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Two-point discrimination responses in children with idiopathic toe walking: A feasibility fMRI study

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Abstract

Idiopathic toe walking (ITW) is a diagnosis given to children who walk with an absence or limitation of heel strike in the contact phase of the gait cycle, that are otherwise typically developing. There is emerging evidence that this gait pattern may occur in children who experience tactile sensory processing challenges. This feasibility study aimed to determine if children were able to respond to a sensory stimulus during a fMRI. Children aged between 8–16 years of age, with and without idiopathic toe walking were recruited from general public advertising. Participants were required to perform a two-point discrimination test (task block) and press a button without being tested (control block) during an fMRI using a standard block design. Activation differences were examined in the left frontal pole, left supramarginal gyrus, left parahippocampal gyrus, left paracingulate gyrus and the right superior temporal. Five children were in the typically developing (TD) group and three were in the ITW group. There were between-group activation differences in the decision-making block compared to the control block in the left frontal lobe, parahippocampal gyrus and the right superior temporal gyrus. There was greater variation in activation in the left supramarginal gyrus and the left paracingulate gyrus in the ITW group compared to the typically

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developing group. Based on this study a future sample size of 15 children per group will be required to detect an adequate effect across chosen regions of interest Conducting fMRI using two-point discrimination testing on this population is feasible. Further research is required with larger population sizes to determine if brain activation patterns during the sensory input decision-making process are different in this population.

Keywords
Idiopathic toe walking, functional MRI, sensory processing

Introduction

Idiopathic toe walking (ITW) is a gait condition present in up to 5% of typically developing children.[1] Key features of this gait type are that children with ITW walk on the balls of both feet, commonly reach all development milestones, have no indicators of neurological disease, and are commonly able to walk with their heels on the ground when requested.[2] There is little high-quality evidence supporting treatments for ITW,[3] leading researchers to continue seeking the reason for this gait pattern. While clinicians are left employing varied treatment options that are strongly family-led and appear to have country and professional variations.[4] Parents express frustration as a result of inconsistent treatment advice.[5]

Rising numbers of studies highlight that ITW may be a result of subtle neurological differences between children with ITW and their typically developing peers.[6] A large audit of birth histories of children with ITW, determined a higher rate of complications at birth compared to a normative population dataset including greater odds of prematurity, more admissions to a special care nursery, or greater numbers with low birth weights (<2500 grams).[6] Other studies found children diagnosed with ITW also have associated speech and language difficulties,[7] motor planning issues[8,9] and variable sensory processing or perception challenges.[8–12] It is unknown if these challenges resolve with time due to brain maturation, neuroplastic changes and life experiences, or have an ongoing impact. Sensory processing and perception is an area of recent focus to try to explain any subtle neurological differences in children with and without this gait pattern.

How children with ITW interpret and process tactile information is poorly understood, yet studies have identified inconsistent differences in children with ITW.[8–12] This means, some children with ITW have no issues with interpreting tactile information,[12] while others appear hyper or hyposensitive.[13,14] The peripheral and central nervous system integrates and processes pressure, vibration and texture input[15] to understand touch. This is through the most sensitive mechanoreceptors, Merkel's disks and Meissner's corpuscles found in the top layers of the dermis and epidermis.[16] Stimulating these mechanoreceptors through vibration has been investigated to identify sensory processing differences between children with ITW and typically developing peers.[12,13] Tactile stimulation has also been used in treatment trials with the use of whole-body vibration or different floor surfaces identified as a short-term means to normalize heel-toe gait in children with ITW.[10–12,17]

Investigating responses to the stimulus of the skin's mechanoreceptors can be undertaken through many different and reliable tests. Both pressure and vibration use the same types of receptors, Merkel's disks, Meissner's corpuscles, Ruffini's corpuscles and

Pacinian corpuscles for both identification and interpretation of touch.[15] Vibration testing has featured strongly in ITW research,[8,10,12–14,18,19] however given the addition of floor surfaces impact on gait,[11] it is feasible that using other pressure type touch testing should be investigated. One common and simple mechanoreceptor pressure test is the two-point discrimination (TPD) test. The TPD test is a test that children perform reliably[20] and with inexpensive equipment.[21] It is also a measure of both sensory perception and cognitive processes in decision-making.[20]

Understanding touch responses using two-point discrimination has been explored through fMRI studies in adults.[20] Adults consistently exhibit activity in the primary sensory and parietal cortices during two-point discrimination.[20,22] It is unknown if children exhibit similar brain activation patterns during two-point discrimination testing and if they are able to perform the task in an unusual environment. It is also unknown if children with ITW activate the same parts of their brain during this sensory challenge. This feasibility study aimed to determine if children were able to respond to sensory stimuli during fMRI. Secondary aims included gathering preliminary task-related brain activation data to inform a future sample size to investigate any differences in brain activation patterns between typically developing children and their peers who were diagnosed with ITW.

Materials and methods

This study was approved by the Monash University Ethics Committee (MUHREC17825) and images were acquired at the Monash Biomedical Imaging facility between July 2019 and March 2020. Eight children aged between eight and sixteen years participated in this study. All parents gave written informed consent and children assented before participation. It was planned that 10 children would be involved in the study however recruitment ceased early due to the Coronavirus pandemic. All parents of participants reported an absence of any neurological or psychiatric problems that could influence sensory testing. Five children walked with a heel-toe gait and three participants had a diagnosis of ITW. Children with ITW were observed to make heel contact during visual gait observation when requested by the research team, and their diagnosis was confirmed by at least two health professionals and through a secondary screening using the *Toe Walking Tool*.[2]

Prior to the MRI, the two-point threshold was determined using a sequence whereby the dorsum of the forefoot was touched in a 5 cm diameter area with one or two touches using a plastic 150 mm Vernier caliper (Autobarn, Australia) (Figure 1). This sequence involved establishing the upper and lower limits of reliability. The distance between points was gradually reduced until the participant reported three accurate one and two points in a row. The caliper was locked at this distance for subsequent testing while the child was in the MRI.

Participants were familiarized with the MRI and testing process by using a mock MRI machine. This machine featured a sliding bed, helmet, and projected usual MRI sounds at a similar intensity as a real MRI. Participants were also oriented to the process where they would press a button in response to a question on the screen and subsequent tactile input delivery. Once the participant was familiar with the process, they were introduced to the scanning room, hand-held buttons and emergency button. The participant was then assisted into the supine position on the MRI sliding bed. Movements of the head were reduced using padding and a helmet to prevent motion artifacts during MRI scanning.

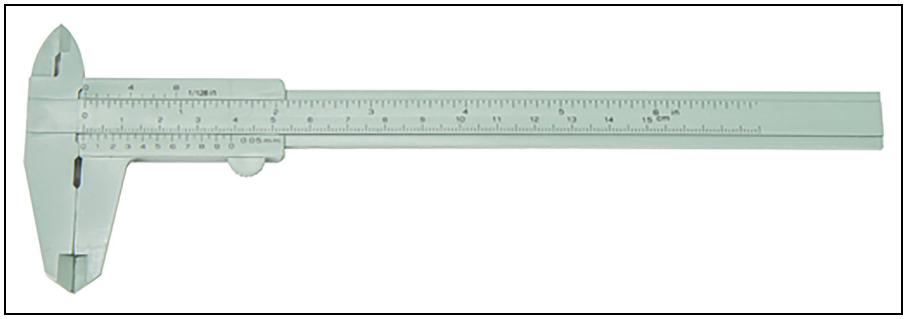

Figure 1. 150 mm Vernier calliper (Autobarn, Australia). A plastic vernier caliper with the ability to accurately measure the distance between two points. Used by researchers to determine the individual's TPD threshold, and test either one or two points whilst in the fMRI.

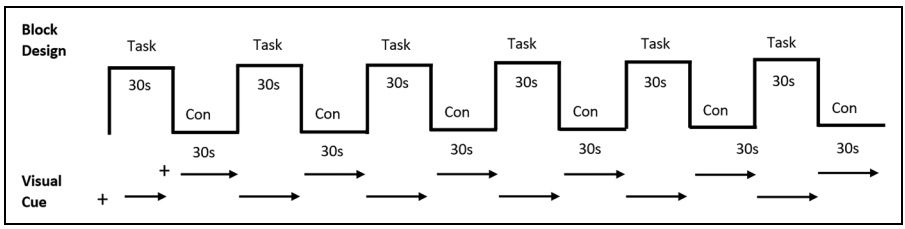

Figure 2. Experimental design. A standard block design featuring alternating 30-s blocks of the task (determining one or two points) and the control block (pushing the left or right button as requested). A visual cue was given to tell the participant what was required. Con = control block, s = seconds.

Children also wore ear plugs to reduce the intensity of the MRI sounds. During MRI scanning, tactile sensory stimulation consisting of either one or two points was delivered to the dorsum of the left foot in a set, randomized sequence. This random sequence was identical for every participant. During the scan, the participant viewed instructions on a screen, informing them to press the corresponding button when they perceived one point (the left-hand button) or two points (the right-hand button).

The fMRI protocol utilized a standard block design. There were two blocks, a task block, and a control block. Block 1 was the task and Block 2 was the control (Figure 2). In the task block, the stimulus was delivered 6 times by the researcher for 2–3 s, followed by a 2-s break. The participant responded to whether they felt a one-point stimulus or two-point stimulus by pressing the corresponding button. In the control block, the participants were not required to perform any discrimination and were provided with visual instructions to push the buttons in a set left only or right only sequence 6 times. The screen was enhanced with the words *left* and *right* and also on the left and right of the screen to minimize any handedness confusion. Blocks 1 and 2 were delivered in an alternating fashion for a total of 6 times each. This was repeated two to three times depending on each participant's tolerance to staying in the MRI machine. A control block was included to ensure that the analysis picked up activation from the TPD decision-making process, and not the pushing of the button to indicate response.

MRI parameters

All scans were performed using a 3T MRI machine (3T SKYRA, Siemens Healthcare, Erlangen, Germany with software version syngo MR E11C). T1 structural scans were acquired using an MPRAGE sequence with the following parameters: Repetition time (TR) 1900 ms, Time to echo (TE) 2.6 ms, Inversion time (TI) 900 ms, flip angle 90, voxel size $0.9 \times 0.9 \times 0.9$, matrix size 288×288 field of view 256 mm. The functional MRI echo planar imaging (epi) sequence was acquired using TR 2000 ms, TE 31 ms, flip angle 90°, voxel size $3 \times 3 \times 4.5$ mm, matrix size of 64×64 and FOV 192 mm.

Data analysis

The following pre-statistics processing was applied; motion correction using MCFLIRT[23]; non-brain removal using BET[24] spatial smoothing using a Gaussian kernel of FWHM 6 mm; grand-mean intensity normalization of the entire 4D dataset by a single multiplicative factor; highpass temporal filtering (Gaussian-weighted least-squares straight line fitting, with sigma = 50.0 s). Standard motion correction parameters were used during the analysis. The average "absolute" motion metric for the toe walkers was 0.79 and 0.38 for typically developing children. Registration to high-resolution structural and/or standard space images was carried out using FLIRT.[23,25] Each participant's functional images were normalized to the Neuroimaging & Surgical Technologies Lab 4.5 to 18.5 asymmetric atlas[26,27] and were statistically analyzed with FEAT (FMRI Expert Analysis Tool) Version 5.4, in FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). Higher-level analysis was carried out using a fixed effects model, by forcing the random effects variance to zero in FLAME (FMRIB's Local Analysis of Mixed Effects).

Contrasts were performed to identify regions showing increased activity during two-point discrimination decision-making compared with the control block. Regional blood oxygen level-dependent (BOLD) percentage signal changes were extracted from regions of interest in the left frontal pole, left supramarginal gyrus, left parahippocampal gyrus, left paracingulate gyrus, and right superior temporal gyrus. Regions of interest were transformed into each participant's own native space and BOLD signal responses were extracted for each run, for each participant using the feat query.

The fMRI-based power analysis employed a novel method implemented in the fMRIpower software package (fmripower.org).[28] This method estimates power for detecting significant activation within specific regions of interest, with the assumption that the planned studies will have the same number of runs per subject, runs of the same length, similar scanner noise characteristics, and data analysis with a comparable model. The effect sizes have been expressed in standard deviation (SD) units, which is analogous to the Cohens ∂ measure.

Results

Participant information including age, sex, height, weight, and percentage of correct responses to stimulus are in Table 1. There were five children (mean age = 10.4, SD = 2.58 years) in the typically developing group and three children (mean age = 10, SD = 0.82 years) in the ITW group. All eight participants fully completed at least two scan

sequences, with no early scan cessation or pausing. All children were visually observed responding to the stimulus by pressing the buttons on the remote by the researcher. Six participants generated task and control block data allowing for the accuracy of their responses to be calculated. Accuracy data was unable to be determined for two participants' results due to equipment malfunction on the day of testing. These two participant fMRI results were still included in the analysis due to full completion of the task and control blocks of testing aligning with the secondary aim of the study (Table 1). Participants in the ITW group had a higher TPD accuracy (mean = 70.14, SD = 4.91) compared with TD participants (mean = 48.26, SD = 8.21). Contrastingly during the control block, ITW participants had a lower accuracy (mean 92.36, SD = 2.95) compared with the TD participants (mean = 93.40, SD = 11.37).

Table 2 provides a summary of shared and between-group differences during task responses. Both the typically developing group and ITW had greater activation present during the task block compared to the control block in the left Lingual gyrus and the right occipital lobe (Figure 3(a)). The control and ITW group had a mean percentage signal increase of 0.256 (0.319) and 0.134 (0.130) and 0.122 (0.029) and 0.159 (0.167) respectively in the left Lingual Gyrus and right occipital lobe.

There was greater variation in activation in the left supramarginal gyrus and the left paracingulate gyrus in the ITW group compared to the TD group. In the left paracingulate gyrus the mean percentage signal change was similar for both groups (0.070% in the ITW group and 0.097% in the TD group), however, the TD group had an SD of 0.136, and an SEM of 0.061, compared to SD 0.0262 and SEM 0.151 in the ITW group (Figure 4). Similarly, the left supramarginal gyrus showed a similar mean for the TD group and

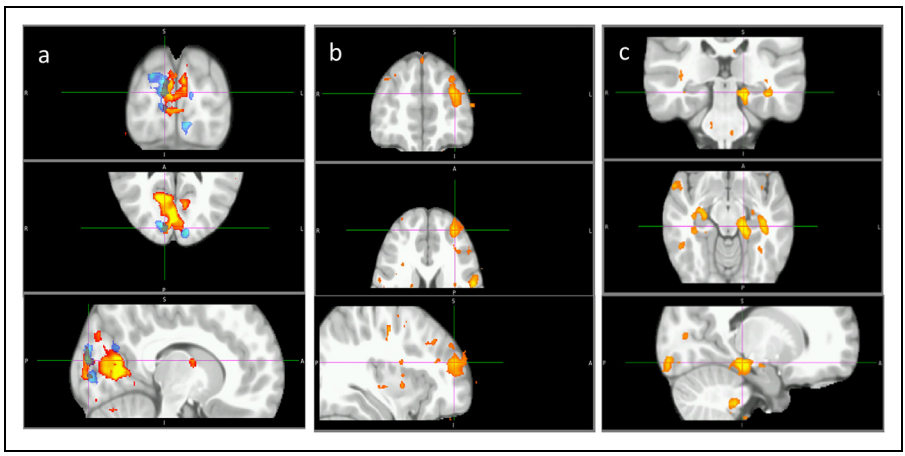

Figure 3. Brain activation in identified regions of interest. (a) R Occipital lobe, (b) L Frontal lobe (c) L super temporal gyrus. Images from top to bottom show the coronal, transverse and sagittal planes respectively. The fMRI images show between-group differences when performing the task is greater than the control block. (a) shows both the ITW and TD group on the same image indicating a shared region of activation. (b) shows an area that the TD group activates more than the ITW group and (c) shows an area that the TD group activates more than the ITW group.

Table 1. Participant information.

Participant	Group	Age	Sex	Height (cm)	Weight (kg)	2ptD (mm)	BMI (Kg/m^2)	Task Accuracy %	Control Accuracy %
1	Control	13	Male	151.0	40	1.4	17.5	56.94	100.00
2	Control	8	Female	140.0	31	2.0	15.8	37.50	98.61
3	Control	14	Male	168.0	47	2.0	16.7	47.22	98.61
4	ITW	11	Male	154.0	40	1.4	16.9	66.67	94.44
5	Control	9	Female	140.5	36	1.5	18.4	—	—
6	ITW	10	Female	147.0	30	1.3	13.9	—	—
7	ITW	9	Female	144.0	40	1.5	19.3	73.61	90.27
8	Control	8	Female	138.5	28	1.4	15.8	51.39	76.38

Table 2. Shared and between group activation regions of interest where R = right and L = Left and BA = Brodmann's area.

Region	R or L	Design	BA	X axis	Y axis	Z axis	p	Z Score
Lingual Gyrus	L	Group mean	18	−4	−67	4	0.001	3.01
Occipital Lobe	R	Group mean	17	11	−91	14	0.003	2.74
Paracingulate Gyrus	L	Controls > ITW	32	−13	18	43	0.003	2.73
Supramarginal Gyrus	R	Controls > ITW	40	56	−43	33	0.014	2.19
Frontal Lobe	L	Controls > ITW	9	−33	50	21	0.009	2.36
Parahippocampal Gyrus	L	ITW > Controls	35	−17	−30	−12	0.004	2.62
Superior Temporal Gyrus	R	ITW > Controls	42	69	−21	10	0.026	1.94

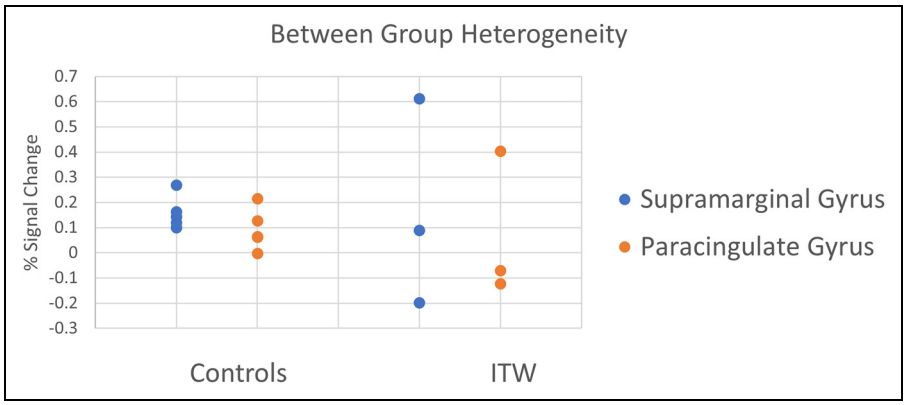

Figure 4. Signal change to demonstrate between-group heterogeneity in the L supramarginal gyrus and L paracingulate when the task > control block. Using fMRI data analysis, percentage signal change for the supramarginal gyrus and paracingulate gyrus in both the TD and ITW groups demonstrate between-group heterogeneity. The data is taken from the ROIs when the task is greater than the control block.

ITW group 0.158 and 0.167 respectively with the TD group having a SD 0.066 and SEM 0.029 compared to a SD 0.411 and SEM 0.237 for the ITW group (Figure 4).

We found more activation in the left frontal lobe during the task in the TD group compared to the ITW group (Figure 3(b)). The percentage signal change mean (SEM) for the TD group was 0.161 (0.072) compared to −0.045 (0.109) for the ITW group (Figure 5).

Conversely, there was more activation in the left parahippocampal gyrus and the right superior temporal gyrus (Figure 3(c)) during the decision-making process in the ITW group compared to the non-toe walking group. The average increase in percentage signal change was 0.252 (0.97) compared to −0.115 (0.023) for the left parahippocampal gyrus and 0.289 (0.168) compared to −0.021 (0.046) for the superior temporal gyrus (Figure 5).

Results indicate that an appropriate sample size for future studies would be 15 participants per group. If a study recruited 15 participants, we will have at least 80% power to

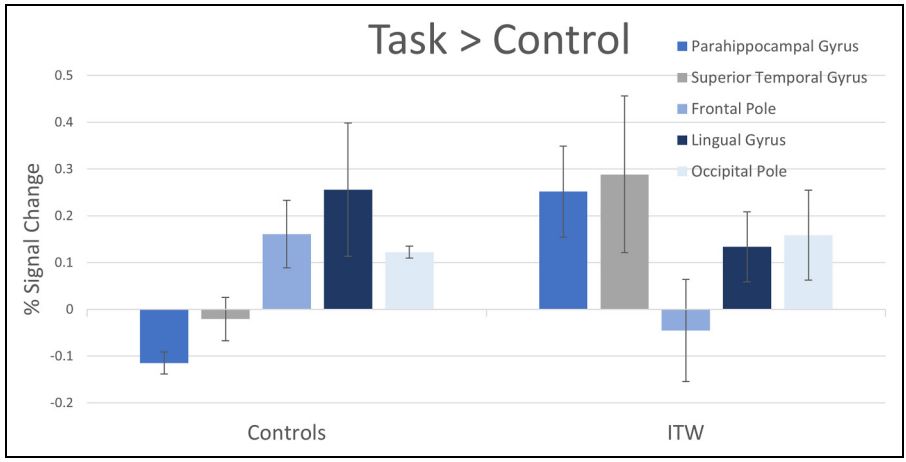

Figure 5. Between-group signal change when the task > control block. Using fMRI data analysis between group activation differences are shown for the parahippocampal gyrus, superior temporal gyrus, frontal pole, lingual gyrus and occipital pole. This graph shows where the activation is greater during the task compared to the control phase for both the ITW and TD groups.

detect an effect of 1.34 with a p-value threshold of 0.001 for a 2-sided hypothesis test in the left frontal lobe. With 11 participants we would have at least 80% power to detect an effect of 1.923 with a p-value threshold of 0.001 for a 2-sided hypothesis test in the parahippocampal gyrus. Averaging across multiple regions of interest suggests that 15 participants per group is suitable for future studies.

Discussion/conclusion

This feasibility study demonstrated that children within the age group of 8–16 could perform the sensory task with variable accuracy while undergoing fMRI. We identified that 15 participants per group would be required to fully test the hypothesis of children with ITW activating different neural pathways during sensory tasks. This study obtained interesting preliminary results, which highlight insights into variations in sensory processing abilities between children with and without ITW. These results could be from brain maturation or neuroplasticity differences.

The brain regions identified as responding differently between the groups are also known areas of interest that respond during sensory decision making. These brain regions are known to activate during touch identification,[20,22,29] touch discrimination[20,22,29] and touch response.[22] The Inferior parietal lobule plays a role in somatosensory discrimination, in particular, discrimination or identification of one point or two touches during two-point discrimination.[22] The supramarginal gyrus (Brodmann's area 40) is also thought to play a major role in two-point discrimination and somatosensory discrimination[20] The paracingulate gyrus has been associated with visuospatial processing and episodic memory[29] and the parahippocampal gyrus thought to play an important

role in spatial memory.[29] While our participants demonstrated activation in these brain regions, activation was also significantly more heterogeneous for the ITW group in the supramarginal and paracingulate gyrus. This is not the first time that children with ITW have had variable responses to sensory identification tasks. For example, three studies using the same vibration perception thresholds protocol and equipment identified large differences between children with ITW gait compared to typically developing peers, one study finding no difference between the groups, while two studies found large differences.[12–14]

Motor skills and complex movement patterns in children mature during growth and as children are exposed to more challenging environments. Children with ITW are known to demonstrate high variation in ability and at times, delays in fundamental motor skills, complex movement patterns and in executive functioning.[30,31] It is thought that the frontal lobe plays a leading role in decision-making and executive control and function.[32] This leads to reasoning, learning, and creative abilities while making decisions and adapting behavior to the task or environment.[32] This preliminary finding of higher activation in the left frontal lobe region in children within the TD group compared to children in the ITW group, supports clinical observations and research findings of children with ITW being delayed in these skills.

Despite this study not requiring any auditory response during the testing, a novel finding of group differences was in activation in the superior temporal gyrus. This region assists with auditory processing and language.[33] It is possible that the loud MRI environment resulted in high activity in this region during the task phase. Auditory interference was reduced through the use of earplugs and padding in the helmet, however, some children may be more sensitive to making complex sensory decisions in loud environments. It is unknown why this would otherwise occur, and greater numbers of participants would enable the determination if this was an artifact of sample size or indeed, relating to processing challenges exhibited by children within the ITW group.

Whilst not an aim of this feasibility study, it is important to note that both TPD and control accuracy during the MRI varied greatly in both the ITW and TD groups. This is likely due to a combination of reasons. One is accuracy in the TPD and the second is the experience of MRI during decision making. Future research in this population should therefore then replicate threshold testing with the number of responses required within the MRI block protocol (six correct responses) as opposed to the three used in this study to determine the threshold. Additionally, greater orientation should be given to explain the process through the use of noises in the mock scanner to ensure children are comfortable and able to focus on the test.

Untangling why some children toe-walk and are given the exclusionary diagnosis of ITW continues to be a work in progress. This research builds on the evidence of subtle variation in sensory processing abilities already observed between typically developing children and some children with ITW.[6,8,11–14] However, clinicians should continue to use tools with acceptable validity and reliability for measurement of the impact of sensory processing difficulties when treating a child with ITW, and not use these preliminary findings as fact at all ITW results from sensory processing difficulties. These preliminary findings further highlight the opportunity for studies to understand how sensory processing affects movement and executive functioning skills, particularly in children.

Testing this protocol with other children who demonstrate toe walking gait such as children with toe walking related to autism spectrum disorder or cerebral palsy could also help researchers understand any other neural difference between different groups of children who toe walk. Lastly, researchers should consider comparing brain volumetrics as previously recommended in research in ITW populations.[6] Brain volume reduction has been correlated with motor and cognitive impairments[34] therefore, building a program of research comparisons brain volumes, fMRI, with functional motor skill assessment and executive motor planning comparisons may be the key to understanding why some children develop this gait pattern that is challenging to address. It is proposed that gross morphological variance between the T2 weighted brain scans and a diffusion scan should also be included in future studies. Children with ITW commonly do not have medical imaging as part of their exclusionary diagnosis therefore limited imaging studies have been conducted on this cohort. We propose that future studies should consider obtaining these images as part of any testing protocol as they will enable further investigation into if this gait type may be associated with subtle brain volume differences. Despite the limitations of sample size, this feasibility study highlights future research opportunities.

Conclusion

This study has demonstrated that conducting fMRI research on this population is feasible and may reveal differences in somatosensory responses that aid in the understanding of the condition. The results suggest that there may be brain activation differences present between the typically developing group and children with ITW. Additionally, an appropriate sample size of 15 participants per group is required for a future study.

Study approval statement

This study protocol was reviewed and approved by the Monash University Ethics Committee, approval number MUHREC17825.

Consent to participate statement

Informed written consent was obtained for both the child and the parents/guardian.

Consent to publish statement

Written informed consent was acquired from the participant's parent/guardian for publication of their brain imaging and relevant information.

Data availability statement

The data that support the findings of this study are not publicly available due to the study ethics approval but are available from the corresponding author [JD] upon reasonable request

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Michael J Farell is an adjunct associate professor. He trained and worked as a physiotherapist before starting his research career. He received the NHMRC Neil Hamilton Fairley Fellowship and led the Interoception Imaging team at the Florey. He joined the Department of Medical Imaging and Radiation Sciences at Monash University, Australia as an associate professor in 2014.

Jessica Kolic graduated from Monash University in 2017 with a bachelor of physiotherapy (Honours) advanced research. She is currently a practicing physiotherapist at Northern Territory

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Michael Fahey is a researcher at Monash University, Head of the Paediatric Neurology Unit at Monash Medical Centre, co-founded a mitochondrial clinic and works in neurogenetics clinics at the Royal Melbourne and St Vincent's Hospitals. He is currently collaborating on research into treatments for Cerebral Palsy with researchers at the Ritchie Centre, part of the Monash Institute of Medical Research, Australia

Cylie Williams is an associate professor. She is a podiatrist, researcher, and educator in the School of Primary and Allied Health Care at Monash University, Australia. She has extensive clinical experience in all health care settings, with a particular focus on paediatric lower limb conditions. She is a leading expert in idiopathic toe walking.