# Analysis of brainstem activitywith fMRI during low-level of pain- a feasibility study with innocuous cold stimuli

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## Abstract

**Background:** In functional magnetic resonance imaging (fMRI) studies, there are limitedpublished data on the functional map of the human brainstem.

**Objective:** To assess the feasibility and to map the neural activity in the human brainstem with Fmri by equal intensity by low-level of thermal stimuli on the peripheral sensors of the skin.

**Patients and Methods:** Functional magnetic resonance imaging studies of the brainstem were carried out on 6healthyindividuals in a 3T MRI machine. A noxious thermal stimulus was applied on the peripheral sensitisation nerves on the arm. Functional magnetic resonance imaging data spanned from the brainstem location by a 32-head channel and analyzed using a fixed-effects General Linear Model to discriminate signal intensity changes from physiological motion. The results were normalised and combined to show the activity at each location on a voxel-by-voxel basis. Areas of physiological activity were recognized with comparison to the number of atlases.

**Results**: Noxious and innocuous related activation clusters were approved in this applied method. There were considerable activity in the midbrain, pons, medulla and reticular formation. The results of this pilot study are similar and in some anatomical regions even better with head coils than obtained with previous functional magnetic resonance imaging spinal coil studies. We obtained evidence of localization of the following nuclei by using this method, as follows: major activities in the inferior anterior parts of pons and the junction with medulla includes the (olive and pyramids),superior cerebella pundicle, rostral portion of medulla (RMV), Broadmann areas [5,2] touch and temperature sensation areas with the innocuous stimuli; activation in the left side of the medulla the (olive and pyramids), the left side of pons, the left side of midbrain, Broadmann area [5,7] pain and temperature sensation areas with noxious stimuli.

**Conclusion**: This pilot study provides useful evidence flow-painful and innocuous information transmitted between the peripheral nervous system and the central nervous system in healthy participants. It also demonstrates how peripheral sensitisation induces physiological changes in the brainstem correlates with noxious and innocuous thermal transmission.

**Key words:** FMRI, pain, brain stem, PAG, RVM, midbrain, rostral ventromedial medulla, pons.

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## Introduction

Acute and chronic pain affects millions of people in the world and contributes substantially to disability, morbidity, mortality and results in demands on the health care system[1]. More than one third of the population suffer from a type of chronic pain during some part of their life. It is estimated that about 50% of these disorders restrict daily life style activity which is associated with a reduced quality of life [1].

Initial studies which tried to understand the effects of pain date back toAD980-1037 which significantly noted that the brain was an organ of feeling and placed pain into a sphere of sensation[2]. Interestingly, until recent day pain-management strategies are still insufficient, for many reasons including: [1] clinical challenges and confounding elements; [2] difficulty to deal with various individuals with one objective tool [3] the difference between pain complaint and pathological condition for example pain type (acute or chronic) [3].One of the human anatomical pain areas within the nervous system which is still not understood with fMRI is the brain stem [4]. In addition to being involved in the regulation of autonomic functions and maintaining vital circulatory and respiratory functions, the brainstem and midbrain structures have been implicated in the descending modulation of pain processing[5].

When nociceptors become activated by a stimulus, they send out signals to the spinal cord. Consequently, these signals will be transformed through the spinal cord to the brainstem and then to the brain. During these transmissions to the brain, there are several areas which are involved in pain processing and will be activated in the brainstem [6][7].

FMRI based on BOLD contrast has achieved a significant role in the study of the human brain and its function[8]. It focuses on both, the characterisation of normal brain activity and applying its utility in clinical practice. While there is considerable amount of research dealing with activation of the cortical, relatively little information exists on functional imaging of subcortical pathways and mapping [9][10]. Functional magnetic resonance imaging of the brainstem has a number of challenges due to special anatomical and physiological condition in this part. The heartbeat, blood flow, cerebrospinal fluid movement, related motion artifact due to the pulsatile nature of surrounding arteries and tissue deformation cause a relative amount of artifacts in FMRI images[10]. Furthermore, when imaging the brainstem structures, there are complex minute structures within the anatomy arranged in a compact nature that are imaged in the millimeter range in the resolution of functional imaging. However, with new techniques and developments of algorithms it is now possible to perform an FMRI on the brainstem. Therefore, the importance to evaluate brain activations in smaller brain structures in a reproducible and perceptive way would add greater and more valuable information to the existing protocols and research in this field [11].

So the primary goals of this pilot study were to assess the feasibility and to map the neural activity in the human brainstem with Fmri by equal intensity by low-level of thermal stimuli on the peripheral sensors of the skin.

## Patients and Methods

### Study cohort

Six volunteers with an age range between25 to 40 years were used in this study. Only male participants were included to avoid any gender associated differences in

pain perception and modulation[12]. All participants were right handed as assessed by the Edinburgh Handedness Inventory[13]. Then they were interviewed face to face and then asked to answer a general health questions to exclude any neurological disorders, previous injury to the brain or any skin diseases following the instructions of the contraindication to cold sensation any peripheral injury that would affect the sensitivity of their hands and any MRI safety risks (pacemaker, implants, etc) [1]. Participants were screened for contraindications to MRI and did not take any analgesics or antiphlogistics 48 hours prior to the investigation.

All participants received detailed information about the experimental procedure, were free to with draw from the study at any time and gave written informed consent. All procedures were approved by the local ethics committee.

**Study protocol**

The study protocol was based on two sessions, the first session included a psychophysical testing session by a questioner to evaluate each participants experience to significant pain sensation. The second session included the FMRI scan session in addition with a questionnaire. Volunteers were imaged in a 3T MRI Siemens (MAGNETOM® Skyra) machine. A four repeated measures design was included for both experimental sessions. During the second session which used the fMRI, the thermal stimulus was applied in parallel with the acquisition of the fMRI brainstem scan.

**First session the Psychophysical Testing**

Prior to experimentation, subjects were informed with a description of how to rate pain intensity and unpleasantness. After each stimulus, subjects were instructed to report their pain intensity using four point numerical scale; where 0 = would not be seen in the person with true pain (no more than a sensation of cold) and (1-4) = pain score according to intensity.

The higher the pain score the greater the pain. The participant's hands were initially marked (approximately 5 cm above where the wrist joint) so that a constant location was used for the stimulus which consisted of a plastic cup of ice with 2 cc of water approximately (0-5 C0) for a duration of 19 seconds. The added (2 cc) of water in cup was to insure that the base area of the stimuli was cold on the group marked area uniformly. This site was chosen as it is commonly a frequent used site to stimulate the medial nerve [1].

**Second Session Imaging**

The second session of this study was performed after two days. The participants were instructed to focus on the stimulus throughout each scanning [14]. To avoid any extra-pyramidal factors such as anxiety and negative emotions or environmental noise created during the scan. The same stimulus was applied as explained in the first testing session however a plastic bag of (40 micron thickness according to the UK standard for polythene bags) was used to avoid any spillage of the contents in the cup. The thermal stimuli was put on the participant’s right hand 5cm above his wrist joint, with the same location, but contralateral to the arm that the psychophysical testing was performed on the previous session. Stimuli were applied in a block paradigm consisting of 6 stimulation periods of 19 seconds duration for the same thermal range (0±5), interleaved with baseline periods of 19 seconds in which no stimuli were applied, and an initial baseline of 19 seconds for a total of 3 minutes and 48 seconds for each block.

**Block Paradigm for Each Stimulus**

The stimulus was applied per run at six time intervals with baseline periods and in a (19 C0) room temperature. The total scan time for a single run was (3 minutes and 48

seconds). Each grouped 4 runs. The stimulus was applied by the experimenter who was in the scanner room throughout the duration of the experiment.

**Acquisition of FMRI data**

A high-resolution structural scan was acquired using a series of T1-weighted images according to following parameters: TR = 22ms, TE = 2.45 ms, matrix size 256 × 256,in-plane pixel size (1 × 1 mm2), flip angle 90°, slice thickness 1.6 mm. The number of slices is 176 and the duration of the scan is 6 minutes. A32-head channels were used for both acquisitions; fast suppression inversion time with 18 ms applied too with the structural scan t. The acquisition of fMRI was performed using gradient echo T*2 weighted EPI sequences(3mm×3mm×3mm) with BOLD contrast, with the following parameters :repetition time (TR) = 3000 m s, echo time (TE) = 30 ms, matrix size 64×64, field of view (FOV) = 192 mm × 192 mm, with number slices [47] in-axial plane(without gaps between the slices), flip angle (90°),These parameters are used for 76 dynamics. The scan time is 228 seconds.

**Preprocessing and analysis of FMRI data**

BrainVoyage(BrainInnovation,Maastricht, Netherlands) was used to perform the data in the pre-processing and analysis in order to minimise the effect of the head movements on data analysis. All volumes were readjusted to the first volume, additional data pre-processing comprised spatial (2 mm full-width half maximum isotropic Gaussian kernel). The anatomical and functional images were co-registered and normalised to the Talairachspace [15]. Statistical analysis was performed by multiple linear regression of the expected signal time course at each voxel. The expected (BOLD) signal change was the time course of the cold stimulation involved with a hemodynamic response function. For each of the six conditions[16]. A fixed-effects General Linear Model was used as it has the sufficient power to infer any associated brain activity in all acquired slices with less participants number[17]. We used the approach as implemented in Brain Voyager. This procedure is based on the estimate of the map's spatial smoothness. After1000 iterations, the minimum cluster size threshold that yielded a cluster-level false-positive rate of 5% were applied to the statistical maps transferred to correct for type 1 error. Clusters reported here survived this control of multiple comparisons. For subsequent visualization of activated brain regions, the location of significantly activated pain and cold sensation regions were assessed by superimposing the results from group analysis on an talarach brain[17].

## Results

The data presented in this section consisted of two groups. Each group has 3 patients this division applied according to the similarity of the psychophysical results.

**Psychophysical Data (first session of experiment):** Psychophysical testing was undertaken twice; once without the fMRI scan and then with the scan to determine each volunteer's reaction. The groups' reactions to pain is shown in table bare [1.A] during session one. It can be clearly seen that highest rate of the noxious feeling during the 19 seconds was recorded with the second group in the second run. While the lowest rate had registered in the first run of the same group with 0 scale. The pain scale rating was more stable with the first group in compare with the second one. The first group scored a consistent pain score for the all runs with 1 grade only.

During the second session of the study the first group showed a less amount of noxious feeling reduced by 1 grade for all runs. But the noxious pain scale had shown in the second run of the second group table bare (1.B).

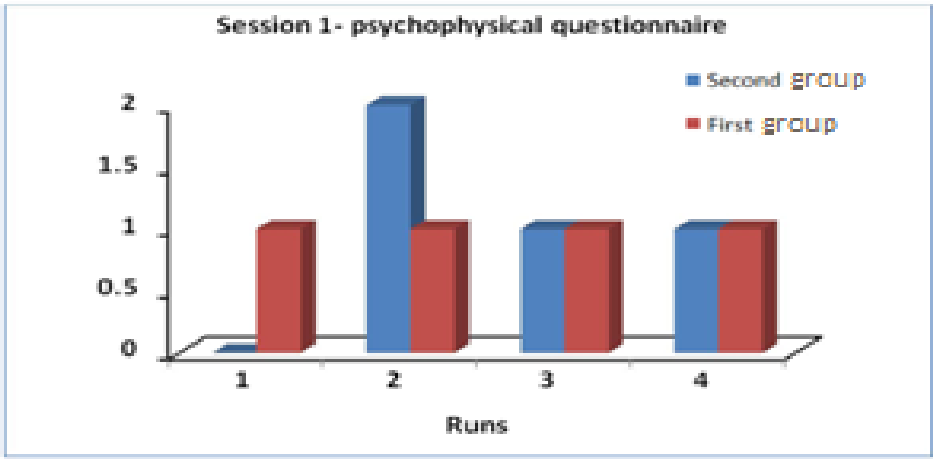



**Figure (1)** (A): psychophysical questionnaire which shows the pain scale for the two groups. The second group represented with the blue colour shows less consistency in comparison with the first group.

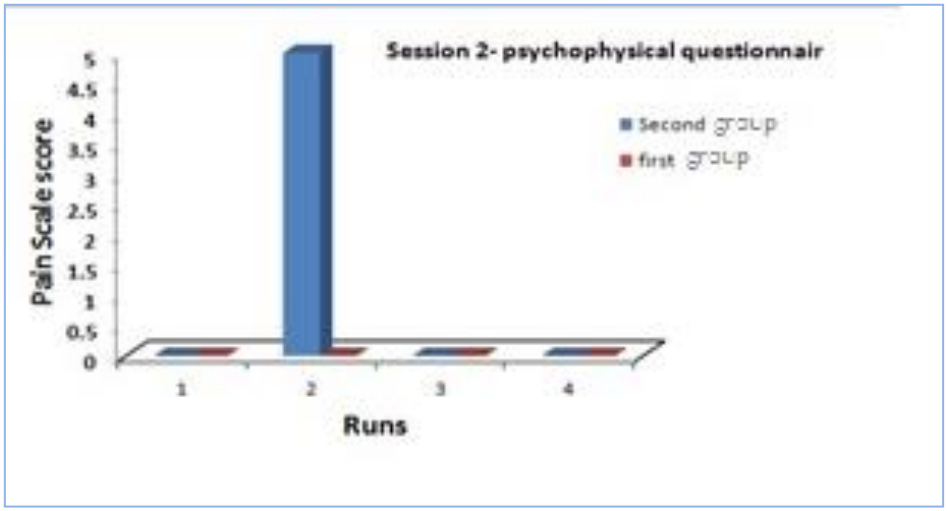



**Figure (1) (B):** The second grouper presented with the blue colour shows the one noxious sensation in the second session.

**Individual data of the groups (second session of experiment)**

The data presented in this section consists of the area (cluster size) that shows the activation which has more than 186 voxel and all Brodmann areas have recognised according to thebroadmannTrans Cranial Technology review in 2012[18].

**Brainstem**

The results showed in Figure [2] as determined by fixed effects analysis, there are areas of consistent activity color-coded, according to the legend indicated in the figure caption. Areas of significant signal changes are inferred to reflect changes in neuronal activity when the stimulus is applied. For the all runs of the first group, the majority of the activities were noted in the inferior anterior part of the pons and the junction with the medulla which includes the (olive and pyramids) in figure 2 (B,No.1 and C,No.1) with talarach values found in the cube range (±5 mm)indicates for the right Brainstem, Medulla [t (7)= 4.52, p <1,000, x, y, z: 8,-15,-42]. There was no clear activity could be detected in the rest pons areas or in the upper part of the brainstem for example the midbrain or PAG figure 2 (A, B and C). In comparison with group2 for all runs. The data which gathered with the T1 anatomical

image, there was no significant activity shown in the main brainstem structures. For the other different areas of the cortical part of the brain the colour-coded areas are limited in small regions as the figure 5 (A,No.1,B,C). In addition, there are right cerebrum and bilateral temporal lobe activities in the 22,42 brodmann areas. According to the Talarach software with ±5 mm [t (1)=5.17 , p <1,000, x, y, z: 59, -11, 12].

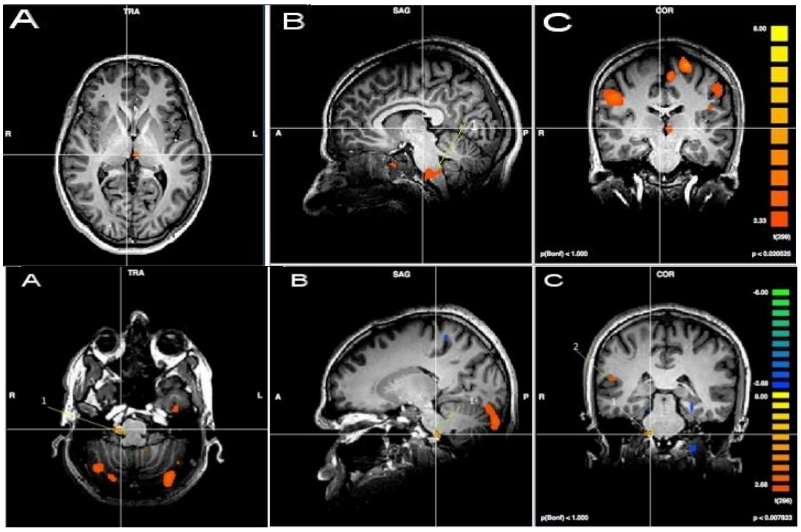



**Figure (2)**: group, there are activities in basilar pons area and medulla (A,B and C; No1).

**Group2 Run 2**

In contrary to the 2nd run of group2. The only run which had the noxious sensation (pain) in comparison with the other runs with the volunteers in the second session of the study in the psychological data. The axial section appears activity in the basilar pons area and medulla (theolivary nuclei, pyramid) figure 3 (A, No.1). The sagittal view figure 3(B) shows the same area of activity in addition to the significant activity in the occipital area of the brain. The coronal section shows figure 3 (C, No.1) the activity in the basilar pons. In the talarch within ±5 mm [t (8)=3.94 , p <1,000, x, y, z: 17, -32, -37],[t (14)=3.31 , p <1,000, x, y, z: -16, -38, -39]. It confirms the finding in the right and left brainstem and pons areas. In the medulla part shows the activation in the left brainstem of the medulla and the left side of the cerebellum [t (10)=2.9 , p <1,000, x, y, z: -7, -53, -39]. It shows there is activity within ±5 mm in the left brainstem, Pons, Left brainstem, midbrain, but it could be notrecognised by the our analysed images [t (17)=3.3 , p <1,000, x, y, z: (-37, -15, -36], [t (16)=2.5 , p <1,000, x, y, z: -19, -17, -21].

**Somatosensory area**

The activation in the somato sensory areas for the same contrast (cold stimulation and rest) are appeared within ±5mm in the (2,3,4 Brodmann areas) [t (1)=6.277 , p <1,000, x, y, z: 50, -17, 36]. As show in the figure 4 (A,No.1,2,3 and B, No1). The mainly activation are in the right and left partial lobe PostcentralGyrus and little in the right cerebrum as shown figure 4 (C, No.3).Also, for the 2ndgroupthere were activities as in different areas figure5 (A, B, and C,No1). Telerach data within ±5 mm apperared the activity in the Right Cerebrum, Parietal Lobe Brodmann area 5 10: Right Cerebrum, Parietal Lobe, PostcentralGyrus [t (2)=5.04 , p <1,000, x, y, z: 44, -44, 66] Gray Matter nearest to (44, -44, 66): Right Cerebrum, Parietal Lobe, PostcentralGyrus, Gray

Matter, Brodmann area 5, Range=4. In addition to the 2ndgroupwith the pain scale shows activities in the left Cerebrum, Temporal Lobe, Inferior ,Brodmann area 20 (vision area). Right Cerebrum, Parietal Lobe, PostcentralGyrus, Gray Matter, Brodmann area 5,7(pain somatosensory area) figure 3 (C,No2) [t (5)=2.6 , p <1,000, x, y, z: 38, -44,57].

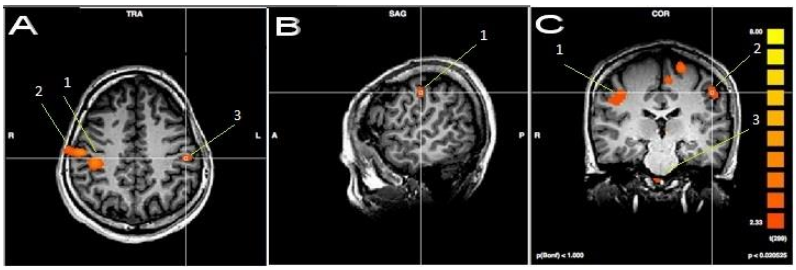
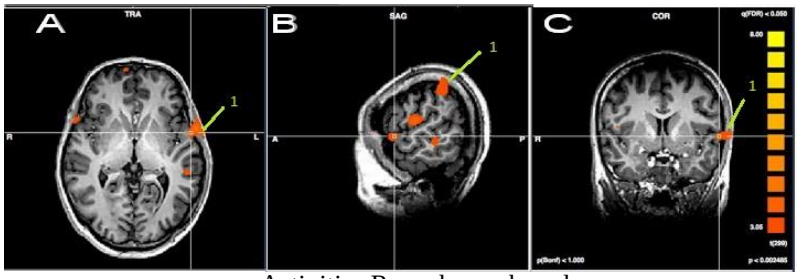
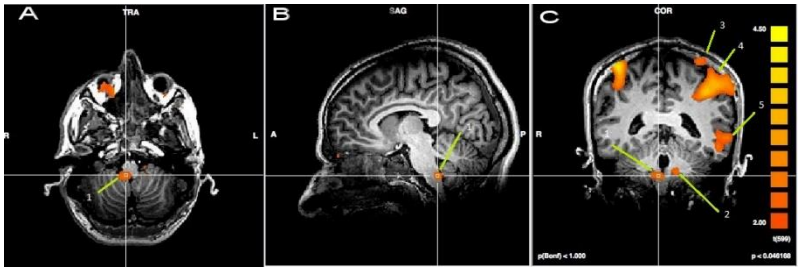



**Figure (3)**:1st group. The main activity is in the (2,3 and 4 brodmann areas)




Activities R cerebrum, broadmann




Activity in the rostral portion of the pons (B, No.1)

## Brainstem

Group FMRI results across the two groups, as determined by fixed effects analysis, are shown in Figure 6 with areas of consistent activity colour-coded, according to areas of significant signal changes are inferred to reflect changes in neuronal activity when the stimulus is applied. There was no activity in the midbrain and the upper section of the pons. Mainly of the activity was in the rostral part of the pons and the medulla (RMV)Figure 6(B). Consequently, the axial section of the brainstem shows there is activity in the rostral portion of the medulla and in the superior cerebella pundiclefigure6(A). Conversely, in the higher brainstem structures, there were no activities in the areas of the reticular formation except that which belong to the medulla part. There was activity in the base of the cerebellum. In the sensor motor areas, figure 6 (C, No.1, 2) there was activity as expected in the left areas more than the right side in the partial lobes. The activity map during the cold sensitisation show the same levels and similarregions within the brainstem structures activated of the rostral part of the pons and medulla of the first subject.

According to the telerach website within ±5 [t (7) =2.68, p <1,000, x, y, z: 8 -41 -39]. Sagital view Labels within 5 mm of, Right Brainstem, Medulla, Right Cerebellum, Posterior Lobe, Right Brainstem, Pons). The [t (8) =2.64, p <1,000, x, y, and z: (-10, -35, -36]. Labels within 5 mm of (-10, -35, -36), Left Brainstem, Pons, Left Brainstem, Medulla, left Cerebellum, Posterior Lobe.

There are activities in the left more than the right side as the figure 6 (5C, No.4,5 and 6) shows. Labels within 5 mm With the coordinates [t (1)=4.72, p <1,000, x, y, z: (44, -41, 66] there are activities in the Right Cerebrum, Parietal Lobes, PostcentralGyrusBrodmann area 5,2.

## Discussion

The purpose of this study was to apply equal intensity subjective stimuli by cold stimuli, to determine if there feasibility to show the classical pain regionsof the brainstem structures with low level of cold stimuli. This section will discuss the findings that were observed with the psychophysical data and fMRI data. We report four major results (i) pain responsive brainstem regions are activated by both the innocuous cold sensation and noxious cold sensation (ii) The pain and thermal somatosensory areas in response to contact with the brainstem were active (iii) Pain areas did not interact significantly as the painful thermal stimulus in some brainstem regions (iv) Neural activity in correlation to touch sensation, visual, auditory were active in the somatosensory areas that might have contaminated the activity in the regions of the brainstem areas.

**Psychophysical Data**

Generally, it can be clearly seen that the highest scale of noxious sensation was recorded just in the second run of the second group.This variation of the reaction could be due to many reasons for example the age,ethnic differences or the different of pain threshold of the person[19].

There is evidence to suggest that the cold evoked pain varies with different skin type[20].It could mean that as our first grouphas glabrous skin in comparison with the hairy skin type of the second group. Therefore, the threshold will be lower for the second groupthan the first[20]. According to the graph (1.B).The significant decreasing in the pain intensity scale for the second groupin the first and second sessions might belong to the repeated thermal stimulation over several time leading to a decrease pain ratings to the same noxious stimuli[21].

**Brainstem**

Neurobiological studies have identified the brainstem parts and structures as a key organ in the processing of noxious sensation[22]. Until recently, the technical methods and the limitations of brainstem imaging, have provided inadequate understanding and information about how the brainstem structures respond with pain [23]. Concordantly, cold stimuli elicited a strong and reliable bilateral brainstem response in the present study. Given this activation we hypothesize that a cold sensation affective state has been formed successfully in the participants[20]. As the cold stimuli are well validated with spinal coil and 3T F MRI [24]. In this pilot study, pons and medulla cluster show a more reliable response than some previous studies for the painful thermal stimuli type and areas[20,21,22]. In most previous studies employing the noxious sensation paradigm or its derivatives, the midbrain and the PAG are dominate[11], while in the present study there are not significant activity shown in the midbrain, PB and PAG or red nucleus areas except the finding with the Talerach daman within ±5mm.

The absent of significant activity in the midbrain area might be due to noxious sensations which did not achieve it adequately in this study [23]. In addition the reduce power of BOLD fMRI to detect signal changes in the

midbrain, only six papers from more than 65 hemodynamic studies on pain trial in healthy subjects found PAG activation in a meta-analysis[27]. The SNR problem can be addressed by synchronising EPI acquisition with the cardiac cycle ('cardiac gating') made limit transmission of innocuous and noxious information at the midbrain through descending projections taking into account the inaccuracies of stereotactic normalization[10].

While the other regions in the brainstem are structured with distinct difference between activities in the areas with the low level of thermal pain as reported in previous studies may perhaps explain the activities in the different results reported in this study.

Brainstem of the groupnumber 1 activity during all the runs is generally related to the cold sensation. In comparison with the same type of the coil used with previous studies with painful cold stimuli [26]. The present study shows strong activities in the RVM of the right medulla as well as the rostral part of the dorsal and rostral (pyramid, olive) parts of the pons figure 2 (A, B, and C) which similar to the Cahill study [28]. Seifert, et al. in 2007 study reported that a 1.5 T MRI could not show any activity in the brainstem areas with similar innocuous cold condition[26], while in our study that had achieved with head coils.

The brain stem activation of the second group with all runs showed that there were no significant activity obtained by images which might belong to the cluster null theory which hypothesised that in cluster there is no signal, and the implication is cluster-by-cluster therefore, an unusually big cluster extent only gives us information that there exists one or more signal voxels within the cluster, but does not identify which voxelswithin the cluster has a signal [29]. On the other hand, there was just activity in the cerebrum and bilateral temporal lobe in 22, 42 broadmann areas figure 5 (A, and C) which may belong to the complex MRI machine sounds [18].

In run 2 of groupnumber 2 figure3(A,B and C). The dorsal part of the pons, RMV and reticular formation include the parts that have been consistently demonstrated in results with painful hot stimuli study with 42 , 46 C0 [28].

The all groups analysis of the participants shows similar activity of the groupnumber 2 with the second run in the pons, while there is significant activity in the bilateral RMV in comparison with the individual analysis which give results similar to the electrical stimulating catheter [30].

In general this brainstem data indicates the evidence that pain and cold sensation activate similar anatomical locations through the middle and lower parts of the brainstem which could be achieved by a head coil in comparison with the same stimuli types studies [24].

**Somatosensory**

The main somatosensory areas of the groups and the all individuals analysis, as determined by fixed effect analysis, for the cold stimuli are shown in the figures 3.(A, B, and C), 5.(A, B, and C), and 6.(A, B, and C)with areas of consistent coded, according to the legend described in the figure header. There exists activity in the different somaosensory areas which are one of the main cortical regions implicated in pain like primary somatosensory area SI [1]. There were similar activation patterns with the participants inareas through the partial lobes figure (2.C) and (4.C)and there brodmann areas(cortical). Additionally, there were significant differences in other brodmann areas. This proves the importance of using pain intensity scores to standardise similar cold stimuli experiences. This is relevant to this study because we can confidently assess the signal changes related to neuronal activity with and without noxious sensitisation because the pain and cold feeling intensity scores for the groups were dissimilar. This significant neural

changes ($p<0.001$) are inferred to reflect response in these areas when the stimulus was applied.

For groupnumber 1. The activity was noted in the left partial lobe and the primary somatosensory which appeared in the brodmann area (2,3,4) related to the touch and thermal sensation as the stimuli was putting on the right hand(cortical function). In comparison with the second groupwhich had noxious feeling, there was activities in the Right Cerebrum, Parietal Lobe, PostcentralGyrus, Gray Matter and the brodmann area 5 which belong to the touch, thermal and the pain as well(cortical funcrion). In the second run of the same groupthere is strong activity in the left cerebrum and temporal lobe and 20 brodmann area which is responsible for the vision area(Trans Cranial Technology, 2012), in addition to that there are activities in the (5,7) somatosensory and brodmann areas which belong to the pain and thermal sensation activities.

The group analysis, shows clearly the activates in the (2, 5) brodmann areas in the partial lobe and right cerebrum figure 6 (A, B and C). Human brainstem structures respond similarly to the cold sensation and pain sensation, because these two brodmann areas (5,2) have similar activities with one of the pain studies[18], but in the PET research of capsaicin -induced tactile (brush evoked)allodynia in healthy individuals[1]. This data in the somatosensory areas of the second groupcorrelate with the activity of the brainstem areas and agree with the pain scale for the participants.

In summary, the data from this pilot study shows that the noxious and innocuous stimuli activate quite similar areas through the brainstem and somatosensory areas. A cold response, examined by means of the cold stimuli, had activated typical areas expected of painful sensory transmission. These include the RMV in the medulla and which considered as one of the descending modulation pain areas with same results of study with the electrical stimuli [30]. At the same time, there was activity in the locus corulus of the pons which is consistent with the Cathrin Cahill in 2011 study which have the same results by thermal stimuli. Peripheral cold sensitisation produced activation patterns typical of a pain response, such as the medulla, pons, reticular formation and brodmann areas which belong to pain response[28].

The cold stimulus (pain score = 1) produced activity in typical sensory centers in most parts of the brainstem which belong to pain ascending paths and modulation except for the higher brainstem structure (midbrain) there was no large activity which may be due to technical enhancement which applied to the MRI sequences to detect the BOLD of stimuli and rest conditions or it activated only with high level of pain. Finally, this pilot study shows how straightforward low level of painful and non-painful sensation information with the cold stimuli are transmitted from the peripheral nerves on the hand to the central nervous system leading to induce considerable similar activities in the brainstem structures. Further studies obviously need to examine more number of participants. The Talarachsoftware which was used to help to locate the coordinate of the fMRI data was not able to slandered coordinate space yet in the interested area of pilot study. For this reason it could not detect more than the three main parts of the brainstem. According to ±5 mm search option this means the fMRI data is more likely to be detect in the brainstem but cannot associate its exact location within the brainstem. In addition to the difficulty in switching pain on and off in a precise manner[31]. Finally, the shavingof the stimuli skin area of the hand will not introducing any effect of the hair withtouch /feel responses with different people, which

should be considered in future work. So Further studies are obviously desirable to take in hand these issues, but the current feasibility study has confirmed that a low level of noxious and innocuous stimuli, match with the MR scanner can, in fact, provide interested information about the brainstem activity.

## Conclusion:

In conclusion, this novel study shows that low level of pain and cold sensation could activate the same pain brainstem regions of the previous papers. Based on our dataillustrate a positive correlation between low level noxious and innocuous. This study can improve to use as control data in order to understand the pain, innocuous mechanism and maps in the brainstem by simple stimuli. Exploring and understanding anxious feeling and pain in one of the main modulation structure may play important role to design improved treatment strategies and perhaps monitor therapeutic interventions with patients suffering from chronic or undetected pain reasons.

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