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Journal of Physical Medicine and Rehabilitation Review Article

No Studies in Stroke Regarding Brain fMRI Activity and Pelvic Floor Muscle Training/Activation - Only Studies in Non-stroke Population: A Review of Neuroimaging Studies

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Abstract

Background: Positive effect on pelvic floor muscle training (PFMT) has been reported in poststroke patients with neurogenic lower urinary tract dysfunction (NLUTD). The effects were measured by bladder diary, pelvic floor muscle function, lower urinary tract symptoms, sexuality, and quality of life. However, measurement on brain activity seems to be missing.

Objective: To identify studies which report brain activity measured by functional magnetic resonance imaging (fMRI) as a response to voluntary pelvic floor muscles (PFMs) contractions and PFMT.

Methods: A literature search in which six databases was screened for this review.

Results: Fourteen studies were identified all published during 2005 - 2020. Twelve studies reported data of brain activity as a response to voluntary PFMs contractions and two as a response to PFMT. The participants (n=277) were respectively healthy adults (n=172, 62%), males with prostate cancer (n=22, 8%), females with stress urinary incontinence (n=10, 4%), older women with urge urinary incontinence (n=62, 22%), and Multiple sclerosis (MS) patients with detrusor sphincter dyssynergia (n=11, 4%). No studies in stroke patients were identified.

All identified studies focused primarily on the cerebral control of micturition circuit, whereas the brain activity as response to voluntary PFMs contractions only played a role in the investigations.

Conclusions: The identified studies indicate that fMRI even provide valuable outcome data supporting clinical outcome data and provide knowledge of the underlying mechanisms in the brain and its control of the bladder by PFMs contractions and PFMT. However, no studies in stroke patients were identified.

There is a call for studies using fMRI, providing knowledge of the brain activity as a response to voluntary PFMs contractions and PFMT in stroke patients with NLUTD.

Keywords: Brain activity, fMRI, Neurogenic lower urinary tract dysfunction, Outcome, Pelvic floor muscle training, Stroke

Abbreviations: BOLD: Blood Oxygenation Level Dependent; fMRI Functional Magnetic Resonance Imaging; LUTS: Lower Urinary Tract Symptoms; M1: Primary motor cortex; MRI: Magnetic Resonance Imaging; NLUTD: Neurogenic Lower Urinary Tract Dysfunction; PAG: Periaqueductal Gray; PFMs: Pelvic Floor Muscles; PFMT: Pelvic Floor Muscle Training; PMC: Pontine Micturition Centre; SMA: Supplementary Motor Area; SUI: Stress Urinary Incontinence; UUI: Urge Urinary Incontinence

Introduction

Neurogenic lower urinary tract dysfunction (NLUTD) [1] is highly prevalent in poststroke patients [2-7], leading to major impact on the quality of life (QoL) [6,8,9] and healthcare resources [10].

Pelvic floor muscle training (PFMT) has, over the past two decades, been recommended as first-line treatment for neurologically healthy patients with lower urinary tract symptoms (LUTS) [11-15]. Later on, a positive effect on PFMT in both male and female stroke patients with NLUTD have been reported [16-20]. The data indicating effect were measured on bladder-related outcomes such as bladder diary [16,18], pelvic floor muscles (PFMs) function [16,18], LUTS [16,18,19], sexuality [21] and QoL [19,22]. But measurement on brain activity seems to be lacking.

The central nervous system (CNS) controls the micturition cycle of storage and the voiding of urine. Micturition frequency in healthy adults with bladder capacity of 500 ml is typically about once every three to four hours, depending on fluid intake. Since the voiding takes two to three minutes, for 98-99% of the time, the bladder is in storage mode. In the healthy and continent state, when to void is determined by the perceived state of bladder fullness together with an assessment of the social appropriateness to do so. Bladder function is controlled by neural programs, which perform and locate to the pontine micturition centre (PMC) and are influenced by supra-pontine processes. The connections between the pons and the sacral spinal cord must be intact along with the peripheral innervation which arises from the pelvic and the pudendal nerves to innervate the bladder and the internal and external sphincter muscles to affect both storage and voiding.

The pelvic floor muscles (PFMs) is an important part of the adequate urethral closure function maintaining urinary continence. The PFMS is located deep within the pelvis and forms the bottom/base of the abdominal cavity. The median PFMs thickness at rest has been reported to be 9.3 mm (range 8.6 - 9.9 mm) increasing to 11.4 mm (range 10.8 - 12.5 mm) during contraction in healthy female [23]. The PFMs include posteriorly located by coccygeus and the elevator ani (M. puborectalis, M. pubococcygeus and M. iliococcygeus) [24-26]. The PFMs are comprised of both passive and active components. The passive support function is mainly contributed by connective tissues (ligaments, fascia). In contrast, the active support function is mainly due to the pelvic floor muscles, which can be contracted voluntarily to elevate the pelvic floor thereby counterbalancing increased abdominal pressure and maintain the normal position of pelvic organs [27]. The striated muscles include 70% of cases are the slow-twitch fibers (type I, aerobic oxidative) [28,29] and 30% of cases are fast-twitch fibers (type II, anaerobic-glycolytic) [30,31]. The PFMs can contract voluntarily and involuntarily contract and relax. The PFMs are directly innervated by S2-S4 efferents with the anterior urogenital diaphragm innervated by the pudendal nerve which arises from these sacral roots. Thus, the innervation needed for physiological bladder control is extensive, requiring supra-pontine inputs. Intact spinal connections between the pons and the sacral spinal cord must be intact, as well as the peripheral nerves [32].

PFMT aims to improve PFMs function. The training has to be in a systematic, intensive treatment program controlled by a specialized physiotherapist. The PFMT program consists of muscle awareness training, training of muscle strength, endurance and coordination. Details of the PFMT program has been published previously [16,18,33].

In nonhuman primates, studies have provided strong evidence of reorganisation following brain damage as a response to motor training [34,35] although, with variability [36]. In stroke patients, these variabilities are associated with the extent and location of the brain damage.

According to Rossini et al., the injured human brain poststroke goes through a process of reorganisation and adaptive brain changes appear to go in line with motor training and rehabilitation, leading to improved functional outcomes [37]. Early motor learning seems essential for a successful recovery, and motor learning mechanisms may be operative during spontaneous stroke recovery and interact with rehabilitative training [38,39].

Basic changes in the brain plasticity must be explored to improve functional rehabilitation in stroke patients.

Askim et al. reported in a longitudinal study, that motor network changes are associated with successful motor skill relearning after ischemic stroke [40] and Favre et al. reported in a meta-analysis that upper limb recovery after stroke is associated with the ipsilesional primary motor cortical activity [41].

Magnetic resonance imaging (MRI) is a non-invasive technique, which has been used in medicine and biomedical research since 1970. The MRI scan can show how the brain responds to different stimuli, enabling researchers to study both the functional and structural brain abnormalities in physiological disorders.

Functional MRI (fMRI) measures brain activity by detecting the changes in blood oxygenation and flow that occur in response to neural activity. The fMRI signal is not a direct measure of synaptic activities or action potential of cortical neurons. Instead, it results from the so-called blood-oxygen-level-dependent (BOLD) effect. An increase in neural activity in a cortical region increases local blood flow.

The fMRI data not only suggest an important role of the primary sensorimotor cortex in controlling motor actions but also indicate that the participation of multiple cortical areas may be essential for planning and executing a voluntary motor action. Therefore, brain imaging methods may be used to examine cortical representation and to predict clinical outcome and contribute to documenting the clinical outcome of the various treatments in a more ethology-based perspective.

An fMRI protocol has been tested for the first time for the short-time repeatability of patterns of brain activation provoked by bladder filling. The authors concluded that the technique provided a framework for comparing different fMRI protocols applied to bladder research [42].

The objective of this study was to identify studies which reported the brain activity measured by fMRI as a response to voluntary PFMs contractions and PFMT.

Materials & Methods

Search strategy

Electronic searches were performed of English literature with no preference of study design, Six digital databases (PubMed/MEDLINE, Embase, CINAHL, PEDro and Cochrane Library) were searched through the keywords "fMRI", "voluntary pelvic floor muscle contractions", "pelvic floor muscle", "pelvic floor muscle training" and "pelvic floor muscle exercise". In addition, articles in the reference lists of identified studies were hand searched.

Brain activity as a response to voluntary PFMs contractions (Table 1)

According to Fowler et al. [43] several neuroimaging studies in healthy adults have reported brain activities as response during PFMs contractions, although with divergent results [44-47]. Seseke et al. observed activity of the superolateral convexity of the semi-smooth cortex and the additional involuntary activity of the supplementary motor area (SMA) [46,47]. These divergent results of imaging studies have been explained by different PFMs exercises such as fast vs slow PFMs contractions. In contrast, Schrum et al. observed mostly activity in the SMA but without any differences between slow and fast PFMs contractions [48].

Seseke et al. measured the brain activity of voluntary PFMs contraction and relaxation in men by fMRI before and after prostatectomy.

In general, all participants had stronger activation during voluntary PFMs contractions than during relaxation in all regions before and after the prostatectomy [49].

Krhut et al. observed brain activity during bladder filling and by voluntary PFMs contractions in healthy females. The brain activity as a response to voluntary PFMs contractions was observed in the medial surface of the frontal lobe primary motor area (M1), bilaterally and left gyri's pre-centralis [50].

Rana et al. reported that voluntary anal sphincter contractions have distinct brain networks to coordinate muscle synergies during functional tasks [51].

Yani et al. examine the degree to which the PFMs representation is described between SMA and the M1, and how this representation is utilized to activate the PFMs in different contraction patterns. The authors concluded that PFMs representation is broadly distributed in SMA and M1 in humans [52].

Furthermore, Seseke et al. demonstrated brain activity in dorsal/ventral part of PMC as a response to voluntary PFMs contractions and relaxation measured by fMRI in a rest model comparing healthy controls with patients with multiple sclerosis (MS) and clinically proven detrusor sphincter dyssynergia patients [53].

Groenendijk et al., newly demonstrated in a study of healthy males, that 7-tesla fMRI can be used to visualize the brain areas involved in pelvic floor control in the whole brain of the single subjects and define the specific brain areas involved in PFMs contraction. Before the scanning, the participants were instructed to perform correct voluntary PFMs contractions and during the scanning the participants performed a cycle of voluntary PFMs contractions in 21.5 s followed by 19.5 s in rest in a cycle repeated 12 times [54].

Brain activity as a response to PFMT (Table 2)

Di Gangi Herms et al. investigated the neuroplastic changes occurring after PFMT in female patients with stress urinary incontinence (SUI). The PFMT were with EMG-biofeedback, and the training was performed for 12 weeks. The results demonstrated after PFMT, more focused brain activity in M1 and the SMA. Significant activation was also found in the insula right frontal operculum and the anterior cingulate cortex, suggesting changes in emotional arousal in micturition after the PFMT [55].

These changes in the brain activity were related to clinical improvement documented by a decreased number of incontinence episodes and increased EMG-active of the PFMs after PFMT.

The changes in EMG-activity were also correlated with heightened BOLD responses in the M1 and primary sensory cortical representation sites of the lower urogenital tract [55].

The findings showed that PFMT with biofeedback might not only improve muscle strength and thereby support urethral support but also optimize central control of PFMs, bladder sensation as well as reflect the emotional neutralization related to symptom reduction.

Griffiths et al. aimed to investigate in a study the underlying mechanism of brain-bladder control and therapy during bladder filling [56].

A sample of women ≥ 60 years old with ≥ 5 urge urinary incontinence (UUI) episodes per week were chosen to give bio-feedback PFMT for 8-12 weeks. The participants underwent fMRI during provocation of urinary urgency before and after training, while normal controls were evaluated once for comparison. After PFMT a reduction of UI episodes (≥ 50%) was demonstrated in 28 (46%) responders. For the fMRI, two different patterns of brain reaction were demonstrated between responders and non-responders. Moreover, the decrease cingulate activation appears to be a consequence of the improvement of UUI indicating by training while prefrontal deactivation may be a mechanism of contributing to the success of training [56]. The authors concluded that in older women with

UUI appears to be two patterns of brain reaction to bladder filling, and they seem to predict the response and nonresponse to bio-feedback assisted PFMT [56].

Based on these data reported by Griffiths et al. [56], Clarkson et al. supported the postulate, in secondary analysis, that responders and non-responders to therapy, may represent different subjects of UUI, one with more central aetiology and one without [57].

In the study by Griffiths et al. in older women with UUI and measured by fMRI, before and after PFMT, most neurological candidates were excluded. However, 7% to 9% of subjects in each subgroup had a history of a possible transient ischemic accident or mini-stroke without residual effect [56].

PFMT in neurological patients

Several studies in neurological patients with neurological diseases and NLUTD have reported a positive effect of PFMT. The diseases include MS [58-61], Parkinson's disease (PD) [62,63], Spinal Cord Injury (SCI) [64,65] and Stroke [16-22,66,67]. However, no PFMT studies in neurological patients with NLUTD have used fMRI as an outcome measure to evaluate the effect.

Results

In total, 14 studies were identified in this review. All the studies were published during 2005 - 2020. Of these, 12 studies reported data of brain activity as a response to voluntary PFMs contractions (Table 1) and two studies as a response to PFMT (Table 2).

The participants (n=277) were of both genders and reasonably healthy adults (n=172, 62%), males with clinically diagnosed prostate cancer (n=22, 8%), females with stress urinary incontinence (n=10, 4%), older women with urge urinary incontinence (n=62, 22%), and patients with MS and detrusor sphincter dyssynergia (n=11, 4%), whereas no studies in stroke patients were identified.

The brain activity was broadly located to PMC, PAG, SMA, M1 and modelling supratemporal regions. The location of brain activity as a response to voluntary PFMs contractions are presented in Table 1 and for PFMT in Table 2.

First author, year	**Study sample (N°)**	**Cortical region (main)**
Zhang, 2005 [44]	Healthy adults (n=12)	[2]SMA, bilateral [1]PMC Basal ganglia Cerebellum
Seseke, 2006 [47]	Healthy female (n=11)	[1]PMC [3]PAG Sensor-motor córtex Basal ganglia Cerebellum
Kuhtz-Buschbeck, 2007 [45]	Healthy adults (n=30: 15females and 15 males)	[2]SMA [4]M1
Seseke, 2008 [46]	Healthy adults (n=23: 11females and 12 males)	[1]PMC [3]PAG

Schrum, 2011 [48]	Healthy males (n=17)	[2]SMA [1]PMC Thalamus
Seseke, 2013 [49]	Males with clinical located prostate cancer (n=22)	[1]PMC [3]PAG Brainstem
Krhut, 2014 [50]	Healthy males (n=16)	[4]M1
Asavasopon, 2014 [76]	Healthy females (n=23)	[4]M1 [2]SMA [1]PMC
Rana, 2015 [51]	Healthy females (n=23)	[4]M1
Yani, 2018 [52]	no info	[2]SMA [4]M1
Seseke, 2019 [53]	Patients with MS[i] and detrusor sphincter dyssynergia (n=11: 8 females and 3 males)	Dorsal/ventral part of [1]PMC
Groenendiik, 2020 [54]	Healthy males (n=17)	[4]M1 [2]SMA Insula [5]MCG
[1]PMC: Pontine micturition centre; [2]SMA: Supplementary motor area; [3]PAG: Periagueductal grey; [4]M1: Primary motor cortex: [5]MCG: Midcingulate gyrus; [i]MS: Multiple sclerosis.		

Table 1: Studies reported brain activity as a response to voluntary pelvic floor muscle contractions measured by functional MRI.

First author, year	Study sample (N°)	Cortical region (main)
Di Gangi Herms, 2006 [55]	Females w. SUI[a] (n = 10)	[4]M1 [2]SMA
Griffiths, 2015 [56]	Older women w UUI [b] (n = 62)	Right ínsula; medial Pre-frontal Cortex; dorsal anterior cingulate córtex
[a]SUI: Stress urinary incontinence; [b]UUI: Urge urinary incontinence; [2]SMA: Supplementary motor area; [4]M: Primary motor cortex		

Table 2: Studies reported brain activity as a response to pelvic floor muscle training measured by functional MRI.

Discussion

In this review, published literature was investigated to identify studies which report brain activity measured by fMRI as a response to voluntary PFMs contractions and PFMT.

The identified studies were all recently published and occurred, in healthy adults or patients with voiding dysfunction. However, the identified studies focused primarily on the cerebral control of micturition circuit. At the same time, the brain activity as a response to voluntary PFMs contractions and PFMT measured by fMRI only played a role in the investigations.

In addition, even though there were many studies in neurologically patients with NLUTD which have reported a positive effect of PFMT, none of the studies have used fMRI as an outcome measure to evaluate the effect. Moreover, recently Harvie et al. identified in a meta-analysis, which regions in the brain were activated during the voiding phase of micturition, studies investigating PFMs contractions and studies with NLUTD were excluded [68].

The brain activity identified as a response to voluntary PFMs contractions and PFMT were broadly located to PMC, PAC, SMA, M1 and modelling supratemporal regions.

In addition, the motor system, studies using fMRI have consistently reported altered pattern of brain activity during activity or passive movement of a limb affected by stroke, compared with movements of healthy controls subjects [69].

Visualised changes in the brain activity as a response to PFMs contractions and PFMT measured by fMRI extend our knowledge to the underlying cortical processes and mechanism of the treatment in patients with voiding dysfunction, particularly if there are correlations between neuroimage observations and clinical data. In a study by Seseke et al. a higher level of brain activity measured by fMRI was reported even before and after prostatectomy in men diagnosed with clinical prostate cancer, when the participants performed PFMs contractions to mimic voiding compere to PFMs relaxation to mimic voiding [49]. This result supports the positive clinical results in a randomised controlled trial (RCT) by Tibaek et al. Evaluating the effect of PFMT before transurethral resection of the prostate (TURP) [70].

PFMT is a non-invasive treatment with no reported adverse effects. By the fMRI, as an outcome measure opens new possibilities for the goal to improve not only muscular strength-enhancing support of the urethra but also optimized cerebral muscular control of the PFMS, modulate bladder sensation as well as reflect the emotional neutralisation related to symptom reaction [63].

Cramer et al. reported, in a study of healthy controls and measured by fMRI, that there is a relationship between different squeezing force and neuronal firing rate in motor cortex activation [71]. Likewise, Dai et al. demonstrated relationship between muscle force measured by surface EMG and brain activation measured by fMRI [72]. In the study by Dai et al. *handgrip* was used performing the voluntary force. Thus, studies investing the relationship between different force levels of the voluntary PFMs contractions and brain activity are still lacked.

Several questions still need to be explored, such as: "Does the voluntary PFMs contractions and PFMT have an inhibitory effect on the overactive detrusor?"[73]; "Does a change of BOLD associated with increased PFMs function?" and "To which extent can the brain structures predict how well an individual will learn a motor task as a response to specific therapies?"[41].

According to Clarkson et al. the analysis of fMRI data among groups of subjects yields valuable insight in the bladder control, mechanisms whereas the fMRI is not yet appropriate for evaluation of brain's role in continence on an individual level [42]. Hence, according to Khavari et al., both data from clinical outcome measures and neuroimage outcome measures as fMRI must be applied as documentation in current and future studies focusing patients with voiding dysfunction [68].

Methodological consideration

This study involved several limitations.

First, the lack of statistical calculations based on the limited available data and the heterogeneous characteristics of patients.

Second, the lack of consistency in the used methods in the fMRI studies [74].

In a study by Kutch et al. focusing on brain structure and function for patients with Urologic Chronic Pelvic Syndrome, fMRI data were used and analysed from, the Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network because of the limitations of previous studies [75]. The MAPP Study protocol provides both baseline and longitudinal data allocated of a large cohort of patients and controls [75]. A similar approach might be considered, focusing on brain structures and function for patients with NLUTD treated with PFMT, to improve the evidence-base for development for future clinical studies, and ultimately, improving clinical management.

Perspectives

Patients with voiding dysfunction need proper diagnosis and treatment.

If brain activity as a response to PFMT positively effects bladder control perform increases and decreases effects on bladder control, we take a step towards understanding underlying mechanisms and its treatment effect. The next step must be to investigate brain activity as a response to voluntary PFMs contractions and PFMT measured by fMRI in large, homogenous groups and subgroups of patients with voiding dysfunction, particularly stroke patients with NLUTD where there is clearly a gap in knowledge.

We expect that the present study can serve as a basis for further investigations whether interventions like PFMT have an impact on cortical and subcortical activation patterns.

Conclusion

This review identified studies which indicate that fMRI even provide valuable outcome data supporting clinical outcome data and provide knowledge of the underlying neurophysiological mechanisms in the brain and its control of the bladder by voluntary PFMs contractions and PFMT. The findings underline needs for studies using fMRI as an outcome measurement in large homogenous groups and subgroups of patients with voiding dysfunction. In particular, there is a call for studies providing knowledge of brain activity as response to voluntary PFMs contractions and PFMT in stroke patients with NLUTD.

Conflicts of Interest

The author reports no conflicts of interest.

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