Functional dissociation within insular cortex: The effect of pre-stimulus anxiety on pain

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\textbf{A B S T R A C T}

Brain activity resulting from changes in pain intensity may not only reflect changes in stimulus intensity but also in emotional distress. The anterior and mid-posterior insula have been associated with anticipatory anxiety and sensory-discrimination, respectively. We hypothesized that the two sub-divisions would exhibit different post-stimulus responses to increased pain intensity after removing the confounding effect of anticipatory anxiety. Using functional magnetic resonance imaging, activity was found in the anterior and mid-posterior insula in response to both low- and high-intensity painful stimuli delivered at the same level of anticipatory anxiety. Anterior insula activity covaried with anxiety ratings. When the pain intensity increased and the level of anticipatory anxiety was matched, increased activity was found in the mid-posterior insula but not in the anterior insula. The increase in activity covaried with increased pain intensity. These findings support the notion that encoding in the anterior insula primarily depends on the pre-stimulus context, i.e., anticipatory anxiety rather than the perceived pain intensity, and encoding in the mid-posterior insula is related to pain intensity changes.

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\section{Introduction}

Pain is an interoceptive sensation with a high threat value (Craig, 2003; Paulus and Stein, 2006). Receiving pain or merely anticipating it can induce anxiety (Asmundson and Katz, 2009; Floghaus et al., 2003) and result in maladaptive behavior, such as fear-avoidance of pain (Vlaeyen and Linton, 2000). This is particularly important in clinical context, such as dental treatment or needle insertion, where patients often anticipate strong pain and perceive increased pain due to anticipatory anxiety (Armfield et al., 2007). Cumulating evidence has shown that the pain experience is associated with the activation of a network of brain regions, including the insular cortex, the anterior cingulate cortex (ACC), the primary (SI) and secondary (SII) somatosensory cortices, and the thalamus (Apkarian et al., 2005; Tracey and Mantyh, 2007). The findings are often obtained by contrasting brain activity in response to high- and low-intensity stimuli. However,
because the increased stimulus intensity is usually linked to increased anxiety towards impending pain, these brain regions may not only reflect a change in perceived intensity of pain but also in pain-related anxiety. It remains unclear how the brain responds specifically to a change in pain intensity when the stimulation is maintained at the same level of pre-stimulus anxiety.

In this study, we aimed to investigate the brain responses to two levels of pain intensities delivered at matched level of pre-stimulus anxiety. We focused on the role of the insular cortex, which participates in both the lateral (sensory-discriminative) and the medial (cognitive-affective) pain systems (Treede et al., 1999). The insular cortex plays a key role in integrating the interoceptive sensation into the subjective experience (Craig, 2003, 2009). The mid-posterior insula reflects change in stimulus intensity (Craig et al., 2000; Critchley et al., 2004), and the anterior insula reflects change in emotional distress and stimulus salience (Wiech et al., 2010). Evidence suggests the involvement of the anterior insula in anticipatory anxiety towards impending aversive stimuli (Nitschke et al., 2006; Schunck et al., 2008; Simmons et al., 2011) and the concomitant modulation of the pain experience resulting in pain bias (Carlsson et al., 2006). Although the anterior insula is known to be engaged prior to delivery of a painful stimulus, e.g., during the anticipatory phase (Ploner et al., 2010; Wiech et al., 2010), it remains unclear if the response in this region following the delivery of the stimulus only reflects emotional distress or also to some extent the physical properties of the stimulus, e.g., the stimulus intensity.

Based on these putative functions of the insular cortex, we hypothesized that the two sub-divisions would exhibit different post-stimulus responses to increases in pain intensity according to manipulations of anxiety. We predicted that (A) the mid-posterior insula would reflect changes in pain intensity and (B) the anterior insula would exhibit a substantially smaller response to pain intensity changes than that of the posterior insula when removing the confounding effect of anxiety prior to delivery of the pain stimuli. We applied an associative learning paradigm (see Section 4) to induce anticipatory anxiety. Painful stimuli were delivered in an unpredictable condition (i.e., the cue preceding a stimulus being unpredictable to the stimulus intensity) and a predictable condition (i.e., the cue being predictive to the stimulus intensity). Tooth pulp stimulation was used to induce pain because it almost exclusively activates nociceptive fibers (Nord, 1976) and dental pain is often associated with substantial anxiety (Armfield et al., 2007).

2. Results

2.1. Behavioral results

All participants had low levels of depression (mean ± standard deviation: 6.3 ± 3.0; range: 2–13) and dental anxiety (9.5 ± 2.6; range: 5–14) as assessed by questionnaires on the scan day. According to the post scan ratings, the non-predictive cue induced significantly higher anxiety levels (score: 2.80 ± 0.65) than the predictive cue (score: 1.03 ± 0.79) (Wilcoxon Signed-Rank Test, Z = 3.38; p < 0.001), showing the manipulation of anticipatory anxiety was successful. In the high-anxiety conditions (HA), the high-intensity (HAHI) (score: 5.73 ± 1.35) was rated significantly more painful than the low intensity (HALI) (score: 3.18 ± 1.62) (Wilcoxon Signed-Rank Test, Z = 3.38; p < 0.001).

2.2. Functional MRI results

In Analysis 1, we investigated the brain regions that con-junctively activated in the HAHI and HALI conditions. Increased activity was found bilaterally in the anterior and mid-posterior insula, the ACC, the posterior cingulate cortex (PCC), the supplementary motor area, the face region of SI, the thalamus, and the cerebellum, and the right (ipsilateral) SII, among others (p < 0.001, uncorrected) (Fig. 1A, Table S1). These regions therefore are involved in pain processing when pre-stimulus emotional distress was matched regardless of the stimulus intensity level.

The regression analyses showed that, in the low intensity condition (HALI), activity in the left anterior insula ([x, y, z] = [−40, 20, −4]) significantly correlated with anxiety ratings across subjects (peak Z score = 4.06, uncorrected p < 0.001; mean parameter estimate: r = 0.75) (Fig. 1B). Furthermore, in the high intensity condition (HAHI), activity in the left frontal operculum, extending to the anterior insula ([x, y, z] = [−48, 20, −4]), significantly correlated with anxiety ratings across subjects (peak Z score = 4.50, uncorrected p < 0.001; mean parameter estimate: r = 0.78) (Fig. 1C).

In Analysis 2, we investigated the differential activity to increased stimulus intensity. Comparing HAHI with HALI, we found an increased activity in the bilateral mid-insula (extend-ing posteriorly), the left temporal pole, the right thalamus, the right orbitofrontal cortex, and the right inferior parietal lobule (p < 0.001, uncorrected) (Table 1, Fig. 2A). Using a lower threshold, we found increased activity in the bilateral SII, the right SI and the bilateral mid-insula (extending anteriorly to y = 6) (p < 0.005 uncorrected) (Table S2). Although the local maxima in the mid-insula and in the temporal pole were located within the same cluster it did not extend into the anterior insula, even at the lowered threshold. The regression analyses showed that, when comparing the high- and low-intensity conditions, activity in the right posterior insula ([x, y, z] = [40, −14, 0]) significantly correlated with pain ratings across subjects (peak Z score = 3.61, uncorrected p < 0.001; mean parameter estimate: r = 0.79) (Fig. 2B), and the right mid-insula ([x, y, z] = [40, 0, −6]) significantly correlated with pain ratings across subjects (peak Z score = 3.24, uncorrected p < 0.001; mean parameter estimate: r = 0.81) (Fig. 2C).

In Analysis 3, the whole-brain exploratory analysis of the high-anxiety anticipatory phase revealed significant activity (uncorrected p < 0.001) in several regions including the left anterior insula ([x, y, z] = [−38, 18, 0]), the right anterior insula ([x, y, z] = [28, 20, 6]) and the right posterior insula ([x, y, z] = [36, −12, 4]) (Supplementary Fig. S1). The locus in the left anterior insula overlapped spatially with that found to correlate with anxiety ratings in the post-pain phase. No overlap was found between the locus in the posterior insula from the anticipatory phase and that which correlated with changes in pain intensity from the post-pain phase.
3. Discussion

3.1. Summary of the major findings

The current study investigated the central processing of pain in context of emotional distress preceding delivery of pain stimuli. The cue-intensity association paradigm from Ploghaus et al. (2001) was modified into an event-related paradigm with online pain intensity rating of each stimulus. In agreement with our hypothesis, we found activity in bilateral anterior and mid-posterior insula in response to both low- and high-intensity painful stimuli delivered at matched anxiety level. Furthermore, when the perceived pain intensity increased, increased activity was found in the bilateral mid-posterior insula but not in the anterior insula (even at lowered threshold). As a conflux of both the lateral and the medial pain systems, the insular cortex plays a key role in pain processing (Apkarian et al., 2005; Treede et al., 1999). Our findings are in accord with this and the differential involvement of the insular sub-divisions in pain processing and their distinct functional connectivity patterns (Cauda et al., 2011; Peltz et al., 2011). It should be noted that the absence of anterior insula activity in the comparison between low- and high-intensity conditions by no means prove that no difference exists. However, the result suggests that the anterior insula is less responsive than the posterior insula to manipulations of stimulus intensity when pre-stimulus anxiety is matched.

3.2. Anterior insula encodes pain-related anticipatory anxiety

Anterior insula activity in response to both low- and high-intensity pain stimuli but not in the comparison between the two intensity conditions suggests that this region is more responsive to changes in perceived pre-stimulus anxiety rather than perceived pain intensity. This is further supported by our finding of covariation between the individual left anterior insula activity and anxiety ratings in both low- and high-intensity conditions. In addition, activity in the left anterior insula was also found in the high-anxiety anticipatory phase preceding the delivery of pain stimuli. Activity in the anterior insula in response to pain stimuli has previously been shown to depend on the predictability of the stimulus (Carlsson et al., 2006) and it has been suggested to reflect the subjective anxiety caused by a mismatch between the predicted and the actual interoceptive experience (Paulus and Stein, 2006). The anterior insula is considered part of a salience network in which it plays an important role by integrating the threat of an impending stimulus into the pain experience (Ploner et al., 2010; Wiech et al., 2010). In agreement with this, the regions found to be engaged in the anticipatory phase of this study overlaps with what is known as the salience resting-state network (Heine et al., 2012). Our results further suggest that the anterior insula not only responds to the heightened pre-stimulus threat but such a response is retained during the stimulus phase as its activity did not differ between the two intensity conditions when the anxiety levels were matched (stimuli were preceded by the same cue). The anterior insula response may thus reflect integrative processing of stimulus-inherent properties with the subjective emotional state such as, e.g., anxiety.

3.3. Mid-posterior insula encodes the changing pain intensity

Increased activity in the bilateral mid-posterior insula, when the perceived pain intensity increased and the anxiety level was matched, and its covariation with pain ratings is in agreement with its involvement in integration of sensory-discriminative information (Coghill et al., 1999; Craig et al., 2000; Derbyshire et al., 1997). The posterior insula is frequently
reported to be engaged in response to nociceptive stimulation (Apkarian et al., 2005). It receives projections from the posteri- or ventromedial nucleus of the thalamus, an important thalamocortical pathway to convey homeostatic information, including pain (Craig et al., 1994). Direct electrical stimulation to this region elicits pain sensation (Mazzola et al., 2009). Its activation increases with the subjective pain ratings (Bornhövd et al., 2002; Alkire et al., 2004), reflecting a qualitative change from nonpainful to painful (Oertel et al., 2012), and is soma- totopically organized to the site of painful stimulation (Brooks et al., 2005) as well as innocuous cool stimulation (Hua et al., 2005). Changing mid-insula activation also reflects the increased intensity of painful electrical stimuli (Alkire et al., 2004) as well as innocuous thermal stimuli (Craig et al., 2000).

Our findings are in accord with these reports, and strengthen the notion that the mid-posterior insula predominantly encodes changes in the physical intensity of interoceptive stimuli and is at the core of a brain network supporting the experience of somatic pain (Craig, 2009; Mazzola et al., 2009).

In our study, painful dental stimuli evoked activity in bilateral cortical and subcortical regions consistent with previous studies on dental stimulation (Jantsch et al., 2005; Ettlin et al., 2009). Although activity in somatosensory areas is known to encode stimulus intensity, the areas only passed a lowered threshold in the present study (uncorrected \( p < 0.005 \)). Using similar pulpal stimulation, Jantsch et al. (2005) found activity in ipsilateral SI and bilateral SII. This discrepancy may be attributed to the difference in the stimulus paradigm. In the present study, we employed brief 10-ms pulses whereas Jantsch et al. (2005) employed 20-s stimulus blocks. It is well known that regions involved in sensory-discrimination are sensitive to stimulus parameters (Tran et al., 2010). Also, although block designs are known to be statistically more powerful than event-related designs they do not provide the possibility of subjectively rating the pain intensity of each stimulus (Friston et al., 2000).

### Table 1 – Brain regions showing increased activity in response to increased stimulus intensity (‘HAHI-HALI’), \( p < 0.001 \), uncorrected.

<table>
<thead>
<tr>
<th>Brain region</th>
<th>BA</th>
<th>Laterality</th>
<th>MNI coordinates</th>
<th>Cluster size (mm(^3))</th>
<th>Z score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mid-posterior insula</td>
<td></td>
<td>L</td>
<td>-38</td>
<td>2</td>
<td>-10</td>
</tr>
<tr>
<td>Temporal pole</td>
<td>38</td>
<td>L</td>
<td>-46</td>
<td>14</td>
<td>-16</td>
</tr>
<tr>
<td>Mid-posterior insula</td>
<td></td>
<td>R</td>
<td>40</td>
<td>0</td>
<td>-6</td>
</tr>
<tr>
<td>Posterior insula</td>
<td></td>
<td>R</td>
<td>42</td>
<td>-8</td>
<td>-6</td>
</tr>
<tr>
<td>Frontal orbital cortex</td>
<td>47</td>
<td>R</td>
<td>48</td>
<td>20</td>
<td>-6</td>
</tr>
<tr>
<td>Thalamus</td>
<td></td>
<td>R</td>
<td>2</td>
<td>-18</td>
<td>2</td>
</tr>
<tr>
<td>Mid-insula</td>
<td></td>
<td>R</td>
<td>38</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>Superior parietal lobule</td>
<td>42</td>
<td>R</td>
<td>68</td>
<td>-32</td>
<td>20</td>
</tr>
<tr>
<td>Temporal pole</td>
<td>38</td>
<td>L</td>
<td>-40</td>
<td>12</td>
<td>-24</td>
</tr>
</tbody>
</table>

![Fig. 2 – (A) Increased activity in bilateral mid-insula (\( p < 0.001 \), uncorrected) when comparing the HAHI condition to the HALI condition. (B)–(C) Regression with the change in pain ratings revealed significantly correlated activity in the right posterior insula (B) and mid-posterior insula (C) across subjects (uncorrected \( p < 0.001 \)). MPI, mid-posterior insula; PI, posterior insula; PE, mean parameter estimate.](image)

3.4. **Limitations of the study**

Several limitations in this study needs to be discussed. First, online trial-by-trial anxiety ratings were not acquired. This constrains a direct comparison of the two regression analyses using anxiety and pain ratings. Furthermore, online anxiety...
ratings would help to elucidate the progression of pain-related anxiety in the task and the trial-by-trial influence of anxiety on pain perception. The insular activation observed in our high-anxiety conditions may reflect a general effect of anxious anticipation, not specific to aversive stimuli (Carlson et al., 2011). Nonetheless, it is noteworthy that repeated self-assessment of the anxiety level may alleviate or dampen the distress evoked by anticipation. Second, State and Trait anxiety scores were not collected. Insular responses are critically associated with an anxiety-related personality. Anxiety-prone individuals show greater insular activation when anticipating threatening stimuli (Simmons et al., 2006). The state and Trait anxiety scores are, respectively, associated with functional and structural connectivity between the anterior insula and the amygdala, which plays a critical role in attending to threat (Baur et al., 2012). Our study focused on the anxiety specifically related to pain anticipation, whereas the role of state- and trait-related impacts on anxiety in a pain-specific context would require further investigation.

3.5. Conclusions

By controlling the emotional context of pain stimulation, our data suggest that the anterior and mid-posterior divisions of the insula preferentially respond to different aspects of pain processing. As expected, the mid-posterior division responded to changes in pain intensity and it correlated with pain ratings in accord with a role in sensory-discrimination. Activity in the anterior division did not differ significantly between the low- and high-intensity conditions when the pre-stimulus confound of different levels of anticipatory anxiety was removed. Together with the covariation with anxiety ratings, this further supports the notion that encoding of information in the anterior insula depends on the pre-stimulus context rather than the perceived stimulus per se.

4. Experimental procedure

4.1. Participants

Sixteen right-handed healthy participants (seven males, nine females,) were enrolled in this study. One male subject was excluded due to failure to follow instructions, leaving 15 participants (mean age ± standard deviation 27.3 ± 11.2 years, age range 22–58) for further analysis. According to the inception interview, participants had no history of neurological or psychiatric disease or chronic pain, and were not taking any medication at the time of the experiment. Oral examination was performed to confirm the stimulation site (the right incisor) was intact. Written informed consent was obtained from participants to a protocol approved by the Institutional Ethics Committee. The study was conducted in accordance with the declaration of Helsinki.

4.2. Experimental design

The experimental design was a modification of the cue-intensity association paradigm implemented by a previous study (Ploghaus et al., 2001) (Fig. 3). Each trial consisted of an anticipatory phase (6–10 s; mean: 8 s) followed by a stimulation phase (8–13 s; mean: 10.5 s) and ending with a pain-intensity rating phase (12 s). The anticipatory phase was initiated by one of two types of visual cues (triangle or square), which differed in predictability of the pain intensity of the impending stimulus and thus induced different levels of anticipatory anxiety (Ploghaus et al., 2003). This was confirmed by post scan anxiety ratings of the cues (see below). The predictive cue (triangle) was always followed by a single low-intensity painful stimulus (LI) and induced low-anxiety (LA). The non-predictive cue (square) was followed by either a low-intensity (as above) or high-intensity (HI) painful stimulus and induced high anxiety (HA). Overall, each of the cue-intensity pairs (LA–LI, HA–LI and HA–HI) was presented in equal numbers throughout the experiment. The visual cue was displayed throughout the anticipatory phase and pain phase to increase cue-intensity association. After the delivery of the painful stimulus, the visual cue was replaced by a visual-analogue scale (VAS) (the rating phase). In this phase, subjects were required to rate the pain intensity of the stimulus just received via an online response box.

Subjects were instructed that two types of cues would be displayed during functional scanning and that attention should be paid to the cue-intensity association. Two sessions were performed with 30 event-cycles per session and a 5-min between-session break. Two fixed sequences were generated

Fig. 3 – (A) An event-related experimental paradigm was used in which each event-cycle consisted of an anticipatory phase followed by a pain phase and ending with a pain-intensity rating phase. A single stimulus was delivered to the tooth at onset of the pain phase. Online pain rating was allowed in a 6-s time window following the visual onset of the pain rating scale. (B) The two visual cue types (square and triangle) differed in predictability of the pain intensity of the impending stimulus. The good predictor (triangle) was always followed by a low-intensity stimulus to induce low anxiety; the poor predictor (square) was followed by either low- or high-intensity stimuli to induce high anxiety.
in which stimuli were randomly presented. The order of sequences with, respect to sessions was counter balanced across subjects. In all, subjects received 20 randomized trials for each condition (LALI, HALI and HAHI).

4.3. Tooth pulpal stimulation

Electrical stimulation (square-wave, 10-ms duration, Grass Telefactor 888, W. Warwick, RI, USA) of the enamel surface of the right upper incisor was delivered via an in-house made electrode. The two stimulus levels to be applied during functional scans were calibrated outside the scanner room for each subject by the method of ascending limits in 4 series (the first was discarded) and corresponded to 3 (the ‘LI’ level) and 6 (the ‘HI’ level) on the VAS (range 0–10; 0, no pain; 10, intolerable pain).

4.4. Psychological assessment

Prior to scanning, participants completed Beck’s depression inventory (BDI; Beck et al., 1961) and the Modified Dental Anxiety Scale (MDAS; Humphris et al., 1995). The MDAS is a widely used tool for assessing dental pain and anxiety (Armfled, 2010), and is used here to assess pain-related anxiety specific to the context of tooth stimulation. Post scan ratings of the perceived anxiety of the two cues were obtained according to a 0–5 scale, in which ‘0’ represents ‘no anxiety towards the impending pain’ and ‘5’ represents ‘extreme anxiety towards the impending pain’. For the behavioral data, a one-tailed Wilcoxon Signed Rank Test was used to test for significant changes and p<0.05 was considered significant.

4.5. fMRI protocol

Data were acquired on a 3T imaging system (Bruker MedSpec S300, Kalsruhe, Germany) with a quadrature head coil. Functional data were acquired with T2*-weighted gradient-echo EPI using blood oxygenation level dependent contrast (TR/TE/\(T1\) = 2000 ms/50 ms/90°) with the parameters: matrix, 64 × 64 × 20; voxel size, 3.6 × 3.6 × 5 mm\(^3\); field of view (FOV), 230 × 230 mm\(^2\) with a 120 mm coverage in the slice direction (axial; 5 mm thickness plus 1 mm gap). The anatomical image was acquired using a T1-weighted, 3D gradient-echo pulse sequence (modified driven equilibrium Fourier transform: TR/TE/TI = 88.1 ms/4.12 ms/650 ms) with the following parameters: matrix, 256 × 256 × 192; voxel size, 0.9 × 0.9 × 1.5 mm\(^3\); FOV, 230 × 230 mm\(^2\).

4.6. Image processing and statistical analysis

Functional imaging data were pre-processed and analyzed with statistical parametric mapping (SPM5 software from Wellcome Trust Centre for Neuroimaging, London). Scans were slice time corrected, realigned and co-registered to the individual anatomical image before being normalized to standard space (Ashburner et al., 1999). Scans were further re-sampled (2-mm\(^3\) voxel), smoothed (8-mm), high-pass filtered, and corrected for temporal serial correlations (Friston et al., 2000). For image statistics at the individual level, the onsets of predictive cues (square or triangle), electrical stimuli (LI or HI) and the VAS were taken as separate events and modelled using a canonical hemodynamic response function with temporal derivatives. Events corresponding to the responses to low-intensity (LI) pain stimulation were further divided into two subtypes according to the preceding predictive cue inducing either high (HA) or low (LA) levels of anxiety and were labeled as HALI and LALI (Fig. 3), respectively. Events corresponding to high-intensity pain stimulation were always preceded by the unpredictable high-anxiety cue and were labeled as HAHI (Fig. 3). Finally, the entire interval between the onsets of the predictive cues and the onsets of the pain stimuli were modelled as pre-pain anxiety (LA or HA) using a canonical hemodynamic response function without temporal derivatives. Head movement parameters were modeled as the regressors of no interest.

4.7. Group analysis

At the group level, random effect analyses were performed on the pain responses resulting from the two levels of electrical stimulation with matched anxiety levels (HAHI and HAHI). In Analysis 1, the main effects of HAHI and HALI conditions were first modeled separately. A conjunction analysis (Price and Friston, 1997) between the two conditions was then performed to reveal spatially overlapping brain regions when pre-pain anxiety levels were matched. To find the brain regions covarying with anxiety ratings, additional whole-brain voxel-wise regression analyses were performed for the two conditions, separately, using the individual anxiety rating as a regressor. In Analysis 2, HAHI and HALI conditions were compared directly (HAHI–HALI) in order to investigate which brain regions were related to increased pain intensity at matched levels of pre-pain anxiety. To find brain regions covarying with changes in pain intensity between the two conditions, an additional whole-brain voxel-wise regression analysis was performed for the comparison ‘HAHI–HALI’, using the difference in individual mean pain rating as a regressor. In all cases, the whole-brain searches were performed at an uncorrected voxel threshold set at p<0.001. To visualize the correlation across individuals, we extracted the individual mean parameter estimate from all the voxels within the above-threshold clusters within bilateral insular cortices found in the respective regression analyses (REX toolbox, Department of Brain and Cognitive Sciences, Massachusetts Institute of Technology, MA). The mean parameter estimate was then correlated with the anxiety ratings and change in pain intensity ratings, across all participants. To avoid non-independency, p-values were not reported for this approach. A third analysis, Analysis 3, was performed on the anticipatory phase following the unpredictable cue inducing high anxiety (HA). A whole-brain search was performed at an uncorrected voxel threshold set at p<0.001 in order to compare regions engaged during the anticipatory phase and the post-pain phase. Data used in the present study are also subject to another approach reported elsewhere.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.brainres.2012.11.035.

References


