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Identifying neuropathic pain using ^{18}F-FDG micro-PET: A multivariate pattern analysis

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ABSTRACT

Pain is a multidimensional experience emerging from the flow of information between multiple brain regions. A growing body of evidence suggests that pathological pain causes plastic changes of various brain regions. Here, we hypothesized that the induction of neuropathic pain alters distributed patterns of the resting-state brain activity in animal models, and capturing the altered pattern would enable identification of neuropathic pain at the individual level. We acquired micro-positron emission tomography with [^{18}F]fluorodeoxyglucose (FDG micro-PET) images in awake rats with spinal nerve ligation (SNL) and without (sham) (SNL group, n = 13; sham group, n = 10). Multivariate pattern analysis (MVPA) with linear support vector machine (SVM) successfully identified the brain with SNL (92.31% sensitivity, 90.00% specificity, and 91.30% total accuracy). Predictive brain regions with increased metabolism were mainly located in prefrontal–limbic–brainstem areas including the anterior olfactory nucleus (AON), insular cortex (IC), piriform cortex (PC), septal area (SA), basal forebrain/preoptic area (BF/POA), amygdala (AMY), hypothalamus (HT), rostral ventromedial medulla (RVM) and the ventral midbrain (VMB). In contrast, predictive regions with decreased metabolism were observed in widespread cortical areas including secondary somatosensory cortex (S2), occipital cortex (OC), temporal cortex (TC), retrosplenial cortex (RSC), and the cerebellum (CBL). We also applied the univariate approach and obtained reduced prediction performance compared to MVPA. Our results suggest that developing neuroimaging-based diagnostic tools for pathological pain can be achieved by considering patterns of the resting-state brain activity.

Introduction

Neuropathic pain is a long term debilitating pain initiated by a primary lesion to either the peripheral or central nervous system. It has been shown that neuropathic pain causes plastic changes of various brain regions (Jaggi and Singh, 2011). These findings are in line with the emerging evidence that pain is a subjective and multidimensional experience comprising sensory, cognitive, and emotional components (Tracey, 2010).

Given the subjective nature of pain, there has been a high demand for developing an objective biomarker in clinical, preclinical and basic research. Brain imaging has great potential to complement current subjective assessment of pain (Borsook et al., 2011; Dolgin, 2010; Sakoglu et al., 2011). Indeed, a number of studies using functional brain imaging have suggested potential biomarkers for pathological pain, however the development and validation of diagnostic tools for use still remain to be achieved (Borsook et al., 2011).

Considering the multidimensional characteristics of pain, it would be a more efficient strategy for developing biomarkers to focus on the altered distributed patterns of the brain than single discriminative regions (Borsook et al., 2011). Therefore, multivariate pattern analysis (MVPA) techniques, which analyze distributed patterns of brain activity by using machine learning classifiers, can be more appropriate approach than traditional univariate methods (See Supplementary Fig. 1) (Cox and Savoy, 2003). While most of imaging studies on pain have focused on the evoked responses of the brain to external stimuli, in recent years, a growing body of studies has been performed on resting-state brain with pathological pain (Cauda et al., 2010; Napadow et al., 2010; Seminowicz et al., 2012). Understanding how diseases affect the resting-state brain has great potential for not only deciphering the disease mechanism, but also for the development of biomarkers for brain disorders (Sakoglu et al., 2011).

Here, we hypothesized neuropathic pain would induce plastic changes of distributed brain regions, and that capturing the altered pattern of the resting-state brain activity would enable identification of neuropathic pain. To address our hypothesis, we used micro-positron emission tomography with [^{18}F]fluorodeoxyglucose (FDG micro-PET)

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and spinal nerve ligation (SNL) models of neuropathic pain. FDG micro-PET imaging allowed us to investigate the whole brain metabolic activity in awake animals. By applying MVPA, we determined the brain with SNL from that of sham animals at the individual level. Linear support vector machine (SVM) was employed as a classifier. Prediction performance was evaluated by leave-one-out cross-validation and compared with the performance of univariate approach using the same brain regions. To our knowledge, this is the first study validating the neuroimaging biomarker for animal models of pain at the individual level.

Materials and methods

All experiments were performed in accordance with the NIH guidelines for Animal Research and approved by the Experimental Animal Care and Ethics Committee of Seoul National University, Seoul, Korea.

Animals and surgery

Adult, male Sprague-Dawley rats (Samtako CO., Osan, Korea) weighing 260–320 g were used. Spinal nerve ligation (SNL) was performed as described previously (Kim and Chung, 1992). Briefly, the right L5 spinal nerve was exposed and tightly ligated with 4-0 silk under isoflurane (2.5% for induction and 2% for maintenance) anesthesia (n = 13). Sham surgery was identical to SNL, except that the nerves were not ligated (n = 10).

Behavioral tests

To confirm the successful induction of neuropathic pain, all rats were tested for mechanical allodynia of the right hindpaw 2 days before surgery, and on postoperative days 1, 4, 7, and 14. Rats were placed in transparent acryl cages on a wire mesh floor, and allowed to acclimate for 20 min before tests. Mechanical allodynia was assessed using von Frey filaments. The filaments were applied to the plantar surface of the hindpaw and brisk withdrawal or flinching response was regarded as positive. There are many methods to determine the withdrawal thresholds. Here, we applied the up–down method (Dixon, 1980). A series of filaments (0.4, 0.7, 1.2, 2.0, 3.6, 5.5, 8.5 and 15.0 g) were applied to the hindpaw. Starting with a filament in the middle of the series, weaker or stronger filaments were applied based on the prior response (positive or negative). The resulting response pattern was used to calculate the 50% likelihood of a paw withdrawal response (50% threshold) (Chaplan et al., 1994). Rats which showed thresholds less than 4 g in 1 day or 4 days after surgery were considered to be SNL model. Rats not to be considered to be SNL model were excluded from the analyses. Repeated-measures ANOVA followed by Bonferroni's *t*-test was conducted for comparison between two groups.

Image acquisition

Micro-PET images of the rat brain were acquired 12–14 days after SNL surgery. All rats were deprived of food for 12–18 h before the scanning to enhance FDG uptake in the brain (Fueger et al., 2006). Rats were placed in acryl cages (13 cm × 10 cm × 10.5 cm) on a wire mesh floor, and allowed to acclimate for 30 min before FDG injection. Afterwards, FDG (500 μCi/100 g in 0.5 ml) was administered via tail vein injection under light isoflurane anesthesia and the rats were moved back to the plastic cages. Rats woke up promptly from anesthesia and stayed in the plastic cages in a quiet room with a dim light for 60 min uptake period. After uptake period, a 60 min static acquisition was performed in 3D mode under isoflurane (1.5%) anesthesia. The acquired images reflected the metabolic activity of the awake rat brain before the saturation of FDG uptake. Image acquisition was performed using a dedicated small-animal PET scanner (eXplore VISTA, GE healthcare), which provides 4.6 cm axial and 6.7 cm transaxial field of view, with spatial resolution of 1.6 mm in full width at half maximum. 3D volumetric images were reconstructed using VISTA OSEM algorithm in a 128 × 128 matrix with a pixel width of 0.385 mm and a slice thickness of 0.770 mm.

Image preprocessing

Data preprocessing was carried out in MATLAB (Mathworks) using statistical parametric mapping (SPM2) software (http://www.fil.ion.ucl.ac.uk/spm/). First, 15 FDG micro-PET images of naïve rats were coregistered to the T2-weighted MR template provided by Schweinhardt et al. (2003), which was placed into stereotaxic space, and then averaged to make a FDG rat brain template. All individual micro-PET images were spatially normalized using this template and resliced (0.2 mm × 0.2 mm × 0.2 mm). Micro-PET images were smoothed with a Gaussian kernel (full-width at half-maximum (FWHM) = 1.2 mm) to increase the statistical power. Proportional scaling was used for global normalization of voxel values between scans (global mean to 50, gray matter threshold of 0.8).

Multivariate pattern analysis (MVPA)

MVPA uses machine learning algorithms that can extract pattern information from multi-dimensional space and classify data samples into different classes. In general, datasets are divided into training sets and test sets, and classifiers are derived by learning patterns during the training sets. Trained classifiers are functions that take the values of features (voxels in neuroimaging setting) from the data samples and predict the class that the samples belong to. The prediction performance of classifiers is evaluated using test datasets. In our study, all MVPA analysis was performed by in-house software developed using MATLAB (Mathworks).

Feature selection

Because not every voxels represent the altered pattern of the resting-state brain during SNL, feature selection was performed prior to developing a classifier. Feature selection enables classifier to more accurately predict classes by removing uninformative features (diminishing noise). Moreover, this process provides information about the discriminative brain regions between conditions. Features were selected using two-sample t-tests between two groups in training sets. A series of *p*-values (0.000005, 0.00001, 0.00005, 0.0001, 0.0005, 0.001, 0.005, 0.01, 0.05, and 0.1) were applied to find optimal features yielding the best performance of prediction. It is important that feature selection was carried out using only training sets, excluding the possibility that prediction of the test sample was guided by the information from the test set itself. In order to avoid an outlier-driven effect on feature selection, we repeated additional two-sample t-tests for selected feature voxels. For these t-tests, each training sample was excluded in turn and additional t-tests were repeated, resulting in the same number of iteration as the training samples. Voxels that were significant for all iterations were retained.

Linear support vector machine (SVM) classifier

Linear support vector machine (SVM) was employed as a classifier for machine learning. SVM is a supervised machine learning algorithm used for data classification (Bishop, 2007), in which classifier is developed based on sample data by searching the optimal separating hyperplane between classes in a high-dimensional space (training phase), then the classifiers are used to predict the class to which unseen data belongs (testing phase) (Pereira et al., 2009). The method has previously been applied to various types of neuroimaging data (Bendfeldt et al., 2012; Focke et al., 2012; Kloppel et al., 2008; Vandenberghe et al., 2013).

Leave-one-out cross-validation

In order to evaluate the prediction performance of the classifier, we used leave-one-out cross-validation. Each of the brain samples was excluded from the analysis in turn, and for the remaining training samples, SVM classifier was trained. The brain samples that were left out then classified as being of SNL or sham animals. This procedure was repeated until every sample once served as test samples (Fig. 1). This validation procedure ensures trained classifiers to be tested using unseen data that never been presented during training phases. The performance of prediction was quantified using sensitivity (the proportion of SNL animals correctly predicted), specificity (the proportion of sham animals correctly predicted), and accuracy (the proportion of total animals correctly predicted).

Mapping discriminative brain regions

To identify the set of distributed brain regions with high discriminating power, a series of selected feature voxels which were derived from two-sample t-tests using different *p*-values were collected. Among these voxels, only those yielding high accuracy (above 85%) were mapped onto a MR template in stereotaxic space.

MVPA vs. univariate approach

To compare the prediction performance of MVPA with that of traditional univariate approach, we repeated the validation protocol (leave-one-out cross-validation tests) by adopting univariate analysis. In univariate analysis, individual discriminative voxels were used for prediction independently, instead of being considered simultaneously. To exclude the possibility that the difference in performance is derived from the different sizes of feature voxels, the same feature voxels with MVPA were used for univariate analysis. For each voxel, a linear SVM classifier was derived and the prediction was conducted independently, resulting in a prediction for each feature voxel. The overall prediction for each sample was determined by comparing the number of voxels that had positive and negative predictions.

Results

Induction of neuropathic pain by SNL

SNL (n = 13) and sham (n = 10) surgery was performed for micro-PET imaging. Behavioral responses to mechanical stimuli (mechanical allodynia) were assessed to confirm the successful induction of neuropathic pain. Significant mechanical allodynia developed 1 day after surgery and was maintained during the 2 weeks of observation period (Fig. 2).

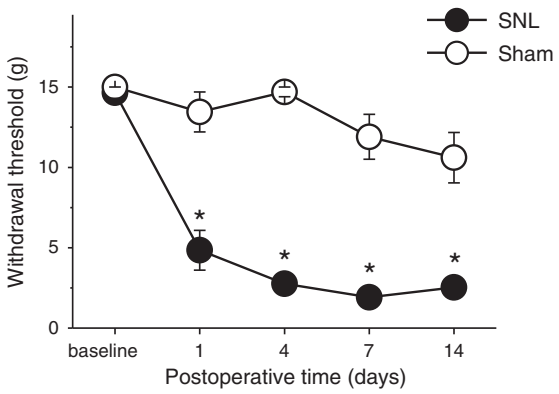

Fig. 2. Pain behaviors following spinal nerve ligation (SNL). Hindpaw withdrawal thresholds to mechanical von Frey stimulation were assessed following SNL. Data are means ± SEM, $^{*}p < 0.01$ (one-way repeated measures ANOVA followed by Bonferroni's *t*-test).

MVPA results

Prediction accuracies of SVM classifiers using different sets of feature voxels with various *p*-values are shown in Fig. 3 and Table 1. SVM classifier achieved the highest accuracy of 91.30% (92.31% sensitivity and 90.00% specificity) at *p*-values of 0.00005, 0.0001, 0.0005, and 0.001 in leave-one-out cross-validation tests. The probability of a 91.30% or better accuracy obtained by chance was calculated from binomial distribution and the *p*-value was 0.000033.

Brain regions with high discriminative power

To investigate the most informative brain regions during neuropathic pain, feature voxels yielding high accuracy (above 85%) in a series of leave-one-out cross-validation tests were mapped onto a MR template in stereotaxic space (Fig. 4). Overall, brain regions in the prefrontal–limbic–brainstem areas showed increased metabolism; the anterior olfactory nucleus (AON), insular cortex (IC), piriform cortex (PC), septal area (SA), basal forebrain/preoptic area (BF/POA), amygdala (AMY), hypothalamus (HT), rostral ventromedial medulla (RVM) and the ventral midbrain (VMB). VMB includes the ventral tegmental area (VTA), interpeduncular nucleus and substantia nigra. BF/POA includes the ventral pallidum, horizontal limb of the diagonal band, vertical limb of the diagonal band, medial septal nucleus, substantia innominata and the preoptic area of hypothalamus. By contrast, brain regions with decreased metabolism were observed in widespread cortical areas including the secondary somatosensory cortex (S2), occipital cortex (OC), temporal cortex (TC), retrosplenial cortex (RSC), and the cerebellum (CBL). Most of the regions with high discriminative power were observed bilaterally although the neuropathy was developed by unilateral nerve lesions.

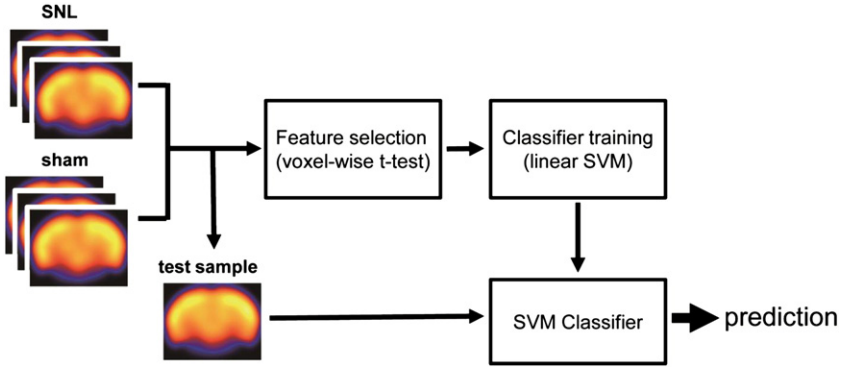

Fig. 1. Flowchart of MVPA classification of neuropathic pain. SVM, support vector machine.

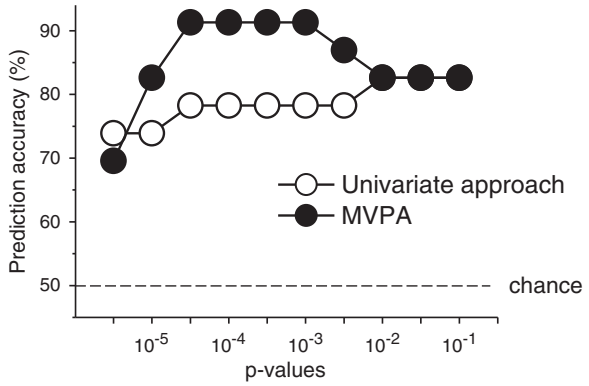

Fig. 3. Comparison of prediction performance between MVPA and univariate approach. Feature voxels were selected by voxel-wise t-tests with a series of *p*-values. The accuracy was measured by leave-one-out cross-validation test.

Comparison between MVPA and univariate approach

We compared the prediction performance between MVPA and univariate approach. Performance evaluation with leave-one-out cross-validation was repeated for univariate approach using the same set of feature voxels with MVPA (see Materials and methods). The univariate approach produced a substantial decrease of prediction accuracy compared to MVPA (Fig. 3, Table 1), suggesting that combinatorial activity patterns of multiple regions better represent the neuropathic pain-induced changes of the brain and provide better biomarkers than single regions.

Discussion

The present study demonstrated that neuropathic pain alters the resting-state brain activity pattern in animal models and multivariate approach using FDG micro-PET can successfully distinguish the animal models of neuropathic pain from sham animals with high prediction accuracy.

There is an urgent need for objective measurements of pain, particularly in basic and preclinical studies. Most widely used reflex methods for pain assessment in animal studies such as tail flick or paw withdrawal have been criticized as they measure the function of the spinal cord and brainstem but do not measure the function of the cerebral cortex which is more important to the clinical assessments of pain (Vierck et al., 2008). Most of the candidate drugs that work well in animal studies have failed to be translated into clinical drugs, and at least in part this failure is due to the commonly used behavioral measures that cannot reflect the multi-dimensional nature of pain (Dolgin, 2010). As a potential complimentary diagnostic tool for animal models of pain, brain imaging techniques, have been used to examine various types of pain models (Hess et al., 2007; Seminowicz et al., 2009, 2012; Upadhyay et al., 2013). However, none of these studies validated the feasibility of the brain imaging-based diagnosis of pain. Our multivariate approach using FDG micro-PET, to our knowledge for the first time, demonstrates the feasibility of the brain imaging-based diagnosis of pathological pain animal models. Furthermore, brain imaging-based diagnosis could provide opportunities to study chronic pain model that is difficult to evaluate the pain due to the lack of motor response, such as phantom pain, headaches, and spinal cord injury induced pain (Zhuo, 2011).

MVPA is an increasingly popular analytical technique in neuroimaging field, because it allows the detection of subtle differences between conditions by considering spatially distributed patterns of brain activity instead of focusing on each voxel in isolation. The technique has been widely applied to brain imaging experiments that identifies the mental representation (Haxby et al., 2001; Lee et al., 2011; Sapountzis et al., 2010; Spiridon and Kanwisher, 2002) or disease states (Ecker et al., 2010; Kloppel et al., 2008; Modinos et al., 2012) in the brain.

In the current study, we showed MVPA achieved higher prediction accuracy than conventional univariate approach in identifying neuropathic pain. Our finding is consistent with the previous studies demonstrating that considering the multiple brain regions enabled more accurate decoding of pain perception (Brodersen et al., 2012; Brown et al., 2011). These studies showed that combined activity of whole brain patterns, or 'pain matrix' regions led to a more accurate prediction of experimentally induced pain than any single brain regions, supporting the multidimensional characteristic of pain perception and distributed representation in the brain. Our results, moreover, suggest that pathological pain-induced plastic changes of the brain are also represented across the distributed brain areas. Taken together, these findings strongly suggest that future development of neuroimaging-based biomarker for clinical pain should focus on the distributed patterns of the brain activity rather than specific single regions.

We found a set of brain regions responsible for the SVM classifier's high discriminating performance between neuropathic pain animals and sham animals. Overall, predictive brain regions with increased metabolism were mainly located in prefrontal–limbic–brainstem networks, which engage in cognitive/emotional modulation of pain (Apkarian et al., 2009, 2011; Lee and Tracey, 2010). Among the prefrontal regions with high discriminative power, insular cortex is believed to play a key role in pain processing (Coghill et al., 1999), particularly in affective component of pain (Singer et al., 2004). It has also been suggested to be importantly involved in the modulation of pain by integrating cognitive and emotional information (Craig, 2009; Gu et al., 2013). Subcortical regions spanning various limbic areas such as amygdala, hypothalamus, septal area, and basal forebrain were predictive with increased metabolism. These limbic regions have been relatively less identified in human studies of pain with functional magnetic resonance imaging (fMRI) compared to cortical regions. This may be due to the low subcortical resolution of fMRI (Walter et al., 2008). Indeed, meta-analyses of pain-related studies revealed that subcortical areas were additionally identified when incorporating the results from animal experiments on human brain imaging studies (Hayes and Northoff, 2012). The prefrontal/limbic regions are reciprocally connected with brainstems and exert top–down modulation of spinal processing of pain. There have been functional imaging studies observing the activation and the altered connectivity of brainstems in response to experimental pain (Becerra et al., 2011; Dunckley et al., 2005;

Table 1
Prediction performance of MVPA and univariate approaches. Sensitivity, specificity, and accuracy were measured using various numbers of feature voxels. # voxels, average number of feature voxels across leave-one-out trials.

	p-Values	5×10^{-6}	10^{-5}	5×10^{-5}	10^{-4}	5×10^{-4}	10^{-3}	5×10^{-3}	10^{-2}	5×10^{-2}	10^{-1}
	# voxels	200	482	2761	5075	15,097	21,725	42,401	53,366	84,092	100,330
Univariate approach	Sensitivity (%)	76.92	76.92	76.92	76.92	76.92	76.92	76.92	76.92	76.92	76.92
	Specificity (%)	70.00	70.00	80.00	80.00	80.00	80.00	80.00	90.00	90.00	90.00
	Accuracy (%)	73.91	73.91	78.26	78.26	78.26	78.26	78.26	82.61	82.61	82.61
MVPA	Sensitivity (%)	76.92	76.92	92.31	92.31	92.31	92.31	92.31	84.62	84.62	84.62
	Specificity (%)	60.00	90.00	90.00	90.00	90.00	90.00	80.00	80.00	80.00	80.00
	Accuracy (%)	69.57	82.61	91.30	91.30	91.30	91.30	86.96	82.61	82.61	82.61

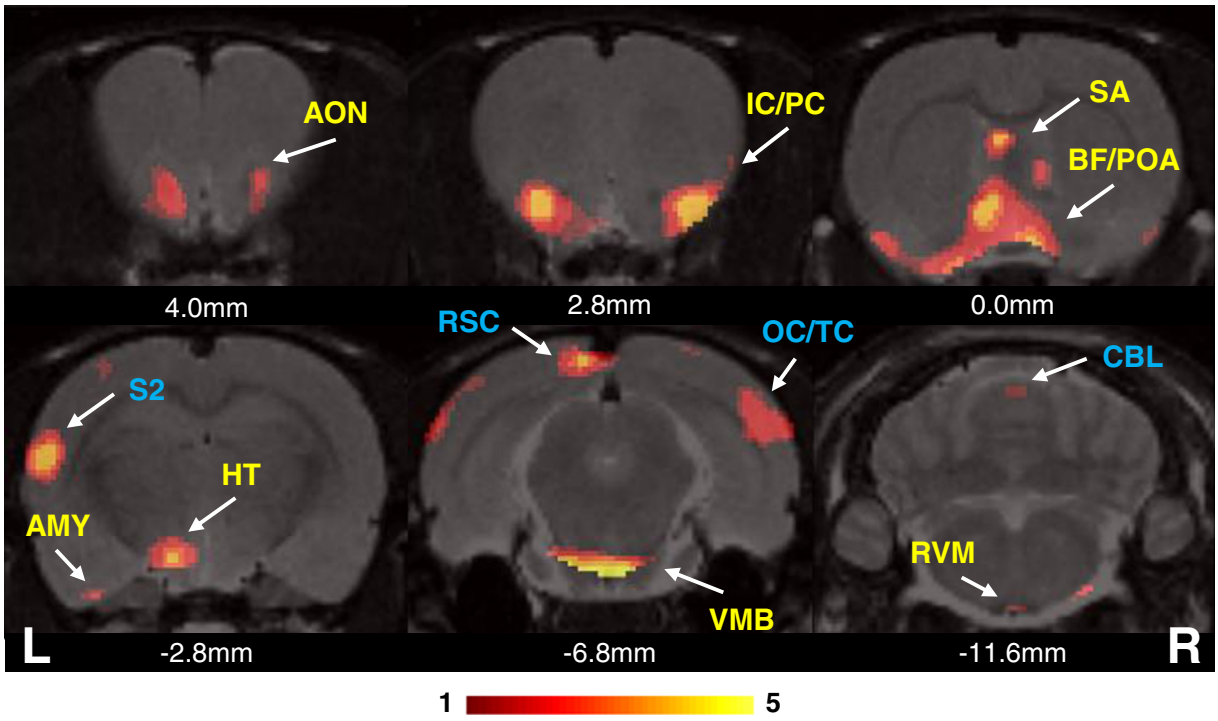

Fig. 4. Brain regions with high discriminative power. The yellow colored texts indicate the regions with increased metabolism following SNL, while the blue colored texts indicate the regions with decreased metabolism following SNL. The color bar indicates the occurrence of feature selection for tests with high accuracy (above 85%). AON, anterior olfactory nucleus; IC, insular cortex; PC, piriform cortex; SA, septal area; BF, basal forebrain; POA, preoptic area; S2, secondary somatosensory cortex; HT, hypothalamus; AMY, amygdala; RSC, retrosplenial cortex; OC, occipital cortex; TC, temporal cortex; VMB, ventral midbrain; CBL, cerebellum; RVM, rostral ventromedial medulla; L, left; R, right.

Zambreanu et al., 2005) or during the modulation of pain (Ploner et al., 2010; Valet et al., 2004). Taken together, one possible interpretation for the predictive regions showing increased metabolism is that neuropathic pain is related to altered cognitive/emotional modulation of pain via prefrontal–limbic–brainstem networks, but how these alterations underlie the pathological pain remains to be clarified. Widespread cortical regions including S2, OC, TC, and RSC were predictive for neuropathic pain and showed decreased metabolism. S2 is one of the most frequently activated brain regions by pain stimulus and thought to be associated with the sensory-discriminative aspect of pain (Seifert and Maihofner, 2009). However, it is uncertain how the decreased activities of S2 and other cortical regions in resting-state are related with the neuropathic pain. It might reflect the altered function of pain perception, or be related to the altered default mode network (DMN). Recently, changes of DMN have been reported in clinical pain (Baliki et al., 2008; Loggia et al., 2013). Rodent brains also have DMN (Lu et al., 2012; Upadhyay et al., 2011) and it might be possible that decreased activities of cortical regions reflect the alteration of DMN activity.

Although the successful prediction results of this study are encouraging, limitation of our study should be noted. First, validation of the classification was performed based on the decision of neuropathic pain with withdrawal reflex measurement, which we aim to complement. This limitation could be overcome by combining a variety of neurobiological indexes of the brain observed in pathological pain, such as activation of immediate early genes or altered electrophysiological properties (Zhuo, 2011). Second, SVM classifier employed in the present study does not provide continuous values for prediction, only classifying subjects in a binary manner. To overcome this limitation, other probabilistic machine learning classifiers, such as Gaussian processes and relevance vector machines could be an alternative choice in future studies (Orru et al., 2012). Third, we did not validate the capability of MVPA to distinguish neuropathic pain from other conditions that have the potential to cause similar patterns of brain activity with SNL animals. Further studies are needed that classifying neuropathic pain from other conditions such as anxiety or other types of pain. Lastly, although our study provides valuable information about which brain regions represent the altered states of neuropathic pain in combination, it is not clear how the regions with high discriminating power changed their interconnectivity, thereby changed the distributed pattern of the brain activity. Graph theoretical approach could provide deeper insight into how the neuropathic pain alters the distributed brain network (He and Evans, 2010).

Conclusions

We demonstrated that FDG micro-PET and multivariate pattern approach can successfully identify animal models of neuropathic pain at the individual level by capturing the altered pattern of the resting-state brain activity. We also showed the superior prediction performance of MVPA compared to univariate approach, highlighting the importance of distributed patterns of brain activity in pathological pain. Our results suggest that developing neuroimaging-based diagnostic tools for pathological pain can be achieved by considering patterns of the resting-state brain activity.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.neuroimage.2013.10.001.

Acknowledgments

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Conflict of interest statement

The authors declare no conflict of interest.

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