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Abbreviated title

Measuring cerebral shoulder apprehension

Abstract

Introduction: Anterior shoulder apprehension is a commonly reported complaint in anterior shoulder instability, which may lead to patient morbidity and impede shoulder function. It is the result of a cognitively complex mechanism, which includes anxiety, salience, fear and anticipation. **Purpose:** The aim of this prospective case-control study was to correlate five clinically established scores using fMRI to assess brain activation patterns in patients with apprehension related to anterior shoulder instability. **Methods:** This study includes 28 consecutive right-handed, male patients (26.8 ± 1.2 years) with positive shoulder apprehension test and ten healthy matched control participants without apprehension or a history of instability. Task-related and functional connectivity fMRI activation patterns occuring during apprehension video cue stimulation were correlated to five clinical tests and scores: Visual Analog Scale (VAS), Rowe score for instability (Rowe), Simple Shoulder Test (SST), Subjective Shoulder Value (SSV) and Western Ontario Shoulder Instability (WOSI). **Results:** Rowe, pain VAS and WOSI correlated with pre-frontal, dorsolateral/dorsomedial pre-frontal cortex, somatosensory areas and parieto-occipital and temporal areas (default mode network). Rowe additionally correlated with frontal pole, anterior mid-cingulate cortex and visual areas. Moreover, SSV correlated with task-related brain activity of bilateral pre- and post-central gyrus, and bilateral superior parietal lobe. **Conclusion:** Overall, the Rowe score provides the strongest link between shoulder apprehension and brain level alterations as it correlated with the highest number of independent components (ICs) involving areas responsible for both motor and cognitive functions, while the pain VAS and WOSI occupy an intermediately strong link recruiting less brain networks. Finally, SST and SSV have the weakest link at the brain level.

Key Terms: Sports medicine, Instability, fMRI, Neuroimagery.

Introduction

Traumatic anterior glenohumeral dislocation is the most frequent type of joint instability and affects approximately 1.7% of the general population.(36) The majority of patients have favorable outcomes after open or arthroscopic stabilization.(9,17,21) However, complications such as recurrent shoulder instability or persistent apprehension have been reported to range from 2% to 13%.(9,21,23,45) This can lead to increased morbidity for the patient: increased pain, decreased activity level, prolonged time away from work and sports, and a general decrease in life quality.

Apprehension is a common sign of anterior glenohumeral instability defined by fear of imminent dislocation elicited when bringing the arm to 90° of abduction and 90° of external rotation. This test has been found to be a particularly accurate predictor for shoulder instability (8,11,26,30). Functional magnetic resonance imaging (fMRI) was recently used to explore the neuronal mechanisms underlying apprehension and found a complex cerebral reorganization in patients with shoulder instability, mainly in the primary sensitive and motor cortex, and in the anxiety networks.(15) This could explain why some patients still complain about persistent apprehension in the absence of any proven recurrence of instability.(4,17)

The current investigation extends these previous findings to further disentangle the cognitively complex mechanism of shoulder apprehension, which includes several high-level processes such as anxiety, salience, fear and anticipation. In particular, we correlated five clinically established scores and tests that assess these different aspects of apprehension to brain activation patterns from functional MRI in patients with a positive apprehension sign.

Materials and methods

Patient Selection

Between 2011 and 2014, all patients with anterior shoulder instability evaluated in a shoulder clinic were considered potentially eligible for this prospective study. Inclusion criteria included right-handed male patients with a positive shoulder apprehension test. Exclusion criteria were a history of drug or alcohol abuse, major medical disorders or use of medication such as psychotropics, stimulants or β-blockers. Institutional ethics committee approval was obtained before the study began and the subjects signed a written informed consent form prior to participation.

This study included a cohort of 28 patients (18 with right-sided and 10 with left-sided glenohumeral instability) with a mean age of 26.8 ± 1.2 years (range, 17 to 46 years). Ten healthy, male, right-handed and age-matched (29.6 ± 1.3 years) participants without apprehension or a history of instability were selected from the general population. The control volunteers had no history of shoulder injury, instability or hyperlaxity. The latter was defined as more than 85° of external rotation elbow against waist,(10) or hyper abduction over 105°.(12)

Clinical scores assessment

All patients were assessed with five commonly used subjective scores in the form of self-administered questionnaires (**Table 1**), prior to fMRI. The pain Visual Analog Scale (VAS)(18) is a widely used single item score where the patient rates pain intensity between zero and ten. This scale is useful for patient pre- and postoperative monitoring, and has also been correlated to

patient anxiety.(29) TheSimple Shoulder Test (SST)(25) consists of twelve binary "yes" or "no" questions evaluating shoulder performance in daily activities. This is a general shoulder questionnaire which is used in a broad range of shoulder conditions. Subjective Shoulder Value (SSV) is a single question, where the patient is asked to rate his overall shoulder function as a percentage of a normal shoulder.(14) It is a quick and easily administered score that has also been validated for various shoulder disabilities, such as instability. The Rowe score for instability(37) is a 3 item score with 4 choices each, measuring shoulder function, stability and motion. The final result is converted to a value between 0 and 100. This score has been specifically developed for shoulder instability. Finally, the Western Ontario Shoulder Instability (WOSI)(22) score is a 21 items score also specific for shoulder instability, measuring the degree of disability in activities of daily living. The final result is also converted to a value between 0 and 100. Except for pain VAS, higher results mean higher function.

fMRI Acquisition

Images were obtained using a 3T scanner (Trio; Siemens, Erlangen, Germany) with a standard 32-channel head-coil. fMRI imaging of the whole brain was performed using echo planar imaging employing the following parameters: whole brain coverage, 96x96 matrix, TR=2.5s, TE=30ms, 39 slices, 148 repetitions. A 3D T1-weighted structural scan (256x256 matrix size, 176 sections, 1x1x1 mm^3, TE=2.3ms, TR=2300ms) and a diffusion tensor imaging (DTI) scan (30 diffusion directions b=1000 s/mm^2 isotropically distributed on a sphere, 1 reference b=0 s/mm^2 image with no diffusion weighting, 128x64 matrix, 2x2x2mm voxel size, TE=92ms,TR=9000ms, 1 average) were acquired.

fMRI task

The paradigm consisted of an on-off block-design with two active conditions (apprehension cue and control videos) and a resting condition (**Figure 1**). During the active condition video cues were used(15) these animation movies (10 seconds) showed common activities that trigger shoulder apprehension. Control videos were matched for content except for the absence of cues inducing shoulder apprehension. After each video, a visual analog scale was presented for 2.5 seconds and participants rated the degree of perceived apprehension using an MR-compatible response box. The rating scale included nine steps from no apprehension to high apprehension. After the rating, a rest period followed, including the visual presentation of a fixation cross for 17.5 seconds. Each participant performed two runs. Within each run, lasting for 370 seconds each, 6 apprehension and 6 control videos were shown in a pseudo-randomized fashion. Before MRI scanning, participants were familiarized with the procedure and performed a training run outside the scanner.

Statistical Analysis

Statistical analyses were conducted using GraphPad Prism (Version 6, GraphPad Software, San Diego, USA) and FSL (Version 5.0.6, FMRIB, Oxford, UK).

Analysis of Clinical and Demographic data

After performing D'Agostino-Pearson omnibus test to check for normal distribution, those variables that were normally distributed, notably pain VAS, Rowe, SSV, WOSI and SST scores, were submitted to Pearson correlations. The participants' age, non-normally distributed, was analyzed using a Mann-Whitney test.

Functional Connectivity Analyses and Correlation with Clinical scores

Independent component analysis (ICA) was carried out using FSL's multi-session multivariate exploratory linear optimized decomposition into independent components (MELODIC) tensor ICA(2) setting the number of components to 25 which is common practice in ICA for fMRI data. The data structure is arranged as *subjects x space x time* for the tensor decomposition; i.e., each independent component (IC) comes with an s-mode vector (measure of strength of this IC for the subjects), a spatial map, and a time-course. To test correlations between the connectivity of different brain areas and the clinical test scores, Pearson correlation analyses were performed between the s-mode values (a measure of the activation strength) and the final scores of each test with False Discovery Rate (FDR) correction for multiple comparisons.(3) To test for differences in activation of different brain networks between patients and controls, the s-mode values were compared between groups using a 2-sample t-test with FDR correction for multiple comparisons.

Post-hoc GLM activation correlation with clinical scores

Processing and analysis of imaging data was performed using FSL FEAT (fMRI Expert Analysis Tool version 6.00, http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FEAT). Preprocessing included brain extraction using FSL's BET (Brain Extraction Tool), motion correction using FSL's MCFLIRT (intra-modal motion correction tool) (20) and smoothing using FSL's SUSAN (noise reduction uses nonlinear filtering.(39) A general linear model (GLM) was employed at three levels of analyses. At the first level, the contrast of apprehension versus control videos was calculated individually for each run of each participant using a fixed-effects analysis. Then, at the second level, a fixed-effects analysis combined both runs of each participant. Finally, at the third level, the 2nd level imaging results were correlated to the scores of the clinical tests for each participant (pain VAS, Rowe, SST, SSV and WOSI). The main predictor was the demeaned and normalized (values between -1 and 1) behavioral score for each subject. Finally, a correction for multiple comparisons by threshold-free cluster enhancement TFCE (47) was applied. P values < 0.05 were considered as significant.

VBM Analysis of T1 Images

To assess gray matter density differences between groups, a voxel-based morphometry (VBM) analysis was performed in FSL (FSL Version 5.0.6; http://fsl.fmrib.ox.ac.uk) using standard processing steps.[40,42] First, BET extraction and tissue-type segmentation were performed using the corresponding FSL tools (Brain Extraction Tool and FAST4). Next, a non-linear transformation into Montreal Neurological Institute (MNI) reference space was applied and a study-specific gray matter (GM) template was created. The native GM images were then non-

linearly registered to this template. Finally, the images were smoothed with an isotropic Gaussian kernel of 2 mm sigma at width-at-half-maximum (FWHM). A voxel-wise GLM was implemented using permutation-based nonparametric testing (Randomize, part of FSL). Results were corrected for multiple comparisons using TFCE (43) and P values <0.05 were considered as significant.

TBSS Analysis of DTI Data

FSL (FSL Version 5.0.6; http://fsl.fmrib.ox.ac.uk) software was used to analyze diffusion tensor imaging (DTI) data, according to the standard procedure (41) to test for differences of white matter integrity between groups. First, all subjects' fractional anisotropy data was projected onto a mean fractional anisotropy tract skeleton by non-linear registration. Later, by using a non-linear registration voxel-wise statistical analysis with threshold free cluster enhancement correction for multiple comparisons was performed, considering TFCE corrected P values <0.05 as significant.

Results

Clinical scores

Mean score results were 4.1 ± 2.47 for pain VAS, 8.97 ±2.06 for SST, 62,52 ±50.77 for SSV, 36.90 ±19.43 for Rowe and 50.77 ±21.45 for WOSI (**Table 1**). Significant correlations ($p<0.05$, multiple comparisons corrected) were found between the test scores of all the clinical tests except between Rowe – SSV, and Rowe - SST (**Table 2**).

Functional Connectivity Analyses and Correlation with Clinical scores

Significant results ($p<0.05$, FDR multiple comparison corrected) were found for the correlation analyses between the s-mode values of different ICs and the final scores of pain VAS, Rowe and WOSI scores. Specifically, final scores of pain VAS, Rowe and WOSI tests positively correlate with the connectivity strength of four almost overlapping networks (IC1, IC2, IC3, IC4) notably including the bilateral anterior insula (aINS), anterior cingulate cortex (ACC), posterior cingulate cortex (PCC), bilateral dorsomedial prefrontal cortex (dmPFC), supplementary motor area (SMA) and somatosensory cortex (**Figure 2**). Additionally, Rowe correlated with the strengths of the components IC5, IC6, IC7, involving networks overlapping to the previous ones plus in addition anterior mid-cingulate cortex and visual and attentional areas (**Figure 2**). Finally, group analyses showed significant differences ($p<0.01$) between patients and controls in brain networks, qualitatively replicating the results of a previous study.(15) The s-mode values of this component significantly correlate ($p<0.05$) with the final scores of pain VAS and Rowe scores.

Post-hoc GLM activation correlation with clinical scores

From the post-hoc correlation analyses between GLM activations and clinical scores, two of the five clinical tests yielded significant correlations. The Rowe score correlated with activity in bilateral frontal pole and in the posterior division of the left inferior temporal gyrus (**Figure 3a and Table 3**). The SSV test correlated with activity in bilateral pre- / post-central gyrus and bilateral superior parietal lobe (**Figure 3b and Table 3**).

VBM and TBSS Analysis

The VBM analysis of gray matter (GM) density and the TBSS analysis of white matter (WM) revealed no statistical differences between study groups.

Discussion

Shoulder apprehension is a cognitively complex condition involving many aspects such as anxiety, anticipation, salience and fear. In a previous study, global changes in cerebral networks were demonstrated for the first time in shoulder apprehension by the comparison of patients versus controls.(15) The current investigation extends these observations and further unravels the complex condition of apprehension by correlating five established clinical scores and tests to functional imaging in patients with a positive apprehension sign undergoing visual cue apprehension stimulation. These five clinical scores assess different aspects of shoulder apprehension. Consequently, the corresponding brain activations partially overlap due to common general aspects of apprehension, such as anxiety and pain regulation, notably for Rowe, pain VAS and WOSI. Conversely, the test-related brain networks partially diverge, notably between Rowe and SSV. This partial divergence in brain activation associated with different clinical scores is in agreement with the fact that they assess different aspects of the complex condition of shoulder apprehension.

In a first step, we analyzed the correlation between the five different clinical scores at the behavioral level to evaluate how much they diverge from each other and how much they capture the same components of shoulder apprehension. Significant correlations were found between all the different tests except between Rowe - SST and Rowe - SSV. These results prove that the tests

are able to measure a common aspect of shoulder apprehension, but as shown by the limited shared variance (between 30% and 60%) the overlapping is partial and the tests diverge qualitatively from each other. Specifically, considering only our behavioral results, pain VAS and WOSI are the scores that share the largest amount of variance with the other tests. Instead, SST, SSV and Rowe measure significantly different phenomena between each other.

In a second step, we correlated functional connectivity networks to these 5 different clinical scores to disentangle overlapping and divergent neuronal networks related to these different tests. Pain VAS, Rowe, and WOSI were correlated with partially overlapping functional networks in the brain (i.e., components IC1, IC2, IC3, IC4) involving notably activations of dorsolateral/dorsomedial pre-frontal cortex, dorsal anterior cingulate cortex (dACC) and somatosensory areas, as well as deactivations of ventral anterior and posterior cingulate cortex (vACC, PCC) and precuneus (Figure 2). This network resembles the default mode network (DMN) that is a resting-state network involved in many clinical conditions and, in particular, in negative mood states,(7) anxiety,(32) and in pain regulation during painful situations.(1) Specifically, medial and dorsolateral prefrontal areas are involved in pain modulation,(6,27) expectancy of pain (16,38) and interaction between pain and anxiety,(35) while the connectivity between ACC and PCC is involved in pain stimulation processing.(13) This indicates that pain VAS, Rowe and WOSI are scores that measure pain expectancy and pain-related movement induced by shoulder apprehension. A higher score means higher activity of these areas to activate these motor and cognitive processes. Rowe additionally presented significant correlations with three partially overlapping components (IC5, IC6, IC7) showing additional recruitment of the frontal pole and of occipital brain areas. The frontal pole activity during pain-related stimulations is generally related to cognitive and attentional processing,(5) while visual

cortex quickly encodes and discriminates between visual cues associated with pain anticipation and no pain.(28)

Overall, Rowe had the strongest effect and was significantly correlated with seven components. Pain VAS and WOSI had an intermediate position and were correlated with four components, while SST and SSV had no significant correlations. The Rowe score is the strongest for measuring shoulder apprehension, as it is correlated with the largest number of components, thus showing the involvement of the networks implicated in several different functions such as sensory and motor and attention and pain anticipation. These results are coherent with the structure of the test: firstly the Rowe score is specific to instability. It is the only of the five tested scores that quantifies shoulder motion that moreover accounts for two thirds of the score; secondly, through this assessment, it measures both motor component (stability and motion) and cognitive component (the perceived pain) of shoulder apprehension. Considering the brain level, pain VAS and WOSI appear to be intermediately strong scores: they capture motor and sensory components as well as the cognitive ones in a weaker way compared to the Rowe score. In fact, they correlate with a smaller number of brain networks and have less involved brain areas. Comparing their structure to the Rowe score, they focus their evaluation mostly on cognitive aspects of shoulder apprehension (pain VAS on pain and WOSI on shoulder function in everyday life activities). Finally, our findings suggest that from a perspective of brain activations, SSV and SST are weak tests that have no associations with brain network activity. At a clinical level, these tested scores do not assess cognitive components of shoulder apprehension. From these considerations, instability specific scores and scores quantifying shoulder motion may more accurately capture apprehension processing at the brain level than general shoulder scores. Thus, this form of evaluation of has to be privileged in shoulder instability.

In a third step, we correlated task-related brain activation with the five clinical scores. The Rowe score was significantly and negatively correlated with activity in the frontal pole and the posterior division of the inferior temporal gyrus. These results are coherent with the ICA results, establishing a link between the measure of stability and mobility of shoulder apprehension and cognitive processes. In fact, multiple studies investigating the neural bases of pain show evidence of dynamic interaction between pain perceived and pain regulation, such that increased orbito-frontal cortex (OFC) activity is related to a decreased activity in regions associated to painful sensation, which in turn leads to a decrease in self-reported pain scores.(24,33,34,46) In addition to the connectivity results, this evidence suggests that the Rowe score is also associated to specific pain inhibition mechanisms involving brain activity in the frontal lobe during shoulder apprehension. From this data, more activity in the frontal lobe relates to less pain perceived and higher shoulder stability and movement allowance. Furthermore, SSV was negatively correlated with brain activity in the motor and somatosensory cortex. From a previous study on shoulder apprehension and fMRI correlates,(15) the motor cortex is one of the main parts of the network involved in shoulder apprehension. From evidence in monkeys,(31) the anterior mid-cingulate cortex and somatosensory area (SMA) are active when motor control and pain processing occurred simultaneously. Therefore, we conclude that less shoulder motor control with respect to normal subjects leads to an increase in brain activations related to motion in patients. These findings suggest that SSV is particularly able to detect reconfiguration of motor functions that leads to impairments and avoidance of certain movements in shoulder apprehension. Finally, patients with shoulder apprehension have a different neural network configuration as compared to healthy controls including notably the anterior cingulate cortex, the

posterior cingulate cortex, sensory-motor areas and the precuneus. These findings are consistent with a previous study.(15)

Although clinical scores are undeniably extremely useful and informative tools in clinical practice, they address subjective and/or objective function of the shoulder but not necessarily the whole extent of the cerebral impact of apprehension and its negative consequences, which may go undetected. A successfully stabilized patient may have satisfying scores with a clinically stable shoulder, but may keep a persistent cerebral 'scar' from apprehension, impeding full performance recovery. This gives rise to the question of what is actually intended to be measured with a clinical score, and emphasizes the further need to extend investigations in this emergent field consisting in the link between peripheral orthopedic pathologies and the central nervous system. These two systems, which at first glance may seem very distinct, are in fact inextricably linked. Inasmuch as it is accepted that the brain is in command of the joint, the opposite seems to become more and more obvious with the use of neuroimaging in the exploration of orthopedic science.

Limitations

A first limitation to this study was the relatively small group size. Because apprehension implicates both lateralized and non-lateralized cerebral regions, patient group constitution had to be selective (same hand dominance). This study therefore did not include any left-handed patients, as there were too few cases. Nevertheless, we observed highly significant brain network and activation changes related to apprehension. This in turn indicates a strong effect of shoulder apprehension on cerebral networks. Notably, results from group comparisons were not widely

discussed in this work as they resemble findings from a previous study.(15) Future studies should include larger study groups, pre- versus post-surgical imaging and follow-up to evaluate the evolution of the cerebral modifications related to shoulder dislocation and its recovery. Moreover, other conditions such as knee, elbow or ankle instability should be assessed to test the hypothesis that apprehension-related modifications in cerebral neuronal networks are presumably generic and not limited only to shoulder apprehension, which is the most common yet not the only type of instability. Unveiling those mechanisms may provide a whole new approach to their management, such as fear extinction or neurofeedback.(19)

Conclusion

Our results give a clearer and better understanding of cognitive components of shoulder apprehension, contributing to unravel this complex clinical condition by combining imaging results and clinical examinations. In particular, we found common neural correlates of shoulder apprehension captured by the clinical scores and tests (except SSV and SST); i.e., the involvement of functional brain networks comprising motor and somatosensory cortex as well as prefrontal areas. Specific features for each test show a recruitment of fronto-parietal and orbito-frontal areas that regulate the expected shoulder pain for the Rowe score (in addition to the common activations). The SSV, then, shows the recruitment of brain areas related to pain during motion. Furthermore, from a clinical point of view our results suggest that the Rowe score provides the strongest link between shoulder apprehension and brain level alterations as it correlated with the highest number of ICs involving areas responsible for both motor and cognitive functions, while the pain VAS and WOSI occupy an intermediately strong link

recruiting less brain networks. Finally, SST and SSV have the weakest link at the brain level, showing no correlation with neural activity or correlation only with motor areas.

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Legends

Table 1. Scores overview and results.

Table 2. Significant correlations ($p<0.05$) were found for all the tests, except between Rowe and SST, and Rowe and SSV scores. The r- scores show the direction and the strength of the correlations. $P<0.05$ are indicated with *.

Table 3. Activation clusters of the GLM analysis. Cluster index, number of voxels, statistical value, location of maximal Z value in MNI space, center of gravity in MNI space, side and anatomic region

Figure 1. The paradigm consisted of an on-off block-design with apprehension cue and control videos as well as a low-level rest condition.

Figure 2. Functional connectivity analyses and Correlation with clinical scores: IC1, IC2, IC3, IC4 were positively ($p<0.05$ corrected) correlated with pain VAS, and negatively correlated with Rowe and WOSI scores. Rowe was additionally negatively correlated with IC5, IC6 and IC7 with additional activation of frontal pole, anterior mid-cingulate cortex and visual and attentional areas.

Figure 3: A. Significant negative correlation was found between Rowe score and activity in the frontal pole and the posterior division of the inferior temporal gyrus**. B.** Significant negative correlation was found between SSV and brain activity of bilateral pre- / post-central gyrus and bilateral superior parietal lobe.

Figure 1

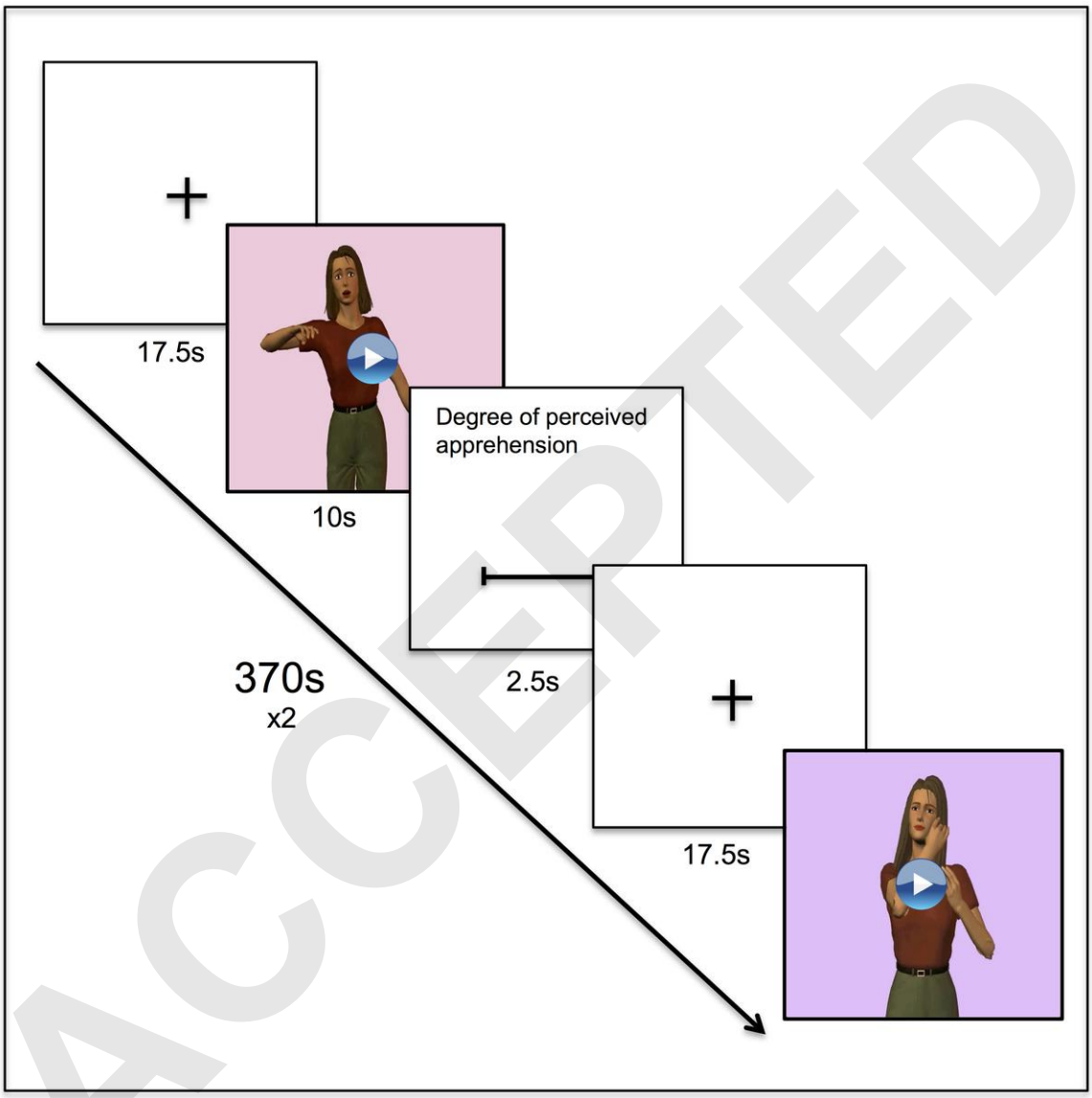

Figure 2

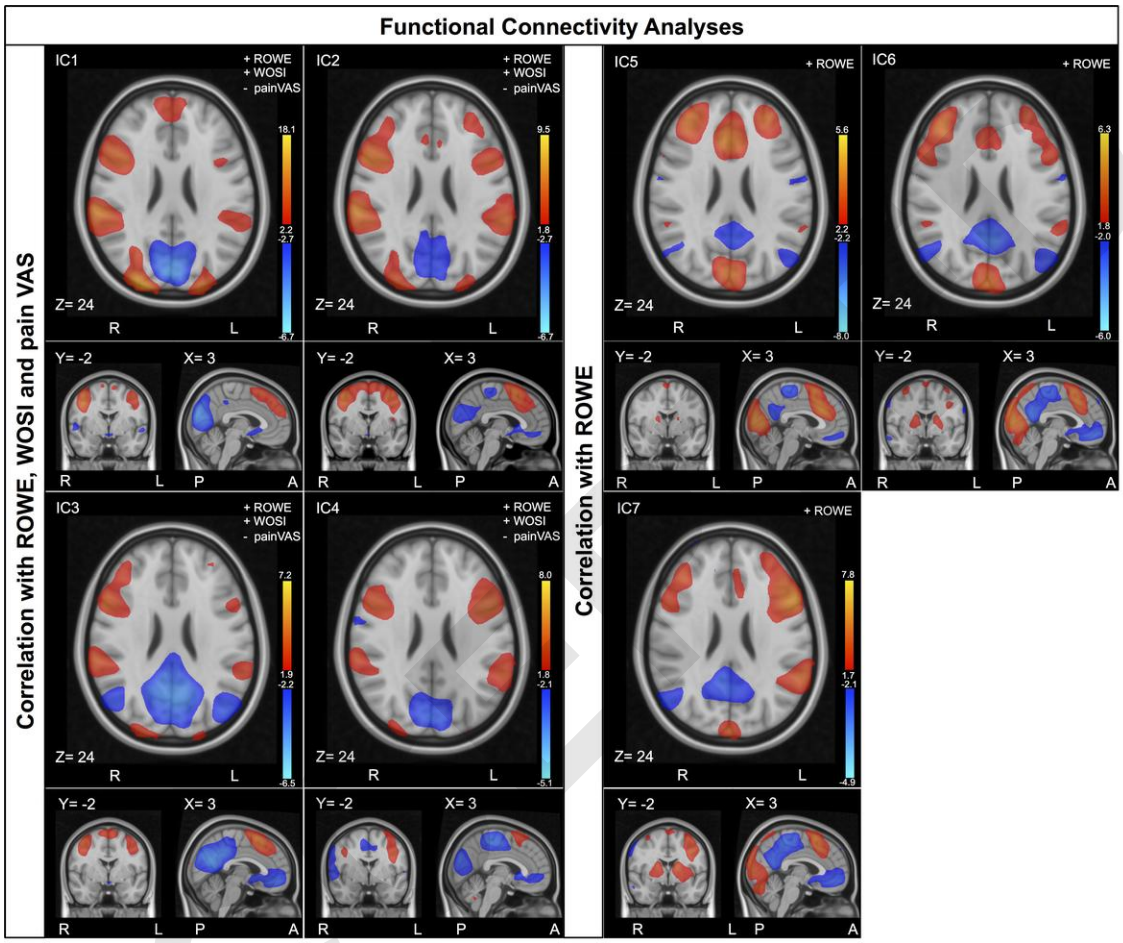

Figure 3

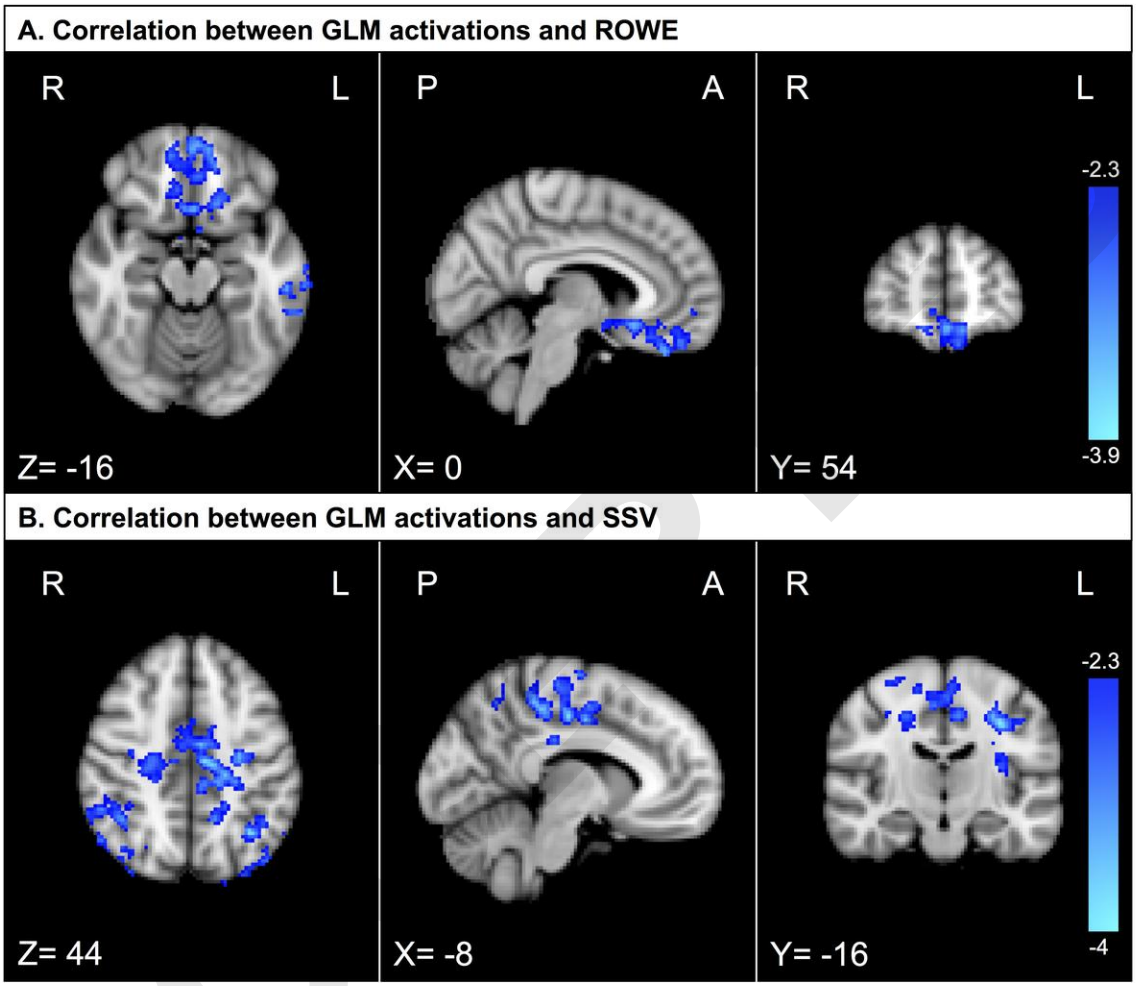

Table 1

SCORE	TYPE	ITEMS	RESULTS
pVAS	Region and condition unspecific	1 (scale)	4.1 (±2.47, 0-9)
SST	Shoulder specific Condition unspecific	12 (binary yes/no)	8.97 (±2.06, 3-12)
SSV	Shoulder specific Condition unspecific	1 (percentage)	62,52 (±50.77, 30-82)
Rowe	Shoulder specific Instability specific	3 (4 grades each)	36.90 (±19.43, 0-83)
WOSI	Shoulder specific Instability specific	21 (percentage for each item)	50.77 (±21.45, 12.4-96.7)

Table 2

	Rowe	*SST*	*SSV*	*WOSI*
pVAS	-0.54*	-0.46*	-0.39*	-0.61*
Rowe		0.31	0.33	0.55*
SST			0.44*	0.43*
SSV				0.61*
WOSI				

Table 3

GLM activation correlation with Rowe clinical scores												
Cluster Index	**Voxels**	**P**	**-log10(P)**	**Z-MAX**	**Z-MAX X (mm)**	**Z-MAX Y (mm)**	**Z-MAX Z (mm)**	**Z-COG X (mm)**	**Z-COG Y (mm)**	**Z-COG Z (mm)**	**SIDE**	**Regions**
1	1612	5.96E-08	7.22	3.7	4	38	-28	-3.43	36.7	-18.3	B	Frontal Pole Paracingulate Gyrus
2	445	0.0111	1.95	3.9	-66	-14	-20	-59.5	-22.3	-20.8	L	Inferior Temporal Gyrus posterior division
GLM activation correlation with SSV clinical scores												
Cluster Index	**Voxels**	**P**	**-log10(P)**	**Z-MAX**	**Z-MAX X (mm)**	**Z-MAX Y (mm)**	**Z-MAX Z (mm)**	**Z-COG X (mm)**	**Z-COG Y (mm)**	**Z-COG Z (mm)**		**Regions**
1	3834	1.67E-15	14.8	4.07	-34	-60	46	-11.1	-32.5	46.9	B	Pre-central Gyrus Post-central Gyrus
2	985	1.7E-05	4.76	3.89	40	-52	48	42.5	-59.7	47.8	L	Superio Parietal Lobe Angular Gyrus Lateral Occipital Cortex