痛患者を例に挙げる．幻肢痛患者は様々な性質の疼痛を訴え，ボスニア・ヘルツェゴビナでの内戦によって四肢を失った幻肢痛患

図2　幻肢の異なる感覚経験によって活性化される脳領域
（文献2より転載）
幻肢は常に一定に知覚されるわけではなく，その時々によって幻肢患者は
異なる感覚経験を知覚する．このような異なる感覚経験時には異なる脳領
域の活性化が観察されるが，感覚運動皮質（一次体性感覚野と一次運動野）
の活性化は共通している

者1,250人を対象とした調査では，'刃物で裂かれるような'，'電気が走るような'，'しみるような'など，皮膚表在感覚に関連した疼痛を約58％の患者が訴える一方で，'幻肢が痙攣するような'，'こむら返りするような'，'幻肢がねじれるような'など運動感覚（自己受容感覚）に関連した疼痛を約42％の患者が訴えていた[6]．このように，幻肢痛患者の半数近くの者が幻肢の不快な不随意運動を知覚している．では，幻肢の運動感覚はどのような神経基盤によってもたらされているのであろうか？　幻肢患者の中には，幻肢を随意に運動することがで

きる（幻肢が運動しているように鮮明に知覚できる）者がおり，その際には健常な四肢随意運動に類似したM1/S1，補足運動野（SMA）の賦活化が脳機能画像研究によって観察される（図2）[7]．幻肢に不快感を伴う不随意運動時には，S1/M1，SMAに加えて，小脳，前帯状回（ACC），後部帯状回（PCC）の賦活化が観察される[7]．ACCとPCCはともに四肢運動の制御と認知にも関連する脳領域であるが，この研究ではACC/PCCの賦活化が幻肢不随意運動によって惹起される疼痛や不快感の程度と相関していたことから，ACC/PCCは不随意運動の制御に関連しているというよりは不快情動の生成と関連していると理解する方が妥当である．これらの不快情動生成領域以外の幻肢運動に伴う脳賦活化パターンは随意運動であろうと不随意運動であろうとよく似ており，さらには健常肢運動時の脳賦活化パターンともほぼ相同であることから，脳内での四肢運動の実行・認知に関しては，幻肢と健常肢には区別がないように推察できる．さらに，中枢神経系における幻肢と健常肢の区別の有無については，次のような興味深い研究が報告されている．両側上肢を同時に運動する際には，両側上肢に対して共通の運動プログラムが出力されていることから，一側上肢の運動パターンがもう一方の上肢の運動パターンに影響を与え，両側上肢の運動が一つの運動パターンに収束する（例：右手で三角形を描きながら左手で円を描くと，右手の三角形が円形に近づいていく）[8]．このような両上肢協調運動の影響は幻上肢随意運動ともう一方の健常上肢の運動パターンにも観察され，幻肢を随意に運動することができない患者では観察されない[9]．このような行動学的評価でも，中枢神経系での四肢運動制御機構では幻肢と健常肢をほぼ相同のものとしてひとまとめに扱っているような知見が得られている．

運動系だけでなく感覚系においても，中枢神経系では幻肢と健常肢をほぼ相同のものとして扱っていると考えられる．ヒトは局所麻酔を受けた身体部位を腫れているように感じ，また，侵害刺激（侵害受容性疼痛）を受けた身体部位も腫れているように感じる[10]．このような身体部位の大きさ知覚の変化は，S1/M1体部位再現地図で隣り合う身体部位にも影響を与えることから，S1/M1再構築と関連している．実際，幻肢痛患者は幻肢を常に一定に知覚するわけではなく，幻肢を正常な長さの肢のように感じたり，断端部に手が埋まっているような非常に短い肢に感じたりと，幻肢の大きさ知覚は様々に変化する．このような幻肢の大きさが変化するテレスコーピング現象も，S1/M1体部位再現地図の手の領域が縮小して体幹の領域に近づく度合いとテレスコーピングを知覚する度合い（どの程度，幻肢を短く感じるか？）が相関する[1]．さらに，神経傷害罹患肢の大きさ知覚が変化している患者は，反対側の健常肢の大きさ知覚も患肢と同様に変化（患肢を通常よりも大きく感じていると健肢も大きく感じ，患肢を小さく感じていると健肢も同様に小さく感じる）しており，この関係性は常に1：1の対応が認められた[11]．運動系の観点からは，両側上肢は一つの手表象として扱われ，運動プログラムが生成される最も初期の段階では，一方の上肢に対する運動であっても両側上肢に対する共通の運動プログラム（generalized motor program）が生成されると考えられている[8]．感覚系から運動系へ情報伝達が行われることを考えると，ひとまとまりの手運動表象には一つの手感覚表象を形成する方が効率的である．これらのことから，神経傷害罹患肢の脳内表象は，運動系と感覚系が相互に作用し合っていることが示唆される．

2. 知覚-運動ループの破綻と病的疼痛の発症

四肢運動の際には，運動の指令に続いて運動

図3　鏡療法の診療風景（文献2より転載）

患者の身体正中矢状断面に鏡を置き，鏡の中に患肢が存在しているような視覚像が得られるように健肢を鏡に映す．健肢の手指を自由に運動させ，あたかも患肢が動いているような鏡像を観察させる．同時に，患肢が鏡像肢と同様の運動をしているようなイメージを想像させる（実際に患肢に対する運動指令を行わせる）．これを1日1回約10分間行い，患者の希望によって数週間継続する．

a：左腕神経叢引き抜き損傷後余剰幻肢痛患者．肘より末梢側に，体幹に対して垂直方向に幻肢を知覚している．

b：戦争後遺症による左下肢切断後幻肢痛患者．われわれの診療グループは，ボスニア・ヘルツェゴビナでも鏡療法を指導している（2006年大阪大学医学部附属病院疼痛医療センター前田　倫医師＆JICA expert）

後に知覚される感覚情報フィードバック（腕の肢位など）の予測（efference copyという）と実際の運動（execution）が起こり，続いて実際の運動によってフィードバックされた感覚情報が運動予測（efference copy）と比較されることによって，新たな運動指令が準備される．この運動に伴う一連の運動系と感覚系の情報伝達は，常に中枢神経系でモニターされ，知覚-運動ループと呼ばれる．自己身体部位のそれぞれについて知覚-運動ループが整合されている状態では，ヒトはその身体部位を自分の身体の一部と認知できる．言い換えると，ある身体部位に関して知覚-運動ループの整合性が破綻した際には，ヒトはその身体部位を自己身体の一部であると認知できない[12]．このような自己身体認知に関わる知覚-運動ループは，体性感覚だけでなく多感覚情報を統合して制御されており，中でも視覚情報が最も重要である[13]．例え

ば，自分の上肢を隠し，その上肢の横に目視できるゴム手を置き，隠された上肢とゴム手に対して触覚刺激を同時に与えるとゴム手を自分の手と認知してしまうことや，自身の身体と連続性があるように見える上肢，言い換えると視覚的に正しい肢位の上肢は他人の上肢であっても自分の上肢と認知してしまうこと[12]などが挙げられる．このように，手の位置を正しく認識するためには，体性感覚情報だけでは不十分で視覚的に認識しなければならず，視覚的情報の修飾によって自己身体部位の認知は容易に攪乱される．身体部位認知における視覚情報の優位性を利用して，健常者上肢の視覚的な運動感覚と体性感覚的な運動感覚を解離させて上肢の知覚-運動ループを破綻させると，病的疼痛や手の喪失感をはじめとする異常感覚が生じることが報告されている[14]．この現象は，“痛み”とはそもそも身体の異常を知らせるための警告信
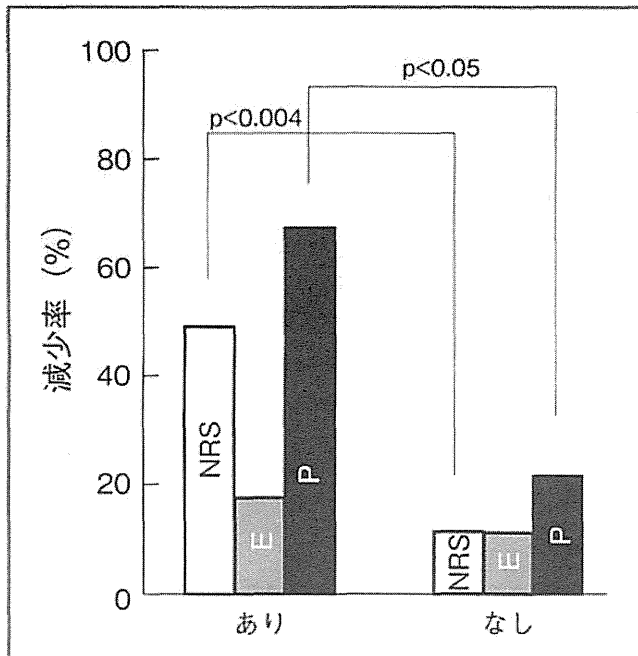
図4　幻肢の随意運動の出現による鏡療法の有効性の差異（文献2より転載）

縦軸は治療前後の疼痛強度（0～10までの11段階で評価したNRS（numerical rating scale）と皮膚表在感覚に関連した性質の疼痛E（exteroception associated pain）の訴え，および自己受容感覚に関連した性質の疼痛P（proprioception associated pain：proprio-pain）の訴え，それぞれの減少率を示す．横軸は，鏡療法施行前後による患肢随意運動の出現の有無によって患者群を2群（あり：n＝15，なし：n＝7）に分けている．
*p＜0.004，**p＜0.05（Mann-Whitney test）

号であるという観点から，生理的には知覚-運動ループの整合性が保たれるべき状態でそれが破綻すると，その異常（破綻）に対する警告として"痛み"が中枢神経系で起こる（認知される），というように解釈されている[15]．

このような知覚-運動ループの破綻を治療する方法として，Ramachandranら[16]が鏡を用いた神経リハビリテーション（鏡療法）（図3）によって幻肢の随意運動の獲得とそれに伴う幻肢痛の緩和を報告して以来，様々な神経リハビリテーション治療が神経障害性疼痛に対して実施されている．われわれも，鏡療法を用いて神経障害性疼痛患者22症例のうち10症例で

50％以上の疼痛緩和，5症例で30～50％の疼痛緩和を得た一方，7症例では無効であった[17]．鏡療法は自己受容感覚に関連した性質の痛み（例：ねじれるような）は有意に減少したが，皮膚受容感覚に関連した性質の痛み（ナイフで刺されたような）にはあまり効果がないことも明らかにした[17]．加えて，鏡療法前後での神経障害性疼痛患肢の随意運動感覚についても評価し，鏡療法が有効な患者では神経障害性疼痛患肢の随意運動感覚が出現し，不快な不随意運動感覚（例：幻肢の"こむら返り"など）が出現した際にそのような不随意運動に拮抗するような神経障害性疼痛の随意運動感覚（例：こむら返りに対して腓腹筋を伸展する）を生じさせることにより，神経障害性疼痛を自己管理できるようになった患者が多かった（図4）．神経傷害とそれに続く神経障害性疼痛を知覚-運動ループの観点から評価すると，「脳からは神経傷害肢を運動する指令（例：姿勢調節など）が常に発動されているが，実際には神経傷害によって患肢の運動が起こらないために感覚情報のフィードバックが欠損し，運動指令に続くefference copyとの間に乖離が起き，知覚-運動ループの整合性が得られていない」状況と考えることができる．上述したように，四肢認知についての視覚情報の影響は極めて強いため，自己身体を認知することが単独では不十分な体性感覚情報を視覚情報は代償することができる[12]．このことから，鏡療法の治療機序は，「神経損傷肢が運動しているかのような鏡からの視覚情報は，神経損傷に起因する自己受容感覚の欠損を代償して中枢神経系に運動感覚をフィードバックし，その結果，神経損傷肢の知覚-運動ループが再統合され病的痛みが緩和する」と考えられる．このような考察は，合目的な運動が知覚-運動ループの統合によって成されていることから，電動義手を用いて患肢を合目的な機能肢として運動学習をすることによって幻肢痛が寛解するという研究[18]と矛盾しない．

　神経傷害罹患肢の随意運動の獲得時には，S1/M1 における患肢の体部位再現地図が拡大する[19]ことも明らかになっており（図1右），S1/M1 の体部位再現地図の機能再構築（患肢領域の縮小）が疼痛強度と相関しているという知見からも，鏡療法のような神経リハビリテーションでは，S1/M1 の機能再構築によってマスクされてしまった神経傷害患部の体部位再現地図を再活性化し，拡大させることによって鎮痛効果が得られていると考えられる．

3．知覚-運動ループの破綻の場としての S1/M1 機能再構築と脊髄刺激療法の効果

　神経傷害患肢の運動出力は，M1 機能再構築によって縮小してはいるものの，残存している体部位再現地図から末梢筋骨格系へと出力されている．そして，この運動出力を受けて損傷神経の支配筋は収縮しないが，M1 領域の機能再構築による下行性神経線維の混線によって近傍の筋収縮が起こり，その体性感覚フィードバックによって神経傷害患肢の運動感覚が生じる[20]．このような筋紡錘からの体性感覚（深部感覚）フィードバックは，S1 だけでなく M1 にも直接的に伝達されているが，特に筋紡錘からの深部感覚は S1 ではなく M1 で認知していることが明らかにされている[21,22]．

　脊髄の感覚上行路は，主に，前索と前側索を上行する前・外側脊髄視床路と後索を上行する後索内側毛帯路があり，前・外側脊髄視床路は痛覚や温冷覚と粗雑な触覚が大脳に伝えられる．後索内側毛帯路では筋紡錘からの情報を主体とする深部感覚の他，振動覚や精密な触覚が大脳に伝えられる．脊髄刺激療法（spinal cord stimulation：SCS）は，一般に脊髄後索を刺激しているとされ，SCS によって誘発される刺激インパルスは，後索内側毛帯路を通じて S1 とともに M1 に伝達され，主に M1 で刺激感が

図5　視覚入力と体性感覚入力を用いた上肢リハビリテーション支援ロボットスーツ（文献2より転載）
　右上肢（健肢）にセンサースーツを着用し，左上肢（患肢）に人工筋肉とワイヤーで構成される駆動スーツを装着する．左下は人工筋肉を駆動させるための空気圧調整器．右上肢を運動すると，受動的に左上肢も右上肢の運動を遂行する（アクティブリンク社との共同開発）

認知されていると考えられる．また，SCS の刺激感が疼痛部位を覆うように知覚されなければ SCS の鎮痛効果は得られない．言い換えると，SCS の刺激インパルスが S1/M1 の患部の体部位再現地図に到達しなければ鎮痛効果を得られない．M1 に対する直接的な電気あるいは磁気刺激療法でも，機能再構築によって縮小しているものの，患部の体部位再現地図を刺激することが必要である[23]．したがって，SCS や運動野刺激療法は，神経傷害によって末梢からの
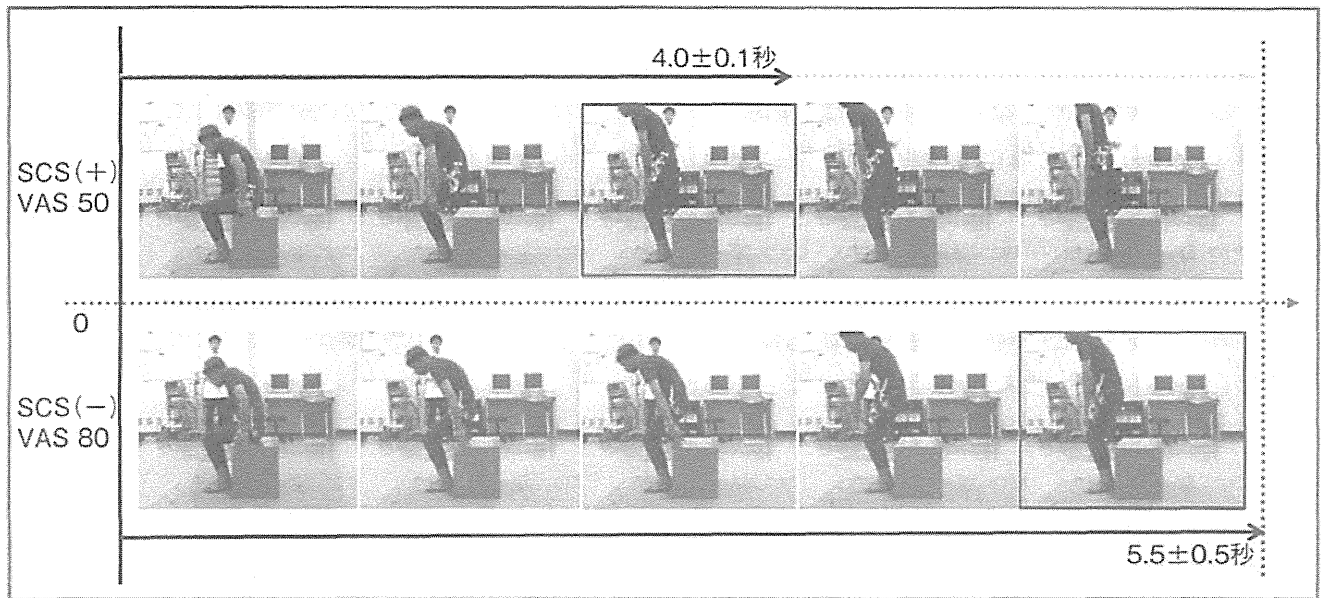
図6　脊髄刺激療法施行前後の3次元動作解析システム用いた3回の立ち上がり動作分析の比較（文献30より転載）
上段はSCS刺激中の立ち上がり動作，下段はSCS刺激前の立ち上がり動作．立ち上がりに要する時間が脊髄刺激療法施行中には有意に短縮した（p＜0.05, Wilcoxon signed-rank test）

入力が減少したことによって縮小したS1/M1の体部位再現地図への入力を行うことによって，機能再々構築を行っていることが，鎮痛効果として得られていると考えられる．残念ながら，現段階では，SCSや運動野刺激療法前後で体部位再現地図の機能再々構築（再拡大）を示した脳機能画像研究はなく，今後の研究に期待される．しかし，SCSによってM1が賦活化されていることは複数報告されており，われわれの考察の傍証となるものと思われる[20]．

4. 神経障害性疼痛に対する視覚入力だけでなく体性感覚入力も利用した神経リハビリテーションの開発

これまでわれわれは，知覚－運動協応の再統合を目的に，視覚入力（鏡）を用いた神経リハビリテーションを行ってきたが，われわれの鏡療法に対して抵抗性を示す難治性疼痛患者も少なくはない．そこでわれわれは，視覚情報に加えて，神経障害による運動不全を呈する患肢を受動的に運動させることによって体性感覚情報も同時に入力するリハビリロボットスーツ（図5）を共同開発中である（四肢切断後患者の場合は義肢も併用する）[25]．このスーツは，健肢に装着したセンサーの情報（例：肘関節を屈曲）を検知し，患肢に装着した人工筋とワイヤーが作動し，鏡の中に存在するような患肢の映像（健肢が鏡に映った映像）を運動させる時と同じように患肢の受動的運動が実行される．運動企図から運動指令が形成され，その運動に応じた体性感覚情報の入力がある状態では，単に受動的に運動が行われた条件よりもより強いS1の活性化が観察され，さらには，単なる受動運動ではM1の活性化はあまり観察されないが，能動運動時には運動しようとする身体部位に応じたM1体部位領域が強く活性化することから，われわれが共同開発中のロボットスーツを使用する際に，患者が健側肢と同様の運動を患肢でも実行しようと意図することにより，ⅰ）
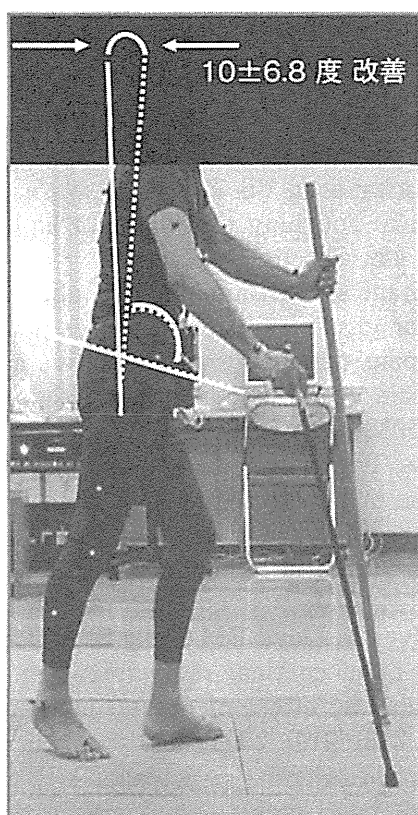
54

図7　脊髄刺激療法施行前後の3次元動作分析システムを用いた3回の歩行動作分析の比較（文献30より転載）
白い実線はSCS施行前の体幹と骨盤のなす角度を示し，白い点線はSCS刺激中の同角度を示す．脊髄刺激療法施行中には歩行時の体幹と骨盤のなす角度が狭小化し，強直性の背部伸展位が生理的な前傾姿勢へと改善した

鏡療法のように，健側上肢を運動した際に患側上肢が同様の運動を行うため，身体運動に関する視覚情報と体性感覚情報が入力されること，ⅱ）ロボットスーツによる患肢運動は受動的な運動ではあるが，理学/作業療法士による受動運動とは異なり，患肢に対する運動企図に連続したS1/M1の神経活動が惹起されるためより強力に患肢体部位領域の賦活化が起こること，の2点が期待できる．

さらに，このようなロボットスーツを用いなくても，神経傷害患肢の積極的な運動はS1/M1の体部位再現地図の拡大につながる[26]．しかし，神経傷害患肢は，弛緩性麻痺だけでなく

痙性麻痺や不随意運動を伴うことも少なくなく，積極的な運動が実施できないことも多い．

SCSは，中枢神経系の変性によって運動障害を呈する代表的疾患のパーキンソン病モデルラットに対して，脊髄-大脳基底核-大脳皮質を介した反射経路を抑制することによって，痙性および不随意運動を改善することが報告されている[27]．また，SCSにより脊髄損傷後の痙性の緩和や歩行が可能となった症例の報告もある[28,29]．われわれも，脊髄変性疾患による腰痛および下肢痛に対してSCSを実施し，痙性が改善された結果，坐位から立位への立ち上がり動作や歩行姿勢が改善したことを光学式動作分析システム（モーションキャプチャー）を用いて定量的に評価した（図6，図7）[30]．したがって，SCSなどのニューロモデュレーション治療は，神経傷害に伴う運動障害の治療としての作用が期待できる．

おわりに

これまで，感覚系と運動系は別個の神経システムとして治療概念が異なっていた．しかしながら，本稿で示したように感覚系と運動系は相互に情報交換を繰り返すループ状の関係性であるため，それらを切り離して議論，治療することは適切ではない．特に，神経障害性疼痛のような慢性疼痛疾患では，その発症機序に知覚-運動ループの破綻が密接に関連していることが示唆されるため，感覚系と運動系を組み合わせた治療が効果的である．大脳メカニズムに対する神経リハビリテーションとニューロモデュレーション治療を併用することにより，鎮痛効果が相乗的に得られると考えている．

文　献

1) Flor H, Nikolajsen L, Jensen TS: Phantom limb pain: A case of maladaptive CNS plasticity? Nat Rev Neurosci 7 : 873-881, 2006

2) 住谷昌彦, 宮内　哲, 前田　倫, 他：幻肢痛の脳内メカニズム. 日本ペインクリニック学会誌 17 : 1-10, 2010

3) Karl A, Birbaumer N, Lutzenberger W, et al: Reorganization of motor and somatosensory cortex in upper extremity amputees with phantom limb pain. J Neurosci 21 : 3609-3618, 2001

4) Saitoh Y, Shibata M, Sanada Y, et al: Motor cortex stimulation for phantom limb pain. Lancet 353 : 212, 1999

5) Hirayama A, Saitoh Y, Kishima H, et al: Reduction of intractable deafferentation pain by navigation-guided repetitive transcranial magnetic stimulation of the primary motor cortex. Pain 122 : 22-27, 2006

6) Karkin-Tais A, Muftic M, Suljevic S, et al: 13-year study of pain in phantom limbs of amputees-victims of war in Sarajevo (period 1992-2005). Proceedings of Pain in Europe V, 2006

7) Willoch F, Rosen G, Tolle TR, et al: Phantom limb pain in the human brain: Unraveling neural circuitries of phantom limb sensations using positron emission tomography. Ann Neurol 48 : 842-849, 2000

8) Swinnen SP, Wenderoth N: Two hands, one brain: Cognitive neuroscience of bimanual skill. Trend Cogn Sci 8 : 18-25, 2004

9) Franz EA, Ramachandran VS: Bimanual coupling in amputees with phantom limbs. Nature Neurosci 1 : 443-444, 1998

10) Gandevia SC, Phegan CML: Perceptual distortions of the human body image produced by local anesthesia, pain and cutaneous stimulation. J Physiol 514 : 609-616, 1999

11) Sumitani M, Yozu A, Tomioka T, et al: Using the intact hand for objective assessment of phantom hand-perception. Eur J Pain 14 : 261-265, 2010

12) Jeannerod M: The mechanisms of self-recognition in humans. Behav Brain Res 142 : 1-15, 2003

13) Botvinick M, Cohen J: Rubber hands 'feel' touch that eyes see. Nature 391 : 756, 1998

14) McCabe CS, Haigh RC, Halligan PW, et al: Simulating sensory-motor incongruence in healthy volunteers. Implications for a cortical model of pain. Rheumatology 44 : 509-516, 2005

15) Harris AJ: Cortical origins of pathological pain. Lancet 354 : 1464-1466, 1999

16) Ramachandran VS, Rogers-Ramachandran D, Cobb S: Touching the phantom limb. Nature 377 : 489-490, 1995

17) Sumitani M, Miyauchi S, McCabe CS, et al: Mirror visual feedback alleviates deafferentation pain, depending on qualitative aspects of the pain: A preliminary report. Rheumatology 47 : 1038-1043, 2008

18) Weiss T, Miltner WHR, Adler T, et al: Decrease in phantom limb pain associated with prosthesis-induced increased use of an amputation stump in humans. Neurosci Lett 272 : 131-134, 1999

19) MacIver K, Lloyd DM, Kelly S, et al: Phantom limb pain, cortical reorganization and the therapeutic effect of mental imagery. Brain 131 : 2181-2191, 2008

20) Reilly KT, Mercier C, Schieber MH, et al: Persistent hand motor commands in the amputee's brain. Brain 129 : 2211-2223, 2006

21) Kleinfeld D, Waters J: Wilder Penfield in the age of YouTube: Visualizing the sequential activation of sensorimotor areas across neocortex. Neuron 56 : 760-762, 2007

22) Naito E, Ehrsson HH, Geyer S, et al: Illusory arm movements activate cortical motor areas: A positron emission tomography study. J Neurosci 19 : 6134-6144, 1999

23) Roux FE, Ibarrola D, Lazorthes Y, et al: Chronic motor cortex stimulation for phantom limb pain: A functional magnetic resonance imaging study: Technical case report. Neurosurgery 62 : S978-S985, 2008

24) Stancak A, Kozak J, Vrba I, et al: Functional magnetic resonance imaging of cerebral activation during spinal cord stimulation in failed back surgery syndrome. Eur J Pain 12 : 137-148, 2008

25) Sumitani M, Miyauchi S, Yozu A, et al: Phantom limb pain in the primary motor cortex: Topical review. J Anesth 24 : 337-341, 2010

26) Stoeckel MC, Pollok B, Schnitzler A, et al: Use-dependent cortical plasticity in thalidomide-induced upper extremity dysplasia: Evidence from somaesthesia and neuroimaging. Exp Brain Res 156 : 333-341, 2004

27) Fuentes R, Petersson P, Siesser WB, et al: Spinal cord stimulation restores locomotion in animal models of Parkinson's disease. Science 323 : 1578-1582, 2009

28) Adams MM, Hicks AL:Spasticity after spinal cord injury. Spinal Cord 43 : 577-586, 2005

29) Harkema S, Gerasimenko Y, Hodes J, et al: Effect of epidural stimulation of the lumbosa-cral spinal cord on voluntary movement, standing, and assisted stepping after motor complete paraplegia:A case report. Lancet 377 : 1938-1947, 2011

30) 牛尾倫子, 住谷昌彦, 辛　正廣, 他：三次元動作分析システムを用いた脊髄刺激療法前後の疼痛関連運動障害の評価（症例報告）. 日本ペインクリニック学会誌 19：44-47, 2012

※　　　　　※　　　　　※

Limited Transfer of Newly Acquired Movement Patterns across Walking and Running in Humans

Tetsuya Ogawa[1]*, Noritaka Kawashima[1], Toru Ogata[1], Kimitaka Nakazawa[2]

1 Department of Rehabilitation for the Movement Functions, Research Institute, National Rehabilitation Center for Persons with Disabilities, Namiki, Tokorozawa, Saitama, Japan, 2 Graduate School of Arts and Sciences, The University of Tokyo, Komaba, Meguro, Tokyo, Japan

Abstract

The two major modes of locomotion in humans, walking and running, may be regarded as a function of different speed (walking as slower and running as faster). Recent results using motor learning tasks in humans, as well as more direct evidence from animal models, advocate for independence in the neural control mechanisms underlying different locomotion tasks. In the current study, we investigated the possible independence of the neural mechanisms underlying human walking and running. Subjects were tested on a split-belt treadmill and adapted to walking or running on an asymmetrically driven treadmill surface. Despite the acquisition of asymmetrical movement patterns in the respective modes, the emergence of asymmetrical movement patterns in the subsequent trials was evident only within the same modes (walking after learning to walk and running after learning to run) and only partial in the opposite modes (walking after learning to run and running after learning to walk) (thus transferred only limitedly across the modes). Further, the storage of the acquired movement pattern in each mode was maintained independently of the opposite mode. Combined, these results provide indirect evidence for independence in the neural control mechanisms underlying the two locomotive modes.

Introduction

In everyday life, humans use two major modes of locomotion: walking and running. By definition, walking is known as a movement in which at least one foot is always in contact with the ground, whereas running involves aerial phases where both feet are off the ground. Both similarities and dissimilarities between the modes have been demonstrated from the perspectives of energetics [1], limb movements [2,3], and muscle functions [2,4,5]. Because of the spontaneous behavior to transit into the opposite modes in accordance with changing speed (walk-run or run-walk transition) [2,6–8], these two movement modes seem dependent on the demand for different locomotion speeds.

On the other hand, by referring to earlier studies focusing on the behavioral aspect of human motion in simple upper-limb movements [9,10] and gait [11,12], neural control mechanisms underlying human movement are considered as very specific to given tasks or contexts. Combined with direct evidence obtained in animal models [13,14], there would be a possible independency in the neural mechanisms specific to different modes of locomotion. Walking and running in humans therefore, may not only be dependent on different speeds but also have discrete control mechanisms capable of the respective modes. The present study addressed the possibility by utilizing motor adaptation paradigms that have been well established in the field of motor control, especially in the last decade [9–12].

Based on the hypothesis that independent neural control mechanisms underlie walking and running, we established working hypotheses as follows. 1) After the acquisition of a novel movement pattern (adaptation) in one of the modes, the emergence of the novel pattern in the subsequent trials is evident only within the same mode and limited in the opposite mode (thus, limited transfer across walking and running). In addition, 2) storage of the novel movement pattern in the respective mode is maintained independently of the opposite mode. The acceptance of these working hypotheses will provide indirect evidence of independent neural mechanisms underlying human walking and running. A section of the results in the present study have been presented in abstract form [15].

Methods

Subjects

Twenty-four healthy male volunteers (age range, 22 to 49 years old) with no known history of neurological or orthopedic disorders participated in the study. Each subject was tested in two of four experimental protocols (Figure 1). Twelve of them participated in experiments 1 and 2, while the other 12 participated in experiments 3 and 4. The order of participation was randomized across subjects.
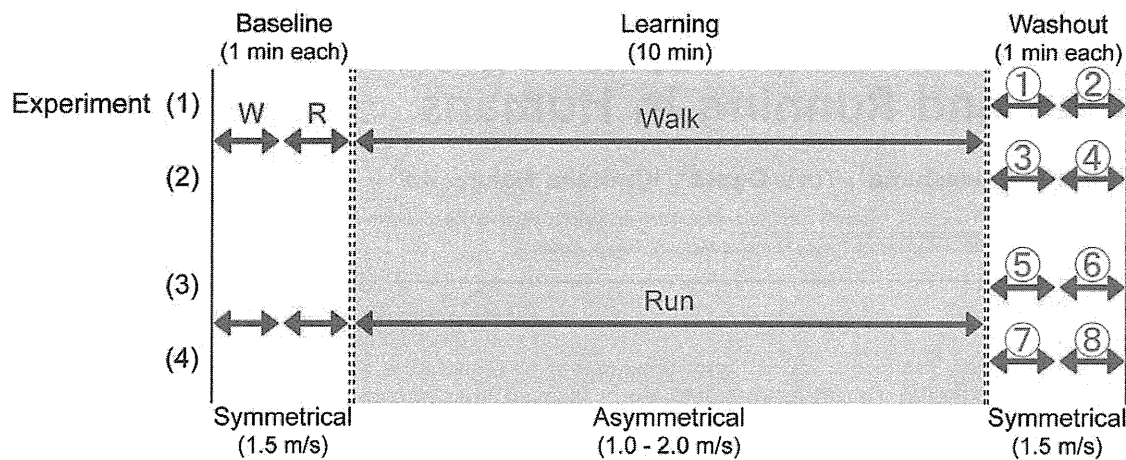
59

Figure 1. Experimental protocols (1 through 4) adopted in the present study. Subjects underwent adaptation tasks of either walking (1 and 2) or running (3 and 4) on an asymmetrically driven treadmill (one belt was set at 1.0 and the other at 2.0 m s^{-1}) for 10 minutes. Walking and running patterns on a normally operated treadmill (at 1.5 m s^{-1} bilaterally and 1 minute each in duration) before and after the adaptation were compared on the basis of the modes of adaptation.
doi:10.1371/journal.pone.0046349.g001

Ethics Statement

Each subject gave written informed consent for his participation in the study. The experimental procedures were approved by the local ethics committee of the National Rehabilitation Center for Persons with Disabilities, Japan, and were conducted in accordance with the Declaration of Helsinki.

Experiment

In the present study, the subjects walked and ran on a split-belt treadmill (Bertec, Columbus, OH, USA), having two belts (one underneath each foot), each driven by an independent motor. The treadmill was operated either symmetrically (both belts moving at the same velocity) or asymmetrically (at different velocities). During the baseline period, the treadmill was operated symmetrically and the velocity was adjusted to 1.5 m s^{-1}. This was the speed where all the subjects could both walk and run comfortably in our pilot experiment. Subsequently, the subjects learned to walk (experiments 1 and 2) or run (experiments 3 and 4) on an asymmetrically driven treadmill for 10 minutes. The speed of one belt was increased by one third from the baseline (0.5 m s^{-1}), whereas that of the other was decreased by one third; thus, the belt speeds were 2.0 and 1.0 m s^{-1}, respectively. The direction of speed change (either faster or slower) was randomized across subjects and the experimental protocol. After the 10-minute adaptation period, the belt speed was returned to symmetry (for the washout periods) as in the baseline periods. Here, the subjects were instructed to walk and run (experiments 1 and 4) or run and walk (experiments 2 and 3) in order for 1 minute each in duration depending on the experimental protocols (Figure 1). Between all testing periods (baseline walk, run, adaptation, washout walk (run), and run (walk)), the treadmill was stopped once and restarted immediately by the experimenter with an acceleration (deceleration) of 0.5 m s^{-2}. The subjects were instructed to walk or run normally as they looked at a wall approximately 5 meters in front of them and were instructed to refrain from looking down at the treadmill belts in order to avoid any visual biases on the speed. The subjects were also instructed to always start their task by either walking or running from the first step depending on the testing sessions. For safety, one experimenter always stood by the treadmill during the experiment, and the subjects could hold onto handrails mounted on both side of the treadmill in case of risk of falling. However, all the subjects satisfactorily completed the testing sessions without using the handrails.

Recordings and Analysis

Three orthogonal ground reaction force (GRF) components (mediolateral (Fx), anteroposterior (Fy), and vertical (Fz)) were detected by two force plates mounted underneath each treadmill belt. The force data were low-pass filtered at 5 Hz and were digitized at a sampling frequency of 1 kHz (Power Lab, AD Instruments, Sydney, Australia). From the Fz component of the GRF, the moments of ground contact and toe-off were detected on a stride-to-stride basis using a custom-written program (VEE pro 9.0, Agilent Technologies, Santa Clara, CA, USA). Data on the first stride cycle of each testing session were removed for later analysis in order to minimize the influences of perturbation induced by the initiation of the treadmill movements.

The aspects of walking and running were investigated by addressing the peak anterior braking force upon foot contact for every stride cycle. In our pilot study, we demonstrated that, among all of the orthogonal ground reaction force (GRF) components, only this component showed clear aspects of adaptation and aftereffects with the return to symmetrical belt condition in both walking and running. A series of previous studies focused on temporal and spatial gait parameters such as stride and step length, stance and swing time, double support time, and the relationship in the gait phase between the two legs to address adaptive behavior of the split-belt treadmill walking [11,12,16,17]. However, given that gait speed is a quotient of length (spatial) and the time (temporal factors), subjects could potentially employ different strategies across individuals (either walking or running with spatially symmetrical with temporally asymmetrical movement patters, temporally symmetrical with spatially asymmetrical movement patterns, or changing the both parameters) with exposure to belt conditions with changing speed.

Since the stride cycles taken during the testing sessions varied across subjects and tasks (walk or run), the obtained data were averaged over stride cycles in 3-second bins and were normalized to the mean during the baseline of each movement task (walk or run) to allow intersubject comparisons.

For statistical comparisons, two-way analysis of variance (ANOVA) with repeated measures was used to test for statistically

significant differences in the aftereffects, with factors of movement modes (walk or run) or the previously imposed adaptation tasks and the time in the respective 60-second washout period. Data are presented as the mean and standard error of the mean (mean ±''' SEM). Significance was accepted when P<0.05.

Results

The number of stride cycles taken under the identical speed differed depending on the movement mode and among subjects. Regardless of the belt condition (symmetric at 1.5 m s^{-1} or asymmetric at 1.0 m s^{-1} and 2.0 m s^{-1}), subjects on average took approximately 60 stride cycles for walking and 80 strides for running every minute.

All of the subjects reported that their movement patterns were disturbed when returning to the symmetrical belt conditions after walking on the asymmetrically driven treadmill, as described in previous studies [11,16]. For running after adapting to run on asymmetrical belts, subjects also reported their movement patterns as perturbed. Figures 2 and 3, respectively, show typical examples of antero-posterior (braking and propulsion, respectively) ground reaction force waveforms under different time points (A), time series changes in the peak anterior force for both fast and slow sides (B), and the differences in the peak force between the sides (C) on a stride-to-stride basis for walking (Figure 2) and running (Figure 3).

During the baseline where the belt conditions were symmetrical, the waveforms were very similar in shape and the amplitude (both anterior and posterior components) between the sides for both walking (Figure 2 (A)) and running (Figure 3 (A)). With exposure to the asymmetrical belt condition, the shapes resulted in prominent differences, an indication of different movement patterns between the fast and the slow sides. For both walking and running, modification in the amplitude of peak anterior braking force took place in the 10-minutes learning periods, including both rapid changes in the earlier phase (up to around 1 minute) followed by slower gradual changes (Figure 2 (B) and Figure 3 (B)). The modification in the amplitude was an increment for the fast side and a decrement for the slow side, respectively. It is especially noticeable here that the braking force in the slow side almost disappeared at the fully adapted state in running (Final of Learning period in Figure 3 (A) and near 10 minutes in the Learning period in Figure 3 (B)). As a consequence, there were large differences between the sides (asymmetry) (Figure 2 (C) and Figure 3 (C)). With return to the symmetrical belt condition (washout), the amplitudes of the force differed to a great extent between the sides despite the identical belt speed to that during the baseline. In detail, there were initially an overshoot in the amplitude for the fast side and an undershoot in the slow side for both walking and running (in comparison to the baseline). In the 1-minute washout period, the amplitudes of both sides decayed toward those found in the baseline (into the opposite direction to the changes during the learning periods). An important fact here is that the movements were initially disturbed upon walking on symmetrical belt after adapting to walk, and running after adapting to run, on the asymmetrically driven treadmill surface. The disturbance in the
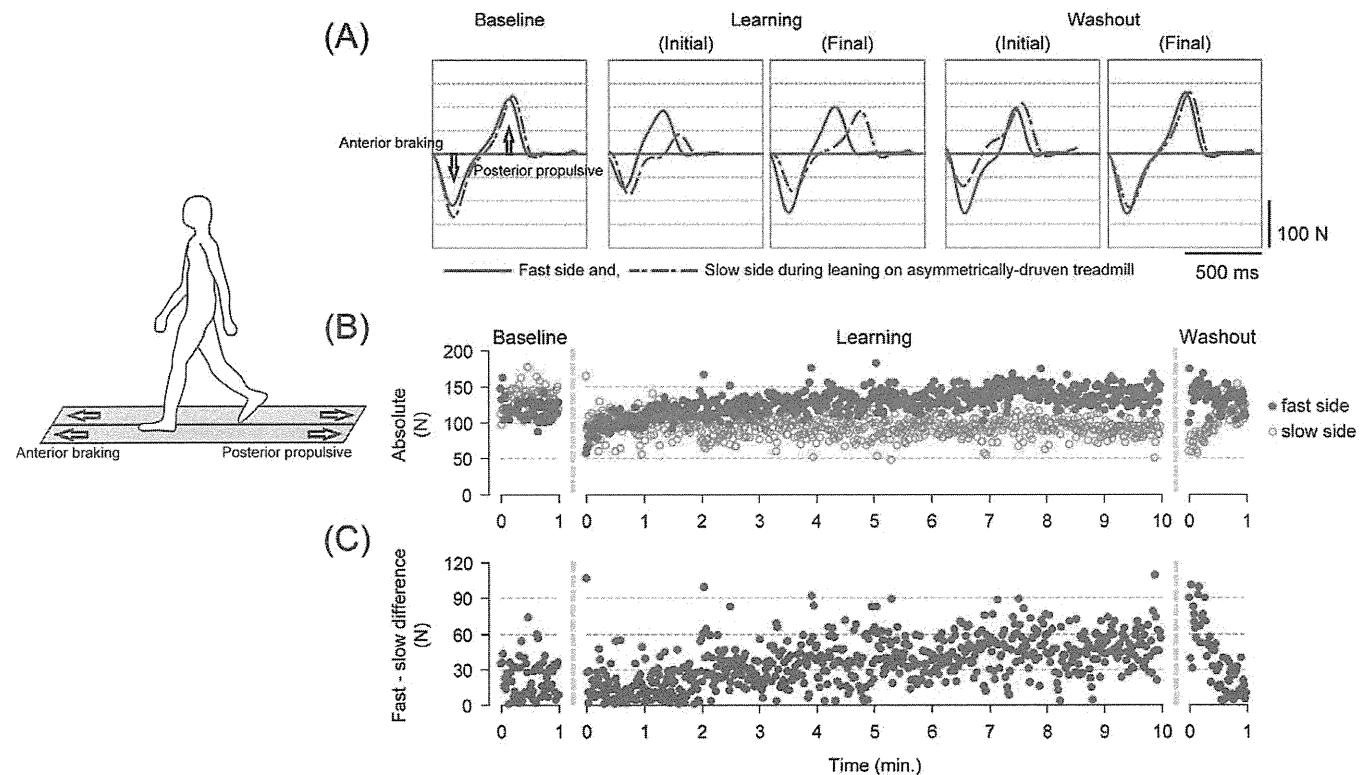

Figure 2. Descriptions of adaptation on the asymmetrically driven treadmill and the emergence of the aftereffect with release from the novel environment in walking in a single subject (showing only the walking periods from Experiment 1). (A) Waveforms of the antero-posterior ground reaction force under different time points in the experiment. Each waveform represents an ensemble average of five consecutive stride cycles (from heel contact to the subsequent heel contact) in the respective time points. The solid lines represent the fast-moving side and the dotted lines are those of the slow side during the adaptation period. (B) Stride-to-stride profile of the peak anterior braking force for both fast and slow sides. Filled circles and open circles represent the fast and slow sides, respectively. (C) Stride-to-stride profile of the differences in peak anterior braking force between the fast and slow sides.
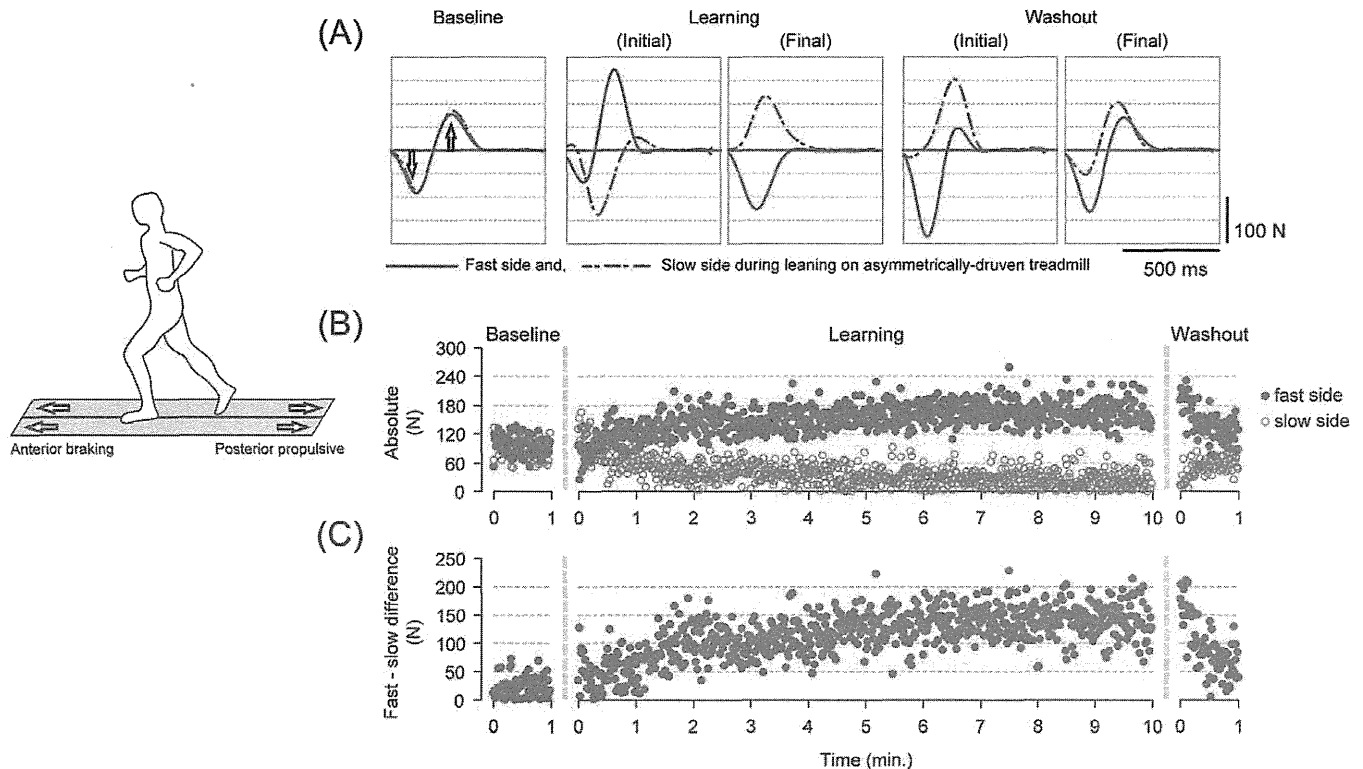doi:10.1371/journal.pone.0046349.g002

61

Figure 3. Descriptions of adaptation on the asymmetrically driven treadmill and the emergence of an aftereffect with release from the novel environment in running in a single subject (only the running periods from Experiment 3 are shown). (A) Waveforms of the antero-posterior ground reaction force under different time points in the experiment. Each waveform represents an ensemble average of five consecutive stride cycles (from heel contact to the subsequent heel contact) in the respective time points. The solid lines represent the fast-moving side and the dotted lines are those of the slow side during the adaptation period. (B) Stride-to-stride profile of the peak anterior braking force for both fast and slow sides. Filled circles and open circles represent the fast and slow sides, respectively. (C) Stride-to-stride profile of the differences in peak anterior braking force between the fast and the slow sides.
doi:10.1371/journal.pone.0046349.g003

movements were then, followed by gradual decay (restoring normal movements) in the following 1 minute.

It should be noted that modification in the force occurred in the posterior (propulsive) component as well. In the representative waveform (Figure 3 (A)), for example, the posterior force in the fast side showed a sudden increase with exposure to the asymmetrical belt but subsequently disappeared at the end of the learning period. Combined with that in the slow side which showed a modification into the opposite direction (increase), there was large asymmetry at the initial state of the washout period. The asymmetry, however, was prominent only in running and not in walking. We therefore used anterior braking force (disturbed both in walking and running) as parameter in the present study.

Given the initial disturbance in the movement patterns (asymmetry in the braking force) in both movement modes after adapting in each mode, the primary interest in the present study was whether the movement pattern acquired through each mode transferred to (or shared with) the other mode. Figure 4 (A) compares the extent of asymmetry in walking on identical belt conditions after adapting to walk (blue line) and after adapting to run (light blue line) as differences in the peak force between the sides. In contrast to the large asymmetry after learning to walk, the emergence of aftereffect was only partial (only reactively present in the first few seconds). ANOVA comparison revealed a significant difference between walking with different history (learned to walk or run) in previously imposed adaptation modes ($F_{1, 22} = 7.285$, P<0.05). On the other hand, the degree of aftereffect during running with a different adaptation history is described in Figure 4

(B). In comparison to the prominent asymmetry in the running patterns after adapting to run, individuals who adapted to walk showed far less asymmetry ($F_{1, 22} = 15.914$, P<0.01).

Secondly, to further consider the independence or commonality of each movement mode in relation to the other, we investigated the extent of a possible washout in the acquired movement patterns in one mode by the other (Figures 5 and 6). As partially described in the results above, the subjects could both walk and run as normal at the end of the first washout period after adapting in the opposite modes (shown in the left columns in Figures 5 and 6). The subsequent attempts to run (right column, Figure 5) and walk (Figure 6) resulted in prominent asymmetry in the movement patterns, demonstrating little or no washout by the execution of the opposite mode. That is, the acquired movement patterns (asymmetry) were maintained independently of the subsequent trials in the opposite modes. ANOVA showed significant differences in the degree of asymmetry in the movement patterns between the first and second washout periods ($F_{1, 11} = 6.109$, P<0.05, for 1) walking, and 2) running after adapting to run ($F_{1, 11} = 6.914$, P<0.05, for 1) run and 2) walk after adapting to walk).

Discussion

The present results strongly confirmed our working hypotheses and demonstrated that 1) transfer of the novel movement patterns learned on an asymmetrically driven treadmill from one mode to another took place only partially for both directions (walk to run and run to walk), and 2) the learned movement patterns in the
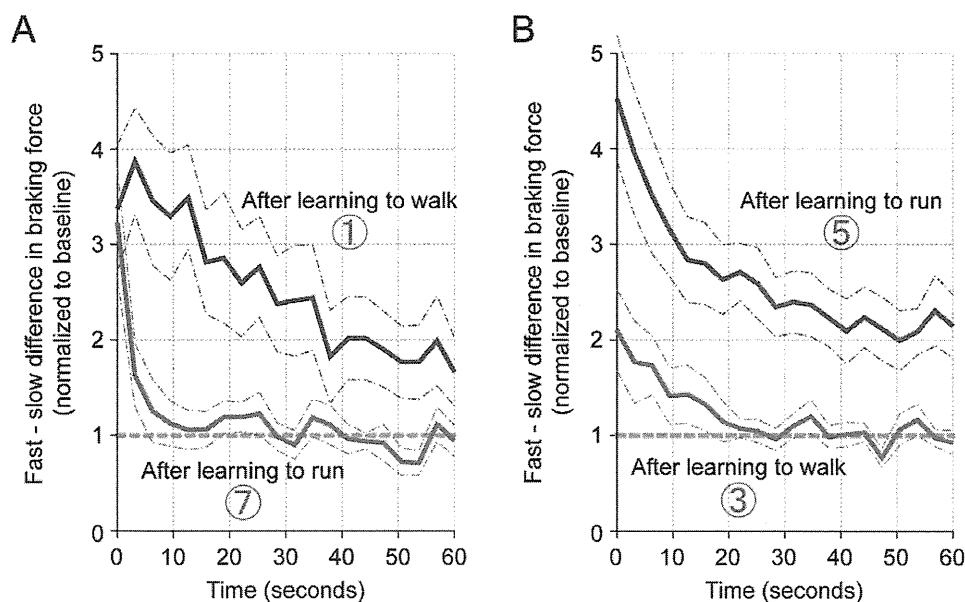
Figure 4. Degree of transfer in the acquired movement pattern across walking and running, shown as differences in the peak braking force between the sides. The extent of asymmetry in (A) walking after adaptation to walk (first washout period in Experiment 1, darker line) and after adaptation to run (first washout period in Experiment 4, lighter line), and (B) running after adaptation to run (first washout period in Experiment 3, darker line) and after adaptation to run (first washout period in Experiment 2, lighter line). Data are normalized to the mean of those during the baseline on a subject-to-subject basis and are presented as the mean (thick line) and the standard errors of the mean (dotted lines).
doi:10.1371/journal.pone.0046349.g004

respective modes were rarely washed out by the subsequent execution in the opposite modes, again, for both directions. That is, the storage of a learned movement patterns were maintained independently of the opposite mode. Combined, these results demonstrated only partially overlapped elements between these two movement modes and thus support the notion of mostly independent functional networks within the CNS for the respective locomotive modes. Walking and running, therefore, reflect not only functions of different speeds of locomotion, but are different forms from the perspective of neural control mechanisms.

The notion of task-specific or context-specific neural mechanisms has been well established by using simple reaching movements in the upper extremities [9,10]. Locomotive movements that are more complex and autonomic have also been found as under the specificity, such as the direction (forward-backward) [11], the limb (right-left) [11], and the speed of walking [12]. Limitations in the transfer or washout in newly acquired movement patterns under certain physical constraints in one movement tasks to or by another have been accepted as indirect evidence demonstrating the specificity [9–12]. By adopting the well-established experimental paradigms in the earlier studies, the present study is the first to address the mode-specificity, comprising an important aspect of locomotion. Because of the well-known spontaneous behavior to transit into the opposite mode (walk-run or run-walk transition) in accordance with changing speed [2,6–8], walking and running may only be considered as a function of demands for different speeds.

The use of split-treadmill walking to modify gait symmetry has been studied extensively in the last decade [11,12,6]. After walking on an asymmetrically-driven treadmill for a certain period of time, the movement pattern after release from the novel environment resulted in prominent asymmetry [11,12,16]. The current study, for the first time, demonstrated that movement patterns in running also could be modified as in the earlier studies focusing on walking. Detailed explanations on how the gait patterns could be adapted

with exposure to the asymmetrically driven treadmill and resulted in the subsequent aftereffect have been provided previously both behaviorally and mathematically on the basis of locomotion in decerebrate cat [18].

In the present study, the modification in the gait patterns was most evident in the anterior braking component of the ground reaction force both in walking and running and we therefore focused on this parameter (detailed description in the Methods). As subjects adapted to walk or run comfortably on the asymmetrically driven treadmill, the patterns of modification in the anterior braking force showed gradual increment in the fast side and decrement in the slow side, both including brief and more rapid changes in the early phases of exposure. As a consequence, with return to the symmetrical belt in the washout period, there was initially an overshoot in the force in the fast side and an undershoot for the slow side, both followed by gradual decay into the opposite direction to those during the adaptation periods (towards baseline). Combined with results in a previous study in which novel motor pattern could be stored intralimb and independently for each leg [11], these phenomena occurring for the each limb may reflect the well-established notion of motor adaptation or learning where motor output is recalibrated to meet new task demands [19]. It is reasonable to consider that the asymmetry in the anterior braking force took place based on the recalibration of motor output in each leg under different velocity on an asymmetrically driven treadmill.

The motor output acquired through the above mentioned recalibration processes, however, were only partially shared across the movement modes. Given the results, with the possibility of specificity in the neural mechanisms underlying walking and running, the discussion will now focus on the possible neural mechanisms comprising the different modes. Based on the results of animal studies and of humans, the neural mechanisms underlying the present results could be attributed to possible contribution of supraspinal structures in the brain and the
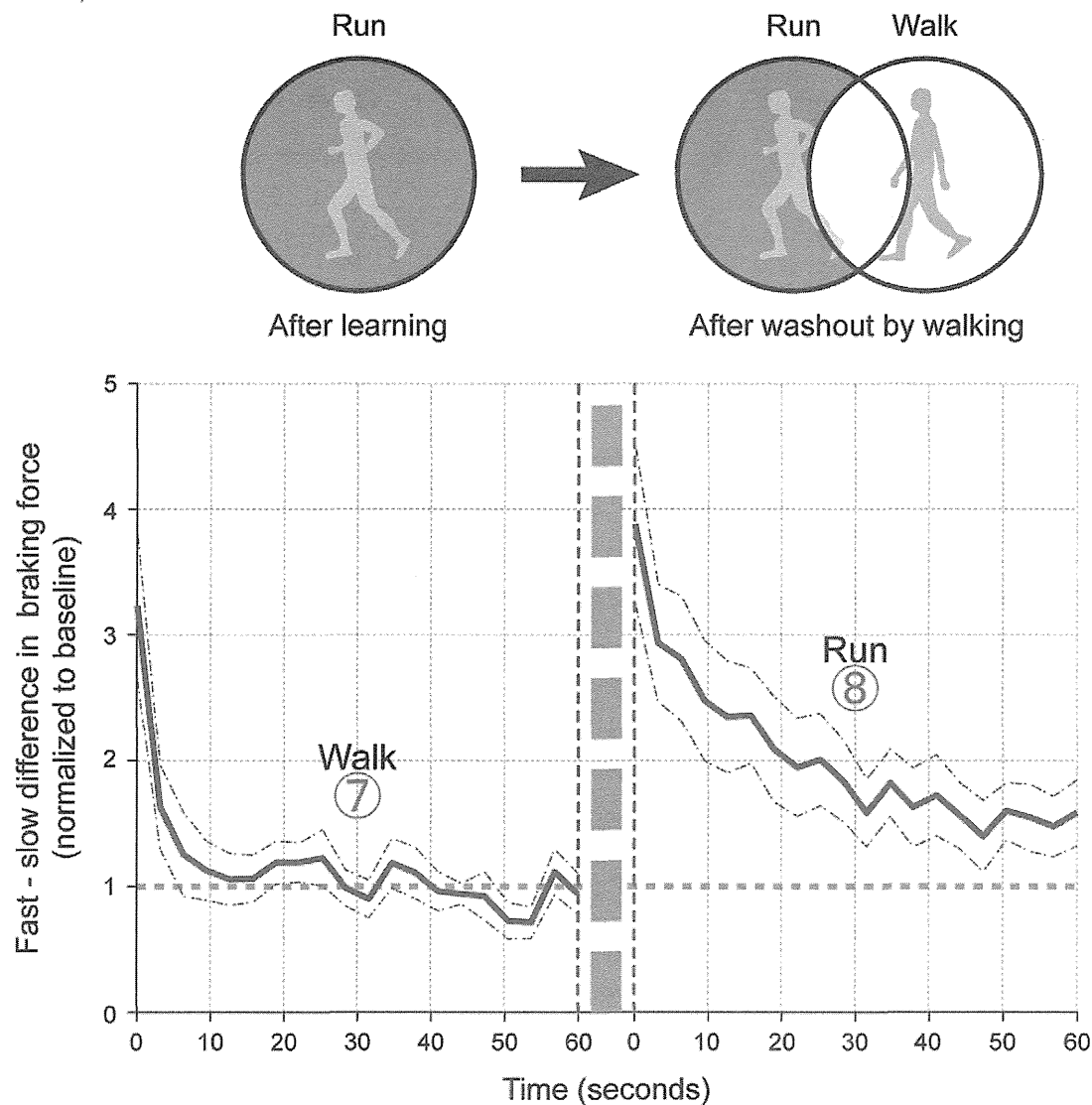
Figure 5. Degree of washout in the stored motor pattern in running by walking (first and second washout periods shown consecutively from Experiment 4). The asymmetrical movement pattern was evident with the initiation of running (red lines) despite a symmetrical walking pattern at the end of the first washout period in walking (blue lines), an indication of only partial washout (also described in the schematic figure). Data are presented as means (thick lines) and their standard errors of the mean (dotted lines).
doi:10.1371/journal.pone.0046349.g005

specificity in the locomotor center in the spinal cord, known as the central pattern generator (CPG).

First, in the emergence of the adaptive phenomena, the cerebellum is considered to play a significant role by recalibrating motor output that satisfies the task or environmental demand [20]. Given its function, any aspect of an aftereffect following adaptation is abolished in humans [17] and in cats [21] with cerebellar lesions. Morton et al. (2006) [17] reported that a predictive feedforward motor adaptation in splitbelt treadmill walking that is demonstrated to occur in healthy subjects [11,12,16] does not in patients with cerebellar damage. More direct evidence showed that plasticity of synaptic transmission efficacy in the cerebellum that was modified by concentration of nitric oxide (NO) played a significant role in locomotive adaptation in decerebrate cat [21]. Interestingly, regarding movement specificity, various aspects of

limb movement such as direction, velocity, acceleration and force have been demonstrated to be represented in the cerebellum, as shown by discharge rate in single unit recording in the cerebellum [22]. In the present study, since the subjects performed both walking and running under identical belt speed, in which the limb movements do not simply depend on locomotion speed but are demonstrated to differ across the modes [3], it is possible that there were different representation for each locomotive mode.

Along with the cerebellar function, the contribution of the descending neural drive from the supraspinal centers, especially those from the mesencephalic locomotor region (MLR) in the brainstem, provides an additional explanation for the mode-specificity. For example, in decerebrate salamander, electrical microstimulation at a particular site in the MLR resulted in a phase-dependent electromyographic (EMG) burst and conse-
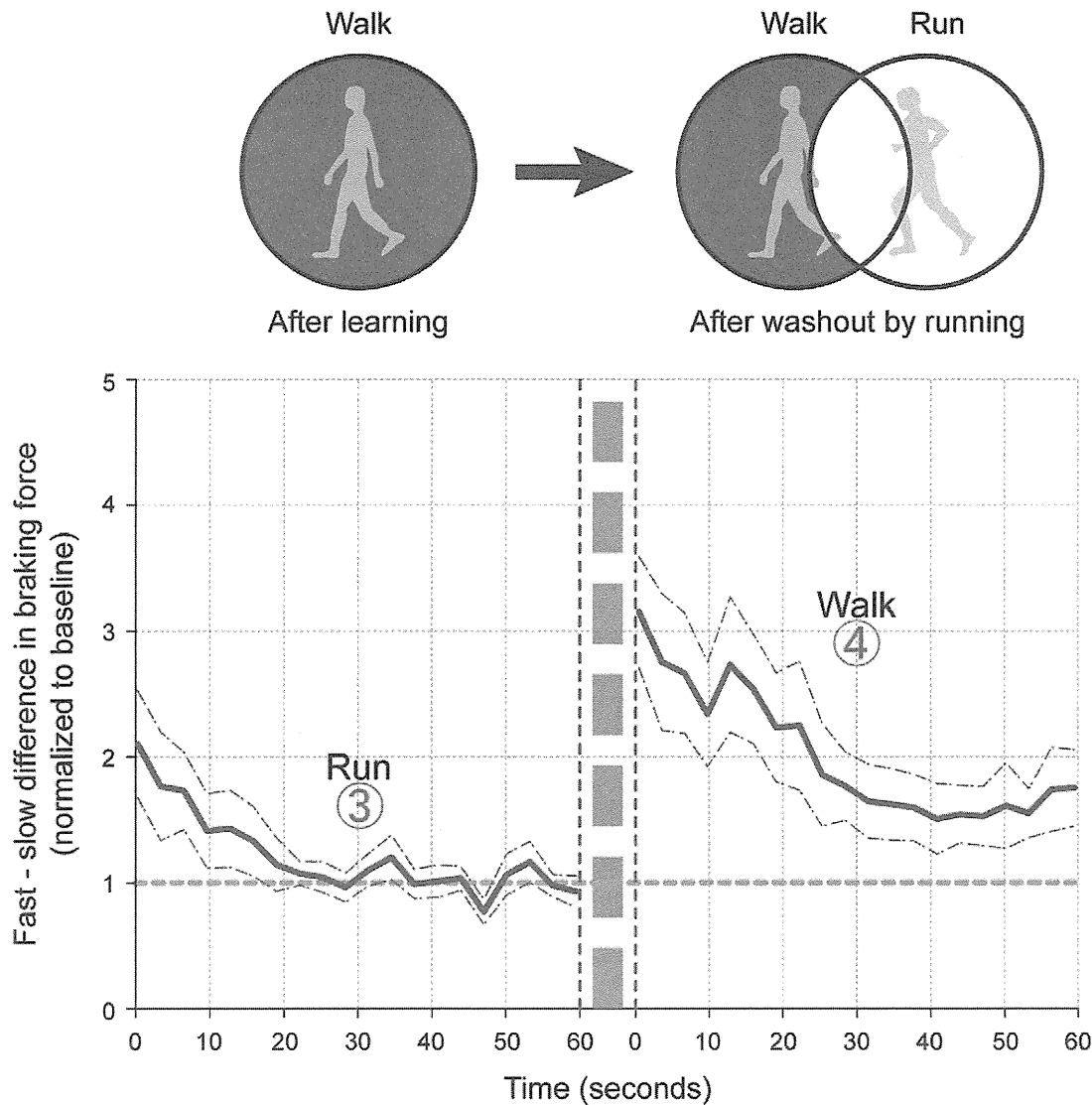
64

Figure 6. Degree of washout in the stored motor pattern in walking by running (first and second washout periods shown consecutively from Experiment 2). The asymmetrical movement pattern was evident with the initiation of walking (blue lines) despite the symmetrical walking pattern at the end of the first washout period in running (red lines), an indication of only partial washout (also described in the schematic figure). Data are presented as means (thick lines) and their standard errors of the mean (dotted lines). doi:10.1371/journal.pone.0046349.g006

quently locomotor-like movements of the body [23]. In the emergence of these behaviors, two different locomotor modes (stepping and swimming) were exhibited with different current intensities [23]. Or, more classically, an increase in stimulus intensity to the mid-brain in decerebrate cats walking on a treadmill caused them to gallop [24]. From these results, the intensities in the descending drive may significantly affect the decision of different locomotive modes. In the current study, although speculative, the gait pattern upon the initiation of walking after adapting to run was reactively disturbed (the prominent asymmetry in the first few seconds, shown by the light blue line in Figure 4). This reaction may reflect the component of running. That is, to accelerate the center of body mass upon acceleration of the treadmill by increasing the descending drive from the locomotor centers. Consequently, this could result in the partial emergence of the asymmetrical movement pattern previously acquired in running.

Regarding the specificity in the locomotor center in the spinal cord, on the other hand, it was recently demonstrated that specific sets of spinal interneurons are activated depending on locomotion (swimming) frequency in larval zebrafish [14]. Locomotion behavior in larval zebrafish was previously characterized as having two different modes [25]. One is the mode used to move routinely in water with lower movement frequencies and small yaw amplitudes, while the other is the escape movement with higher frequencies with larger yaws [25]. On the execution of these locomotor behaviors by zebrafish, McLean et al. (2008) [14] showed that, in contrast to motoneurons that are additionally recruited with increasing swimming frequencies following classic size principle, the activities in some sets of interneurons evident