

DISAMBIGUATION OF VISUAL STIMULI CORRELATES WITH ACTIVITY IN BILATERAL MEDIAL TEMPORAL LOBE STRUCTURES

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ABSTRACT

We are organisms adapted to recognise patterns around us in order to avoid ambiguity and indecision and there are inter-individual differences at this level. Ambiguity can be studied in the context of the decision making process, problem solving, perception of images or text comprehension. The purpose of our study is to investigate with fMRI the neural correlates of inter-individual differences related with healthy people's performance of ambiguous images perception using a modified form of Snowy Pictures Task. We found a significant positive correlation between performance in disambiguating the pictures and bilateral activation of entorhinal cortex, perirhinal cortex and hippocampus (Pearson chi square = 3,86, df = 1, p < 0.05, N = 22). It is documented that tasks having a higher level of ambiguity seem to take place gradually on the ventral visual circuit axis, from occipital and occipito-temporal cortices to perirhinal cortex and finally hippocampus. Other studies revealed that hippocampus is also a key structure in modulating anxiety so our results raise the hypothesis that anxiety, at least in some situations, could be triggered by an inability of hippocampus to manage ambiguous situations.

Key words: dealing with ambiguity, visual perception, medial temporal lobe, anxiety

We are organisms adapted to recognise patterns around us in order to avoid ambiguity and indecision. This wish to counteract uncertainty and to maintain control has always been considered a primary force, fundamental in the human life and one of the most important variables governing mental well-being and physical health. On the contrary, the feeling of lack of control results in perception of illusory patterns, like in the Whitson and Galinsky (2008) experiments. In these experiments subjects identified coherent and meaningful relations into a succession of random events like perceived false correlations or imaginary figures, superstitious rituals, and conspiracy scenarios. This phenomenon of illusory patterns perception could be interpreted as a compensatory mechanism to regain the feeling of control (Whitson and Galinsky, 2008). In this way,

people make the world predictable, regain their self-esteem, and feel the need to engage in exploration and approaching new challenges.

Imaging studies have shown that when people make decisions under uncertainty, several brain regions are recruited : medial prefrontal cortex/dorsal anterior cingulate cortex (BA 9, 8, 6, and 32), middle frontal gyrus (BA 10, 9, and 46), right inferior frontal gyrus (BA 45, 44, and 47), right inferior parietal lobule (BA 40), posterior cingulate cortex (BA 23 and 31), intraparietal sulcus (BA 7), insular cortex and right dorsal caudate nucleus (Knutson et al., 2001; Keri et al., 2004; Huettel, Song and McCarthy, 2005; Rushworth et al., 2007). It is interesting that perception of a low instrumental control, in addition to the preparation of instrumental behavioural responses, also amplifies the subjective per-

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ception of pain in mid-anterior cingulate cortex. For instance, a high perceived uncertainty during an economic decision making task activates the above mentioned zone of cingulate cortex, and negative affect, pain and cognitive control are all sensible to the manipulation of uncertainty level, described either in terms of ambiguity, risk, controllability, predictability or volatility (Shackman et al., 2011).

When the outcomes of a decision can not be specified, not even probabilistically, the decision process is called under ambiguity condition. Most of the time, people are more reluctant toward ambiguity even than facing risk (Platt and Huettel, 2008). Beside activation of anterior cingulate, ambiguous situations or stimuli are also characterised by activations in lateral orbitofrontal cortex, anterior insula and amygdala (Platt and Huettel, 2008; Rangel, Camerer and Montague, 2008).

There are inter-individual differences in reaction to uncertainty. Hence, neurotic people react stronger to it, preferring to endure the discomfort of a negative feedback than to experience the lack of feedback. They tend to see the unknown as more threatening than the usual, and it seems that this trait is related with a higher activity into the neural network linking amygdala with rostral anterior cingulate cortex, similar with the activity observed in people with anxiety disorders (Hirsh and Inzlicht, 2008). This overactivation of amygdala and rostral cingulate, in addition with a deficit in the coupling of these two structures, seems to affect efficient integration of information and consequently emotional and behavioural adaptation. This abnormal activity is related with an elevated and longer presence of dopamine into this network (Kienast et al., 2008). This particularity of dopamine functioning could be determined by several factors, like T102C polymorphism of the gene encoding 5-HT2A receptor of serotonin, or the A1 allele of the DRD2 gene encoding D2 receptor of dopamine. A1 allele leads to a 40% reduction in the D2 receptor density (especially in ventral striatum) and is associated with neuroticism and anxious attachment type (Gilllath et al., 2008).

Ambiguity can be studied in the context of the decision making process, problem solving, perception of images or text comprehension. Concerning the perception of ambiguous images, several paradigms and several imaging and electrophysiological studies have investigated the neural correlates of this process. One paradigm is «bistable perception». When sensory input allows for multiple, compelling interpretations, observers' perception can fluctuate over time, which is called bistable

perception. Imaging studies in humans have revealed transient responses in a right-lateralised network in the frontal-parietal cortex around the time of perceptual transitions between interpretations (Knapen et al., 2011).

There is a large amount of unexplained variability between individuals in the rate of such spontaneous alternations in perception. In an attempt to study this inter-individual variability, Kanai, Bahrami and Rees (2010) have recorded reports of spontaneous alternations for an ambiguous rotating structure-from-motion (SFM) stimulus that evoke bistable perception fluctuating between two rotation directions using three measures for testing the variability in perception : gray matter density, cortical thickness and fractional anisotropy of white matter. They have found a significant negative correlation between cortical thickness and percept duration across individuals in the bilateral superior parietal lobule and bilateral postcentral gyrus – the thicker the cortex in these regions, the faster the switch rate of an individual. Also, they found significant correlations between gray matter density in the right superior parietal lobe and individual's perception duration, and significant negative correlations between fractional anisotropy in the white matter beneath the left superior parietal lobule and bistable perception duration.

The purpose of our study is to investigate with fMRI the neural correlates of inter-individual differences related with people's performance of ambiguous images perception using a modified form of Snowy Pictures Task similar with the one used in Whitson and Galinsky's study. Our hypothesis is that people with high performance in disambiguating degraded images in Snowy Pictures Task have a different activation pattern in brain regions involved in visual perception and object recognition than people with low performance.

Subjects

22 volunteers participated, 12 women and 10 men, mean age 30,6 years. The subjects had normal seeing ability, no psychological training (in order not to be familiar with the pictures), and also no psychiatric history.

MATERIALS AND METHODS

Participants completed a modified form of the Snowy Pictures Task similar with that used by Whitson and Galinsky (2008) in their experiment. The task is drawn from the aptitude literature, and

was originally used to test perception. It consists of a series of ‘snowy’ pictures – pictures that are grainy and granulated so that it is difficult to make out an image in them. For the purposes of this experiment, half of the pictures were taken and manipulated using digital media software such that no traces of the original image remained (See Figure 1).

Participants were told the task involved visual perception and that “it is helpful to be able to see objects quickly in spite of their being partially concealed by snow, rain, haze, darkness, or other visual obstructions. Describe what you see only if you are sure that is an image hidden there. Your score on this test will be the number of pictures that you name correctly.” The scanning session consists

of 3 slides with snowy pictures and 3 control slides. Each slide with a picture was followed by a control slide, and each slide was exposed for 30 seconds. The images were projected on the wall in front of the MRI, and the subject could see them by using the optical system part of the helmet. The subjects were told to examine each slide containing snowy pictures and to restrain from commenting or answering. After each slide was a pause, during which the scanning was put on hold, and in this time window the subject had to give the answer. The answers were noted down by the experimenters. During control slides, the subjects were instructed to wait with their eyes closed, until they were told to open them and look at another picture (see Figure 1).

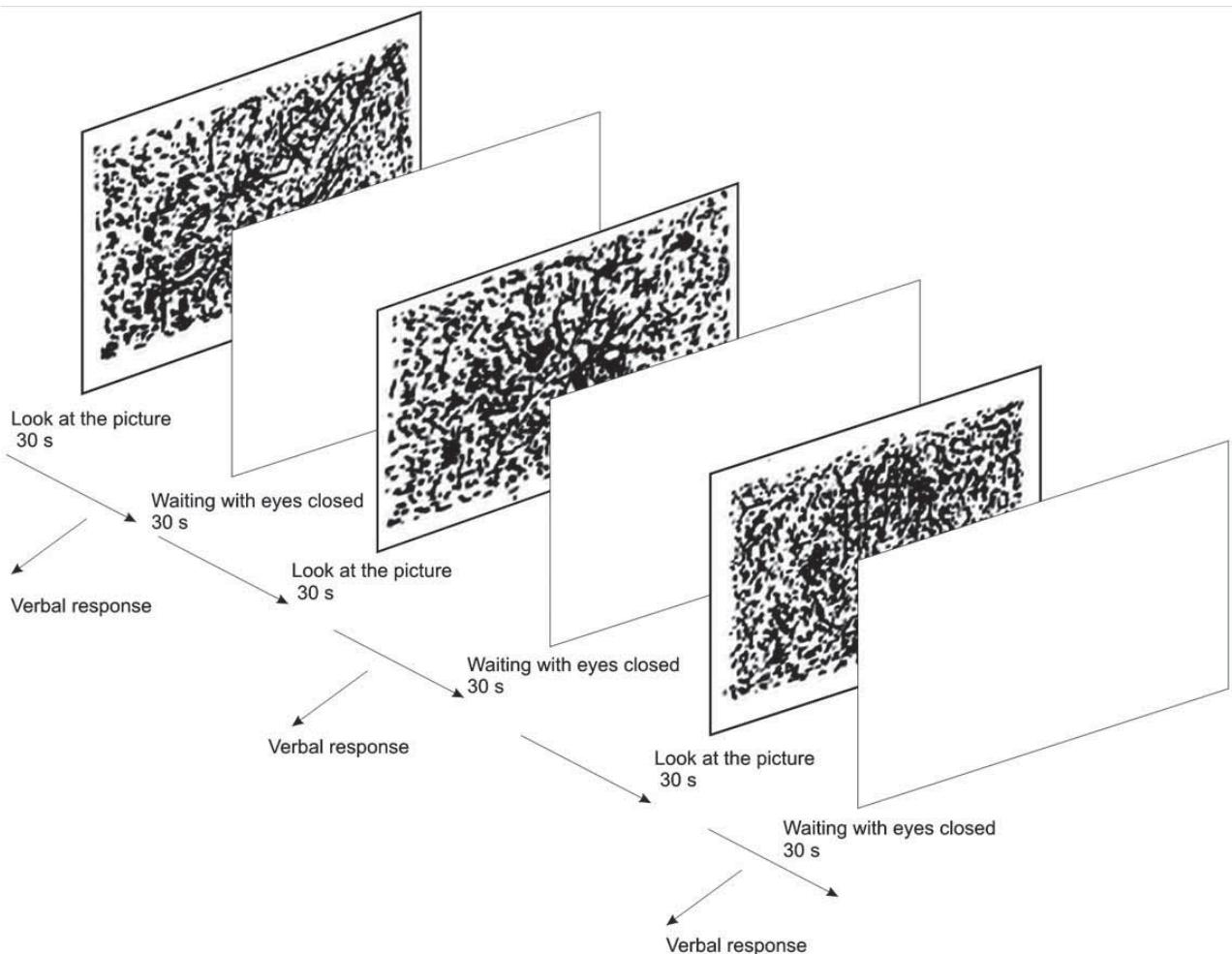


Figure 1. Participants completed a modified form of the Snowy Pictures Task similar with that used by Whitson and Galinsky (2008) in their experiment. Participants were told the task involved visual perception and that “it is helpful to be able to see objects quickly in spite of their being partially concealed by snow, rain, haze, darkness, or other visual obstructions. Describe what you see only if you are sure that is an image hidden there”. Your score on this test will be the number of pictures that you name correctly. “The scanning session consists in 3 slides with snowy pictures and control 3 slides. Each slide with picture was followed by a control slide, and each slide was exposed for 30 seconds. The images were projected on the wall in front of the MRI, and the subject can see them by using the optical system part of the helmet. The subjects was told to examine each slide containing snowy pictures and to restrain from commenting or answer. After each slide was a pause, during which the scanning was put on hold, and in this time window the subject has to give the answer. The answers were noted down by the experimenters. During control slides, the subjects were instructed to wait with the eyes closed, until they are told to open them and look at another picture.

Data acquisition

Images were acquired using a 1.5 tesla GeneralElectric (Milwaukee, WI) scanner with echo planar imaging method by using a quadrature brain coil provided by the manufacturer. The scanning took place in Medix Co. laboratory, within the Centre for Diagnostic and Treatment of Victor Babes hospital in Bucharest. The scanning parameters were the following: repetition time (TR), 3000 ms; echo time (TE), 40 ms; flip angle, 90°; matrix size, 64 x 64; field of view, 22 cm; slice thickness, 4 mm; number of slices, 30. These scanning parameters resulted in a 3.437 x 3.437 x 4 mm voxel size. Two runs of 6 min (180 images) were acquired, one with each experimental task. A high-resolution, T1-weighted three-dimensional image was also acquired (spoiled gradient-recalled acquisition in a steady state; TR, 21 ms; TE, 8 ms; flip angle, 20°; matrix size, 256 x 256; field of view, 22 cm; slice thickness, 1 mm).

RESULTS

Data analysis was performed using statistical parametric mapping (SPM2) (<http://www.fil.ion.ucl.ac.uk/spm>) running with MATLAB. All the volumes were spatially realigned to the first volume to correct for head movements. Sync interpolation was used to minimize timing errors between slices (Henson et al., 1999). The functional images were co-registered with the anatomical image and normalized to the standard T1 template volume (Montreal Neurological Institute, Montreal, Quebec, Canada). Normalized images were smoothed with an 8 mm full-width at half-maximum isotropic Gaussian kernel. A temporal high-pass filter (cutoff, 256 s) was applied, and temporal autocorrelation was modeled as an AR(1) process.

Significant hemodynamic changes for each condition were examined using the general linear model with boxcar functions convolved with a hemodynamic response function. Statistical parametric maps for each contrast of *t*-statistic were calculated on a voxel-by-voxel basis. The statistical analyses at the first level were calculated using an epoch-based design, with the two tasks as the conditions of interest. Images from the two separate runs were entered as a single session to form a single time series for each individual. Individual participant images were analysed at the first level to produce estimates for the contrast of interest and contrast images were then analysed at the second level in a group random-effects analysis using a one-sample *t*

test (threshold significance set at *p* < 0.001, uncorrected).

Behavioral performance was measured function by the number of correctly disambiguated pictures from Snowy Pictures Task. High performers were considered the subjects which correctly guessed all three pictures, while low performers were considered the subjects which didn't guess any picture. Correlating the behavioral results with the imagistic results, we found a large network activated for both high and low performers comprising the following areas: bilateral superior frontal gyrus (BA9), bilateral medial frontal gyrus (BA 9, 10, 32), left dorsal anterior cingulate (BA 24, 33), bilateral middle frontal gyrus (BA 9, 10), left inferior frontal gyrus (BA 47), right inferior frontal gyrus (BA 45, 47), bilateral insula (BA13), bilateral posterior cingulate (BA 30, 31), left inferior temporal (BA 20, 21), bilateral lingual gyrus (BA 17, 18), bilateral inferior occipital cortex (BA 17), fusiform gyrus (18, 19), and left amygdala. We have seen a difference between high and low performers at the level of medial temporal lobe structures. While low performers exhibited only activation of right entorhinal and perirhinal cortices (see Figure 2), high performers exhibited bilateral activation of these structures and also a bilateral activation of the hippocampus (see Figure 3).

We found a significant positive correlation between performance in disambiguating the pictures and bilateral activation of entorhinal cortex, perirhinal cortex and hippocampus (Pearson chi square = 3.86, df = 1, *p* < 0.05, N = 22) (see Figure 4).

DISCUSSION

In our study, both groups – low and high performers – manifested activations in several brain regions that could be seen as a network responding to ambiguity, but not being critical for the success in disambiguating the stimuli. These regions are: superior frontal gyrus, middle frontal gyrus, inferior frontal gyrus, medial frontal gyrus/dorsal anterior cingulate cortex, anterior insula, posterior cingulate cortex/precuneus, inferior frontal gyrus, inferior occipital cortex and lingual gyrus, and amygdala. These structures can be seen as a network, their involvement in ambiguity processing being confirmed by different studies. These individual differences of correlated brain activation with performance in disambiguating stimuli seems to be similar with Baldassarre and colleagues results, who found that individual differences in performing novel perceptual tasks is related to indi-

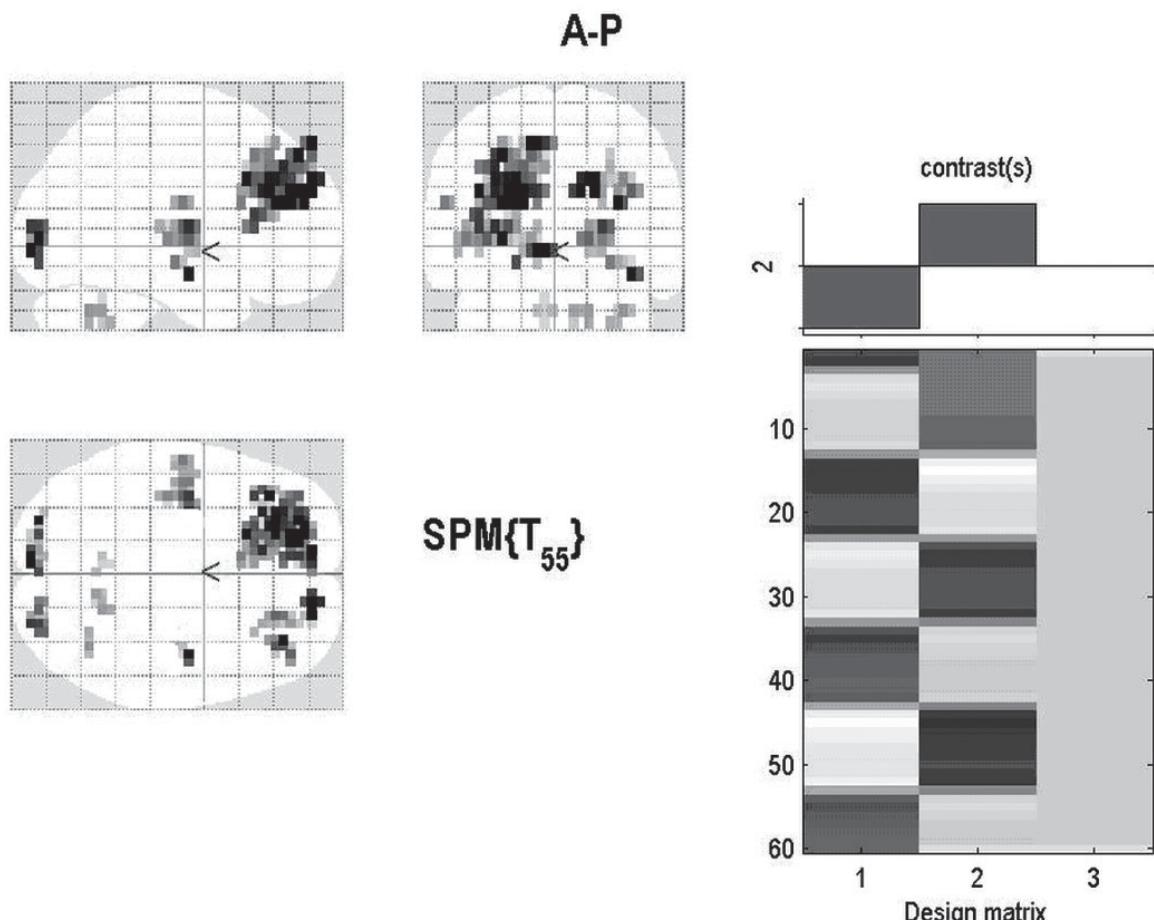


Figure 2. For low performance we found activated a network comprising the following areas: bilateral superior frontal gyrus (BA9), bilateral medial frontal gyrus (BA 9, 10, 32), left dorsal anterior cingulate (BA 24, 33), bilateral middle frontal gyrus (BA 9, 10), left inferior frontal gyrus (BA 47), right inferior frontal gyrus (BA 45, 47), bilateral insula (BA13), bilateral posterior cingulate (BA 30, 31), left inferior temporal (BA 20, 21), bilateral lingual gyrus (BA 17, 18), bilateral inferior occipital cortex (BA 17), fusiform gyrus (18, 19), left amygdala, right entorhinal cortex and right perirhinal cortex.

vidual differences in spontaneous cortical activity (Baldassarre et al., 2012).

As we mentioned earlier, ambiguity can be studied in the context of the decision making process, problem solving, perception of images or text comprehension, and we presented some data from bi-stable perception studies. Another paradigm is the so-called The “Aha! reaction”. The Aha! reaction is the familiar abrupt change in mental perspective that leads one to the solution of an otherwise intractable problem. Using event-related fMRI, Luo, Niki and Phillips (2004) have identified the neural correlates of the Aha! reaction in a study where subjects read incomprehensible sentences followed by solutions cues that were used to evoke Aha! reaction by triggering an alternative interpretation of the critical concepts. They found a network including anterior cingulate cortex, inferior frontal gyrus, middle frontal gyrus, superior frontal gyrus, insular cortex, precuneus and inferior temporal gyrus. They concluded that because Aha! reaction involves a

breaking mental impasse, the contribution of anterior cingulate cortex to breaking a mental impasse was related to its well documented function of conflict detection/resolution. In a more recent study using a learning-testing paradigm to examine brain activation of Aha! Reaction also with event-related fMRI during solving Chinese logographs, Qiu and et. (2010) found that increases in activity in the pre-cuneus, left inferior and middle frontal gyrus, inferior occipital gyrus and cerebellum were specifically associated with the Aha! Reaction. Regarding the activation of amygdala we found in our study, it is interesting in the context of the data mentioned in the introduction about high activity of amygdala in neurotic people who are reluctant to the lack of feedback and tend to see the unknown as more threatening than usual. Also it is known that amygdala is coupled with the cingulo-opercular network comprising dorsal anterior cingulate cortex, right inferior frontal gyrus, anterior insula, ventral striatum, hypothalamus, dorsomedial thala-

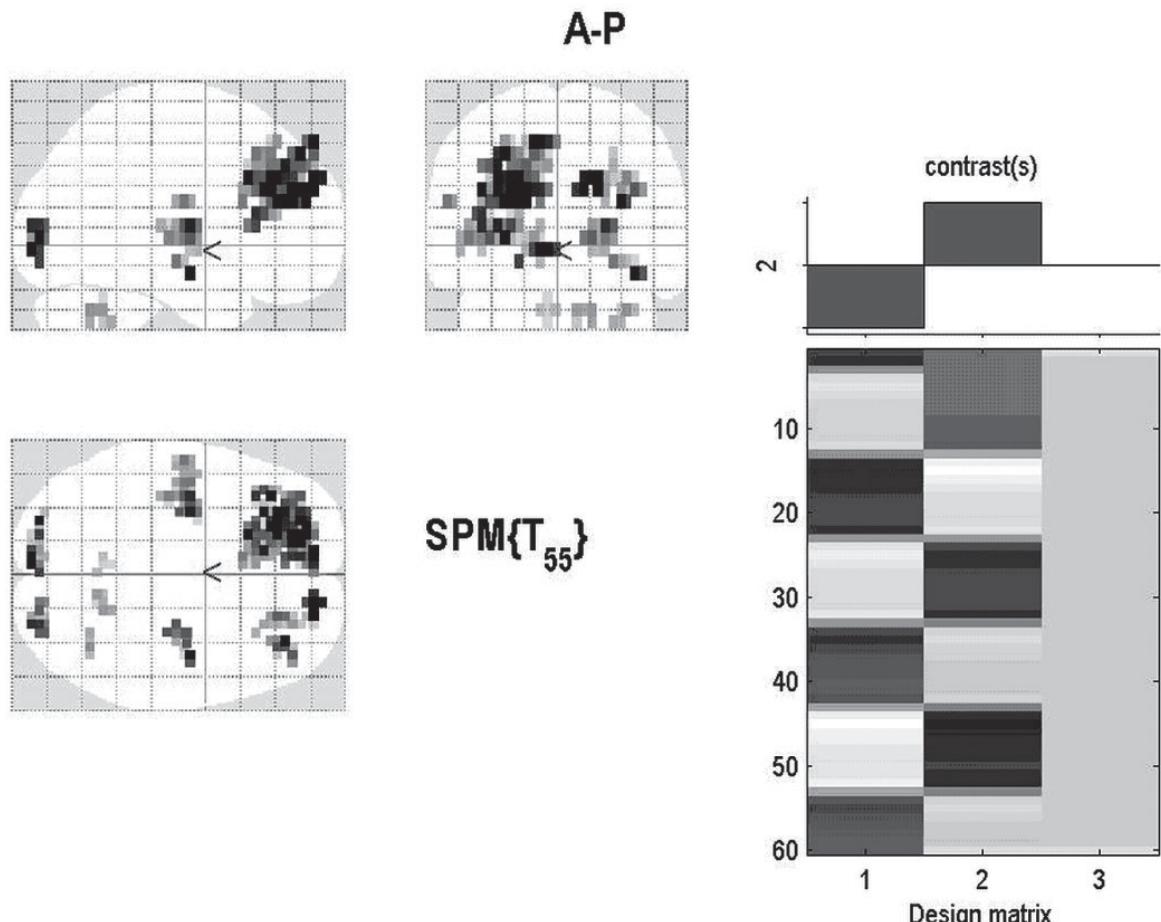


Figure 3. For high performance we found activated a network comprising the following areas: bilateral superior frontal gyrus (BA9), bilateral medial frontal gyrus (BA 9, 10, 32), left dorsal anterior cingulate (BA 24, 33), bilateral middle frontal gyrus (BA 9, 10), left inferior frontal gyrus (BA 47), right inferior frontal gyrus (BA 45, 47), bilateral insula (BA13), bilateral posterior cingulate (BA 30, 31), left inferior temporal (BA 20, 21), bilateral lingual gyrus (BA 17, 18), bilateral inferior occipital cortex (BA 17), fusiform gyrus (18, 19), left amygdala, bilateral entorhinal cortex, bilateral perirhinal cortex, and bilateral hippocampus.

mus, PAG, and substantia nigra/VTA. This network processes cognitive and emotional conflict, interoceptive/vegetative information, the emotional dimension of pain, empathy towards others' pain, and social rejection. People with a stronger connectivity between dorsal anterior cingulate and the rest of the network manifest an intense anticipatory anxiety (Seely et al., 2007).

In our study, the difference between low and high performers lies in the activation within the medial temporal area: while in low performers only right entorhinal and perirhinal cortices were activated, in high performers the activation was bilateral and in addition there appeared a bilateral activation of hippocampus. So, we can conclude that this bilateral activation of the medial temporal area is the key in successfully disambiguating the visual stimuli when presented in a Snowy Pictures Task. There are studies linking hippocampal activation with ambiguity processing. A concept related with Aha! reaction is “insight” – meaning the reorienta-

tion of one's thinking, including breaking of the unwarranted “fixation” and forming of novel, task-related associations among the old nodes of concepts or cognitive skills. Luo and Niki (2003) investigated the neural correlates of “insight” using Japanese riddles, by imaging the answer presentation and comprehension events, just after the participants failed to resolve them. Their results of event-related fMRI analysis demonstrated not only the involvement of a wide cerebral cortex network, but also that the hippocampus is critical in the “insight” process.

Usually hippocampus is divided in the following regions: the parahippocampal gyrus, CA1 and a combined region consisting in dentat gyrus, CA2 and CA3. In addition, the parahippocampal gyrus is divided itself in the anterior zone comprising the entorhinal cortex and the perirhinal cortex and the posterior zone comprising the parahippocampal cortex. The dentat gyrus and CA2/CA3 are considered input zones and are active in experience en-

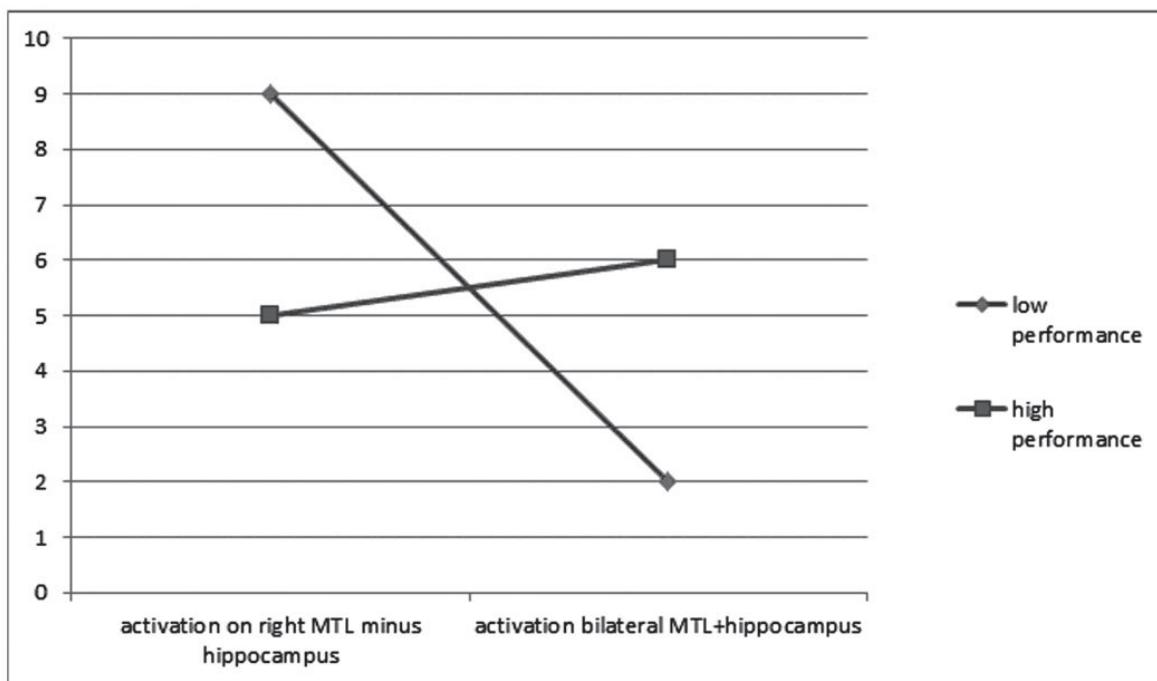


Figure 4. We found a significant positive correlation between performance in disambiguating the pictures and bilateral activation of entorhinal cortex, perirhinal cortex and hippocampus (Pearson chi square = 3,86, df = 1, at p = .05, N = 22)

coding and new memories formation, while CA1 and parahippocampus are considered output zones and are active in memories recollection. The perirhinal cortex is involved in processing the conjunction between one item and its various features, while the parahippocampal cortex plays a more general role in context representation – spatial or non-spatial – including the differences between these two (Carr, Rissman and Wagner, 2010). Large amounts of data support the idea that the brain is hierarchically built in anatomical regions in which more and more complex representations are generated while moving through the posterior-anterior axis. Traditionally the medial temporal area – comprising hippocampus and adjacent formations – is seen as a memory centre, while occipital and occipito-temporal areas are seen as visual perception centres. Nevertheless, recent data indicates that the medial temporal area could be seen as a superior hierachic extension of the ventral visual circuit. In this type of functional organization, occipital and occipito-temporal cortices have the role of processing rather simple information, and as the ambiguity of information increases (i.e. more data should be taken into account in order to recognise an object or a scene, or when we must decide what is the difference between two objects or scenes), the processing is handed over by perirhinal cortex and further

by hippocampus (Bussey and Saksida, 2007; Baxter, 2009). It is known that the perirhinal cortex solves “feature ambiguity” on the objects level, while hippocampus on the scenes level. „Feature ambiguity” represents the discrimination between stimuli having multiple features in common. Tasks which possess a higher level of ambiguity are managed by putting in conjunction several representations, this complex processing seems to take place gradually on the ventral visual circuit axis, from occipital and occipito-temporal cortices to perirhinal cortex and finally hippocampus (Bussey and Saksida, 2007; Baxter, 2009).

Related to the role of the amygdala in processing ambiguity and inter-individual differences on amygdala activity connected with ambiguity/uncertainty, we should say that the anterior region of the hippocampus (parahippocampal gyrus) sends projections to amygdala, bed nucleus of stria terminalis, HPA axis and nucleus accumbens shell, and also is known to modulate dopaminergic transmission from accumbens and prefrontal cortex. This is the reason why an altered functioning of the anterior hippocampus influences activity of the nervous circuits from prefrontal cortex, amygdala and nucleus accumbens associated with emotions (Sahay and Hen, 2007). Both lesion studies on animals and imaging studies on humans have confirmed that the

ventral region of hippocampus – named anterior hippocampus on primates and human – plays a critical role in anxiety (McHugh et al., 2011). Also, developmental data from animal studies pointed out to the role of hippocampus in anxious reactions. Habituation to novelty and emotional reactivity does not exist in rats at day 15 but emerges by day 20, this time window comprising a period during which the mature patterns of hippocampal connectivity are being established. It is clear that in order to have emotional reactivity to novelty, the animal must be able to integrate sensory information into long-term representations (Leonardo and Hen, 2008). In conclusion, behavoiural evidence suggests that the circuits that mediate anxious responses to novelty are rapidly maturing in this time window and the adult response to novelty, including anxiety, depends by the factors which interfere with these processes. And here we return to our introductory paragraph saying that we are organisms adapted to recognise patterns around us in order to avoid ambiguity and indecision because the feeling of certainty counteracts anxiety and apprehension. It appears that a large part of the brain is involved in these processes, medial temporal cortex structures making the difference in disambiguating visual images and hence helping us in dealing with anxiety. In our study we didn't investigate the level of anxiety so the ideas mentioned above are not directly linked with our data, but this connection can be a subject of a future study.

CONCLUSIONS

We found that a large network comprising several frontal, parietal, temporal and occipital areas is

involved in the processing of ambiguous images, congruent with other studies using different ambiguity processing paradigms (i.e. decision making under uncertainty tasks, bistable perception, Aha! reaction, and insight). In addition we found that successful disambiguating of an image from a modified version of Snowy Pictures Task in healthy adults correlates with bilateral activation of hippocampus, entorhinal and perirhinal cortices. Our data confirms the critical role of these medial temporal structures in construction of visual images - especially under ambiguous conditions - congruent with their proposed role of a superior hierachic extension of the ventral visual circuit. This data in connection with other data from literature can be seen in the context of the possible involvement of these medial temporal structures, in conjunction with amygdala and anterior cingulate cortex, in triggering emotional reactions to unknown/ uncertainty, a common trait of neurotic personality style, anxiety disorders and anxious attachment style. Therefore, we can conclude that some emotional manifestations of personality and also some symptoms of traditionally named “emotional disorders” could have their root in the ability, or inability, to create a meaningful image in ambiguous situations, hence a visual perception characteristic.

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