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Engagement of multifocal neural circuits during recall of autobiographical happy events

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Happy emotional states have not been extensively explored in functional magnetic resonance imaging studies using autobiographic recall paradigms. We investigated the brain circuitry engaged during induction of happiness by standardized script-driven autobiographical recall in 11 healthy subjects (6 males), aged 32.4 ± 7.2 years, without physical or psychiatric disorders, selected according to their ability to vividly recall personal experiences. Blood oxygen level-dependent (BOLD) changes were recorded during auditory presentation of personal scripts of happiness, neutral content and negative emotional content (irritability). The same uniform structure was used for the cueing narratives of both emotionally salient and neutral conditions, in order to decrease the variability of findings. In the happiness relative to the neutral condition, there was an increased BOLD signal in the left dorsal prefrontal cortex and anterior insula, thalamus bilaterally, left hypothalamus, left anterior cingulate gyrus, and midportions of the left middle temporal gyrus ($P < 0.05$, corrected for multiple comparisons). Relative to the irritability condition, the happiness condition showed increased activity in the left insula, thalamus and hypothalamus, and in anterior and midportions of the inferior and middle temporal gyri bilaterally ($P < 0.05$, corrected), varying in size between 13 and 64 voxels. Findings of happiness-related increased activity in prefrontal and subcortical regions extend the results of previous functional imaging studies of autobiographical recall. The BOLD signal changes identified reflect general aspects of emotional processing, emotional control, and the processing of sensory and bodily signals associated with internally generated feelings of happiness. These results reinforce the notion that happiness induction engages a wide network of brain regions.

Key words: Functional magnetic resonance imaging; Autobiographical recall; Emotion induction; Affective states

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Introduction

In recent years, many studies using functional magnetic resonance imaging (fMRI) have investigated non-invasively the functional anatomy of transient emotional states in the healthy human brain (1,2). One kind of stimulation paradigm often employed in these studies involves the provocation of emotional states during the remembrance of autobiographical events (3). In such investigations, subjects are presented with modality-specific stimuli (cue words, pictures, films, sentences, or narratives) intended to elicit memories of autobiographical events marked by significant emotional content and vivid sensory details, and they are asked to re-experience the emotions that were present during such past events. These paradigms enable, in experimental settings, the induction of robust

emotional reactions in a reliable and more personal fashion (4-6).

Investigations of positive emotions such as happiness using fMRI and autobiographical recall paradigms have been scarce in healthy subjects. This is a relevant issue since the mapping of the brain circuitry underlying the normal experience of happiness may provide clues about the neural substrate of psychiatric conditions characterized by exacerbated and/or reduced expression of positive emotions, such as depressive or bipolar spectrum disorders. A study using visually presented words to trigger the recollection of personal events (6) reported increased activity when happy memories were contrasted with memories of neutral emotional content in medial prefrontal, lateral prefrontal and posterior temporal neocortical regions, as well as in the anterior cingulate gyrus, precuneus and ventral pallidum/dorsal amygdala. In a companion paper, the same authors reported a contrast of brain activation patterns between memories of positive versus negative valence and showed greater activity in the orbitofrontal cortex, temporal pole and entorrhinal cortex during the remembrance of positive events (7). Such patterns of brain activity changes in association with happy emotions are in relative consistency with the results of previous functional imaging studies of emotional processing that used the positron emission tomography (PET) technique with similar emotion-inducing paradigms (8-10). However, the fMRI studies conducted to date have not repeated other findings reported in the PET literature of positive emotional processing, for instance in regard to the engagement of the hypothalamus, striatum and thalamus during the recall of happy events (5,10).

The discrepancies in the findings of functional imaging investigations of autobiographical recall may be partially due to inter-study differences in instructions and structure of stimuli leading to variations in the control of the content of retrieved memories, as well as to variations in the degree of vividness and arousal intensity of the memories elicited (4,6,11).

In the present fMRI study, we investigated the brain circuitry engaged during the provocation of happiness as compared to neutral and negative emotional states using narratives of personal memories. We tried to minimize the variability of our results by selecting healthy individuals taking into account their ability to vividly recall previous experiences, using triggering events chosen according to the same criteria of emotional intensity, and using exactly the same structure and length for the construction of narratives to be presented during fMRI data acquisition, for both the emotionally salient and neutral situations. We tried to repeat previous fMRI findings of brain activity differences in happy versus emotionally neutral and negative personal memories in prefrontal and temporal lobe regions (6,7,11), as well as to investigate the changes of brain activity in additional foci implicated in previous PET investigations of positive emotional processing, such as the hypothalamus, thalamus and basal ganglia (5,8,10).

Material and Methods

The Ethics Committee of the University of São Paulo Medical School approved the study, and written informed consent was obtained from all subjects. This study was conducted according to the declaration of Helsinki.

Eleven healthy subjects who had completed at least elementary school were included (5 females; mean age = 32.4 ± 7.2; mean years of education = 10.5 ± 1.0), all of them right-handed according to the Edinburgh Handedness Inventory (12). They were recruited through newspaper and radio advertisements, and were screened using the following exclusion criteria: age of less than 21 or more than 50 years; current or previous history of neurological and/or general medical conditions, as assessed by non-structured clinic interviewing, physical examination, electrocardiogram and blood/urinary work-up; current or previous history of psychiatric disorders including substance abuse or dependence, according to Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (13) criteria, based on information obtained with the Structured Clinical Interview for DSM-IV (14); first-degree family history of psychiatric disorders including psychosis, recurrent mood disorders and substance dependence, using the Family History Screen (15); current use of any drugs with potentially psychoactive effects, and for female subjects, a history of pregnancy or lactation within the last 6 months.

Subjects were interviewed by one of the researchers (C.T.C.) within two weeks before fMRI scanning. Initially, the Vividness of Visual Imagery Questionnaire, translated from its Spanish version (16), was applied; all individuals had ratings above the score of 20, indicating a good level of visual imaging capacity (mean score = 31.9 ± 11.4). We then obtained from each subject autobiographical information with a degree of remoteness of 6 to 12 months in order to allow the subsequent construction of nine scripts: three to elicit feelings of happiness; three to elicit negative valence emotions of irritability, conceptualized as a subjective reduction in the control over temper in response to sensorial or psychic stimuli (17), and three of neutral emotional content. For the selection of events in which they had experienced feelings of happiness, subjects were prompted to recall situations such as festivities, personal achievements, birth of loved relatives, etc. For each situa-

tion recalled, they were asked to give ratings (1-10) for the degree of happiness experienced. Only episodes for which subjects gave ratings for happiness greater than 5 were selected (mean scores = 9.0 ± 1.2) and without associated negative emotions (5) (including anger, fear, frustration, sadness, and irritability). For the selection of episodes of negative emotional content, subjects were presented with a list of situations that could potentially be associated with the feeling of irritability (e.g., waiting in long queues, dealing with bureaucracy, traffic jams), prepared on the basis of the Hassles and Uplifts scale (18) and the Buss-Durkee Hostility inventory (19). Subjects were asked to give ratings (1-10) for the intensity of each of the above-mentioned negative emotions experienced in the events. The 3 episodes for which subjects gave the greatest ratings for irritability (minimum of 5; mean scores = 7.5 ± 1.8), and which had lower scores for the other negative emotions, were selected. The same procedure was repeated in order to allow the selection of three emotionally neutral personal events. Finally, the interview was also used to select general contextual or conceptual subject matters from local newspapers, magazines and internet sites, rated by the subjects as emotionally neutral to them; this aimed to provide material for the construction of non-personal texts to be interleaved with the presentation of personal scripts during the fMRI session, in order to help subjects in the dissipation of the immediately previous script-driven emotional reaction and to keep their attention continually engaged over the entire length of the trial.

The nine personal scripts for each subject were written as 1-min long narratives in the second person, using the present tense, by a professional writer. A predetermined text structure was employed, partitioning each script into three separate paragraphs respectively describing: the sensorial context in which the experience developed; the temporal, personal and interpersonal contexts, and the details of the emotional reaction elicited. Each paragraph contained 40 ± 4 words and 240 ± 30 characters (including spaces). Scripts were read by a professional narrator of the same gender as the subjects, in a normal tone voice (5), and were recorded digitally. Audio editing of scripts was conducted using the Protus® software in order to adjust the duration of each paragraph to 20 s without distortions, and to a mean volume of 46 dB after normalization. The same structure was used in the recording of the non-personal scripts of neutral emotional content (20 s).

During the fMRI session, personal scripts and non-personal texts were presented using non-magnetized earphones (Commander-XG(r), Resonance Technology, USA). Before image acquisition, room lights were turned down, and auditory instructions were provided while subjects lay down on the scanner bench. Subjects were asked to keep their eyes open and to pay attention to the content of each script, recalling the emotions felt during the situation as if it was occurring at the moment of fMRI scanning; they were also instructed to avoid thinking about other memories not specifically cited in the scripts. Three separate runs were performed, each including an initial baseline period of no stimulation (80 s) and the presentation of one personal script of each emotional kind (60 s), each interleaved with one non-personal text (20 s). The order of the three personal scripts was counterbalanced both within and between subjects. Subjective ratings of five different emotions (happiness, sadness, irritability, fear, and anxiety) were obtained immediately after the presentation of each personal script (in a pseudo-randomized order), as well as after the initial baseline period. Responses were provided using a set of purpose-built conductors previously installed with Velcro on the ventral surface of each of the five fingertips of the right hand. For each visual scale, subjects chose from 1 (not at all) to 4 (much), by press-tapping the conductor placed on the thumb to one out of the four conductors installed on fingertips 5, 4, 3, or 2, respectively. This apparatus was used in order to speed up the process of response selection and to minimize errors. A desktop computer recorded subject choices and response times, with its screen displaying to the examiners the same scales as seen by the subjects. In four subjects, visual scales were presented via a mirror mounted on the head coil of the fMRI scanner, in direct view of the supine participant, at a distance of 390 cm from a projection screen. In the remaining seven subjects, scales were displayed using goggles with binocular vision (MRI-Vision2000®, Resonance Technology, USA) from the onset of the fMRI examination. In order to determine the levels of anxiety across the scanning procedure, subjects answered the State-Trait Anxiety Inventory (STAI-state) (14) immediately before and after image acquisition.

For each fMRI run (including baseline, emotional/neutral personal scripts, subjective scales and neutral non-personal texts), a total of 220 gradient-echo T2* echo planar imaging sets were obtained using a GE LX-MR 1.5T scanner (General Electric, USA), each consisting of 15 interleaved non-contiguous 7.0 mm-thick transaxial slices, with a 0.7-mm gap, parallel to the intercommissural line. Imaging parameters were: TE = 40 ms, TR = 2 s, 64 x 64 matrix, interslice gap = 0.3 mm, field-of-view = 200 x 200 mm and flip-angle = 90. Stimulus presentation was synchronized with image acquisition via an optical relay triggered by the radiofrequency pulse. A purpose-written software was used for synchronizing the presentation of stimuli, visual scale displaying, subject responses, and image

acquisition. Following fMRI scanning, high-resolution morphological data were acquired using an axial T1-3-D spoiled gradient recalled acquisition in steady-state sequence, with the following parameters: 124 slices (1.5 mm thick), TR = 20 s, TE = 3 s, matrix = 256 x 192, field-of-view = 220 mm, flip-angle = 20; as well as a fluid-attenuated inversion recovery sequence aimed at excluding structural brain lesions (twenty 5-mm thick slices, TR = 10,000 ms, TE = 140 ms, IR = 2200 ms, field-of-view = 240 mm).

Skin conductance signals were recorded simultaneously with fMRI acquisition. Standard fingertip AgCl leads (20) were placed on the middle phalanges of the index and middle fingers of the left hand. The electrode leads were connected through a high pass filter on the penetration panel to a skin conductance response (SCR) transducer connected to a stand-alone monitor unit (Psylab®, USA) outside the scanner room. Analog signals were recorded at 100 Hz, passed to an AD converter, and recorded using the Psylab software (Psylab®), on a purpose-configured laptop. Measurements were expressed as the difference between skin conductance levels (SCL) of each script type and the respective baseline value. Runs during which curve variation in signal intensity was lower than 0.05 µS were discarded (21).

Within 5 days prior to the fMRI session, subjects were trained in a sham session, lying down inside a mock scanner that replicated the MRI environment and the sounds emitted during image acquisition, in order to habituate each subject to the fMRI procedure. In this sham session, each subject was trained to use the response glove and became accustomed to the paradigm projection, gradient noise and room temperature.

The fMRI data processing first involved image realignment to minimize motion-related artifacts, and Gaussian smoothing at 7.2 mm FWHM. Although subjects were scanned continuously, the statistical analysis of fMRI data referred only to the contrasts between the time periods of presentation of emotional versus neutral personal scripts. Aspects of the time series related to the baseline period, non-personal texts and scale presentation were not included in the analysis. Changes in blood oxygen level-dependent (BOLD) signal in association with each condition (happiness, irritability and neutral personal scripts) were detected by time-series analysis using two Poisson functions, convolved separately with 4 and 8 s to model the BOLD response. The weighted sum of these two convolutions that gave the best fit to the time-series at each voxel was calculated, and a goodness of fit statistic was computed at each voxel (22). The ratio of the sum of squares of deviations from the mean intensity value due to the model (fitted time-series) was divided by the sum of squares due to the residuals (original time-series minus model time-series; SSQ ratio). In order to test the hypothesis that observed SSQ ratio values at each voxel were determined by the experimental design, the SSQ ratio distribution under the null hypothesis was obtained by permutation of the time-series using wavelet-based resampling, as described previously. This permutation method has been shown to provide good type I error control with minimal distributional assumptions.

In order to extend statistical inferences to the group level, the observed and randomized SSQ ratio maps were initially transformed into standard space by a rigid body transformation of the fMRI data into high-resolution morphological images of the same subjects, followed by affine transformations onto a Talairach and Tornoux template (23). In order to identify voxel clusters showing significant BOLD response differences between conditions, median observed SSQ ratios over all subjects during each condition were initially tested at the voxel-wise false-positive probability of 0.05 against the null distribution of median SSQ ratios computed from the previously obtained wavelet-permuted data. The “activated” voxels in one of the script conditions against the other were then assembled into 3-D connected clusters and the sum of the SSQ ratios (statistical cluster mass) was determined for each cluster. The same procedure was repeated for the median SSQ ratio maps obtained by wavelet-permuting of data for the specific script conditions, in order to compute the null distribution of statistical cluster masses under the null hypothesis. This distribution was then used to determine the critical threshold for the cluster mass statistic under the null hypothesis at a type I error level of $P < 0.05$, and applied to the observed cluster mass data to determine significantly activated clusters (24). We have applied an extent threshold of 10 voxels to report clusters as significant. Pearson’s correlation coefficients between BOLD signal and SCL and between happiness subjective ratings and happiness scripts were also calculated on a voxel-by-voxel basis using the same statistical threshold.

Results

The comparison of STAI scores before and after the fMRI procedure did not show significant differences ($t = 1.04$; d.f. = 10, $P = 0.325$, paired *t*-tests). The mean emotion intensity scores provided by subjects at the end of each kind of personal script are presented in Table 1. There were significant between-condition differences in the subjective scores of happiness, with subjects showing higher happiness scores after presentation of the happiness scripts relative to all other conditions (Table 1), as

well as in the neutral condition compared to the irritability condition. There were significant differences in subjective scores for irritability and sadness across the four different conditions (P < 0.001, one-way ANOVA), with subjects reporting feeling significantly more irritated and sad immediately after presentation of the negative emotion scripts relative to the other conditions (P < 0.001, *post hoc* *t*-tests; Table 1).

The results of the comparisons of BOLD effects between the happiness and neutral conditions are displayed in Figure 1. Table 2 provides the coordinates for the voxels of maximal statistical significance in each cluster showing BOLD signal differences be-

Table 1. Subjective self-report ratings of emotions during each personal script presentation and the baseline condition (N = 11).

Affective scales	Scripts				
	Irritability	Happiness	Neutral	Baseline	F value
Irritability	3.28 ± 0.74*	1.25 ± 0.53	1.50 ± 0.90	1.72 ± 0.84	17.01
Sadness	2.39 ± 0.69*	1.30 ± 0.52	1.17 ± 0.41	1.25 ± 0.38	14.95
Happiness	1.42 ± 0.62	3.64 ± 0.56^{+}	2.56 ± 0.82**	1.96 ± 0.64	24.37
Anxiety	2.22 ± 0.74	2.39 ± 1.12	2.56 ± 0.82	2.03 ± 1.09	0.90
Fear	1.47 ± 0.52	1.39 ± 0.46	1.19 ± 0.39	1.36 ± 0.52	0.71

Data are reported as means ± SD. *Significantly greater than the scores for the presentation of personal neutral scripts, happiness scripts or the baseline condition (P < 0.001, *post hoc* paired *t*-tests). $^{+}$Significantly greater than the scores for the presentation of irritability scripts, personal neutral scripts or the baseline condition (P < 0.001, *post hoc* paired *t*-tests). **Significantly greater than the scores for the presentation of irritability scripts (P < 0.01, *post hoc* paired *t*-tests).

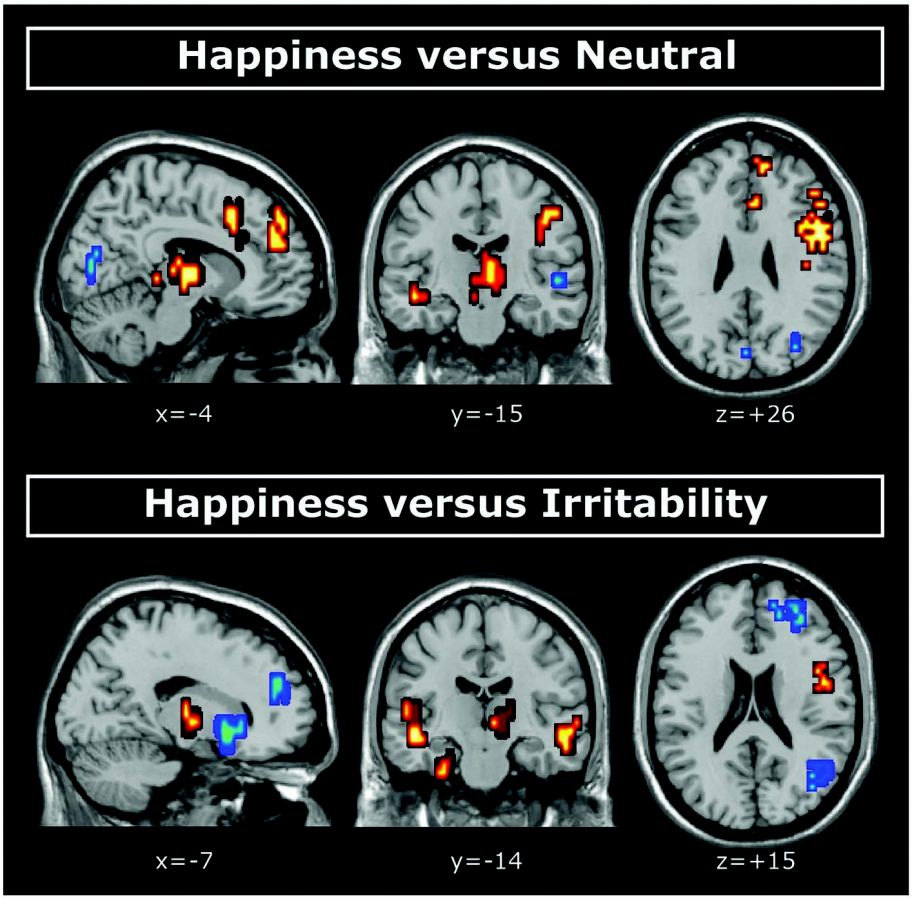

Figure 1. Areas showing significant blood oxygen level-dependent (BOLD) signal differences during happiness scripts relative to either emotionally neutral or negative emotional scripts. The statistical threshold was set at P < 0.05 for cluster and voxel analysis. The areas highlighted in yellow-red colors represent increased activity and blue-green colors represent decreased activity. Foci of significance have been overlaid on a T1 morphometric template, and are displayed on selected sagittal (left-hand frames), transaxial (middle frames) and coronal planes (right-hand frames). The number at the bottom of each frame corresponds to the coordinates of each plane, in standard Talairach and Tornoux (23) space. The right side of the transaxial and coronal images corresponds to the left side of the brain (radiological convention). In the top row, clusters of significantly increased BOLD signal during happiness scripts compared to emotionally neutral scripts are seen on the left dorsomedial prefrontal cortex, dorsal anterior cingulate gyrus, insula and dorsal posterolateral prefrontal cortex, as well as on the thalami, left hypothalamus and left middle temporal gyrus; foci of de-activation are seen in occipital regions. In the bottom row, foci of significantly increased BOLD signals during happiness scripts compared to irritability scripts are shown on the left anterior insula, left hypothalamus, thalamus bilaterally, inferior and middle temporal gyri bilaterally and right posterior insula, while areas of decreased BOLD effect are seen on the left dorsomedial prefrontal and dorsal anterolateral prefrontal cortices, subgenual cingulate gyrus and left lingual gyrus.

tween conditions, as well as the size of those clusters and the corresponding statistical test values.

Significant foci of activation in the happiness condition relative to the neutral state were detected in: the left dorsomedial prefrontal cortex (Brodmann area, BA9); the left anterior insula, extending to the dorsal posterolateral prefrontal cortex and precentral gyrus (BA44/13/6/4); the dorsal anterior cingulate cortex bilaterally (BA32); the left hypothalamus; the thalamus bilaterally, and the midportion of the left middle temporal gyrus (BA21; Figure 1 and Table 2). Regional BOLD signal decrements during the happiness condition relative to the neutral condition were seen in the left orbitofrontal cortex (BA47), left posterior temporal neocortex involving the middle and inferior temporal gyri (BA21/37), left fusiform gyrus (BA37) extending to the cerebellum, left lingual gyrus extending to the middle occipital gyrus (BA17/18/19), and precuneus bilaterally (BA7; Table 2).

When contrasted against the irritability condition, the presentation of happiness scripts was associated with an increased BOLD signal in: the left anterior insula, as well as in the right temporal pole, the left hypothalamus and thalamus and the anterior and midportions of the inferior and middle temporal gyri bilaterally (BA20/21/37/38; Figure 1 and Table 2). There were also foci of relatively decreased BOLD signals in the happiness condition relative to the irritability condition in the left subgenual anterior cingulate gyrus (BA25) extending towards the head of the caudate, left dorsal anterolateral prefrontal cortex (BA10), left dorsomedial prefrontal cortex (BA9), and left cerebellum and fusiform/lingual gyri (BA19/37; Table 2).

The SCR measures of four subjects had to be discarded due to curve variation intensity lower than 0.05 µS. Mean scores for the SCL difference relative to the baseline condition in the remaining 7 subjects showed positive values for the three types of scripts, indicating that all of

Table 2. Location and statistical significance of foci of blood oxygen level-dependent (BOLD) signal differences between irritability, happiness and neutral scripts in healthy volunteers (N = 11).

Brain region (Brodmann area)	Coordinates (mm)			Probability	Size (voxels)
	x	y	z		
Happiness > neutral					
L Middle temporal gyrus (BA21)	-46.9	-3.3	-7.1	0.022	13
L Hypothalamus/thalamus	-3.6	-14.8	-1.6	0.013	63
L Anterior insula/dorsal posterolateral prefrontal/precentral cortices (BA44/4/6)	-43.3	3.7	25.8	0.001	102
L Dorsomedial prefrontal cortex (BA9)	-7.2	51.8	14.8	0.029	17
L Dorsal anterior cingulate gyrus (BA32)	0.0	8.5	42.3	0.025	29
Happiness > irritability					
R Temporal pole (BA38)	8.8	-14.8	-40.1	0.032	13
L Inferior/middle temporal gyri (BA20/21/37)	-50.5	-37.0	-18.1	0.001	64
R Inferior/middle temporal gyri (BA20/21)/posterior insula	46.9	0.0	-23.6	0.005	55
L Hypothalamus/thalamus	-7.2	-7.4	-7.1	0.035	19
L Anterior insula	-43.3	3.7	14.8	0.024	17
Irritability > happiness					
L Fusiform gyrus (BA37)/cerebellum	-25.2	-29.6	-29.1	0.044	11
L Subgenual cingulate gyrus (BA25)/caudate nucleus	-14.4	14.8	-12.6	0.016	21
L Lingual gyrus (BA19)	-46.9	-55.5	-1.6	0.007	52
L Dorsomedial prefrontal cortex (BA9)	-14.4	51.8	14.8	0.048	10
L Dorsal anterolateral prefrontal cortex (BA10)	-25.2	1.8	4.8	0.017	17
Neutral > happiness					
L Cerebellum/fusiform gyrus (BA37)	-21.6	-37.0	-23.6	0.040	27
L Lingual/middle occipital gyri (BA17/18/19)	-10.8	-70.3	-1.6	0.027	18
L Orbitofrontal cortex (BA47)	-32.5	37.0	-7.1	0.040	14
L Inferior/middle temporal gyri (BA37/21)	-50.5	-44.4	-1.6	0.001	79
R Precuneus (BA7)	7.2	-70.3	36.8	0.027	13

Significance was set at $P < 0.05$ for cluster activation. BA = Brodmann area; L = left; R = right.

those personal script conditions were associated with greater SCR in comparison to the baseline state. Regardless of the type of condition, there was an overall tendency towards lower values from the first run (P = 0.055) to the second (P = 0.691) and to the third run (P = 0.987) (one-way ANOVA). A trend towards significant differences between conditions occurred only in the first run, with a tendency to higher SCL values both in the happiness (P = 0.057) and neutral (P = 0.096) script conditions (*post hoc* paired *t*-tests, d.f. = 6) relative to the irritability state.

The BOLD signal was not significantly correlated either with SCL or happiness subjective ratings for happiness scripts.

Discussion

This fMRI study used autobiographical scripts to investigate, in a group of healthy subjects selected according to their ability to vividly recall personal experiences, the brain circuitry engaged during the remembrance of happy memories in comparison to the recollection of negative or emotionally neutral situations. Since there was a rigid control of the structure and length of the narratives presented across the emotion-eliciting and neutral conditions, the contrast between such conditions presumably favored the detection of brain activity patterns specifically related to the emotional components of the autobiographical recall experience. Even with such degree of matching between conditions and the use of statistically significant values corrected for multiple comparisons to protect against false-positive findings, significant BOLD changes were detected in a wide network of cortical and subcortical gray matter structures in association with the happiness condition.

The happiness condition was associated with BOLD signal increases in a number of anterior cortical areas, including medial and lateral aspects of the prefrontal cortex and the dorsal anterior cingulate gyrus. Medial prefrontal activity increments have been the feature most consistently identified in association with the remembrance of happy memories in previous functional imaging studies that used autobiographical recall paradigms (1,5-8,10). It is relevant to note that in our investigation, medial prefrontal BOLD signal increases in association with the happiness condition were detectable only when this state was contrasted against the neutral condition, while activity in this region was actually lower in the direct comparison of the happiness condition with the irritability state. These findings indicate that activity increases in the medial prefrontal cortex are not specifically related to the emergence of positive emotions by autobiographical recall. Instead, our pattern of results, added to the previous evidence of medial prefrontal engagement in imaging studies that used different paradigms of emotion induction, further supports the notion of a general participation of this brain region in emotional processing and in the elaboration of experiential feelings of self (1,25,26). The engagement of the dorsal anterior cingulate gyrus in our study is also consistent with the findings of previous imaging investigations that used autobiographical scripts to investigate brain activity changes associated with the recall of both positive and negative emotions (5,6,27,28). The anterior cingulate has been traditionally implicated in cognitive aspects of emotional regulation (29,30), performance monitoring, detection of conflict and errors, and decision making (31,32). In comparison to passive emotional tasks, paradigms of autobiographical recall of emotions involve a greater number of cognitive operations, including both attentional processes and the re-evaluation of past memories (6,7). The happy scripts in our study pertained typically to situations of personal pleasure and achievement that were described by subjects, at their post-scanning debriefing, as easy to retrieve; in contrast, the emotionally neutral events were described by subjects as difficult to access due to their lack of salience or relevance, and this might presumably have led to a lesser degree of their cognitive re-evaluation in comparison to the happy situations. The engagement of the dorsolateral prefrontal cortex in our study is also likely to have been related to the degree of cognitive re-evaluation and/or retrieval success during the presentation of happy scripts relative to neutral scripts (6,7). In previous PET and fMRI studies in healthy subjects, the dorsolateral prefrontal cortex has been frequently engaged during the performance of highly cognitively demanding tasks, involving selection processes, long-term episodic memory, executive functioning, working memory, attentional control, and semantic knowledge (32).

Differently from previous fMRI studies of happy autobiographical recall (6), we detected significant BOLD signal increments in subcortical nuclei, including the hypothalamus and thalamus, when the happiness condition was contrasted against the presentation of either neutral or irritability scripts. The involvement of the thalamus could be related to its role in relaying sensory information to cortical structures. A greater intensity of such processing during the happiness condition would be consistent with the notion that the remembrance of happy situations is associated with greater vividness relative to neutral or negative emotional situations (6,7,33,34). This might have occurred to a greater extent in our study compared to previous fMRI experiments due to our choice to select subjects according to their capacity to vividly recall previous experiences. Along the same lines, the greater activity

increments of the hypothalamus in association with the happiness condition could be related to the explicit instructions given to subjects to re-experience and appraise the emotions recalled, which would drive attentional resources to the characteristics of their internal milieu and thus engage brain structures involved in neurovegetative processing. A greater degree of such neurovegetative processing would be expected in association with the greater vividness of happiness situations. The tendency that we found towards higher SCL during the happiness condition compared to the presentation of irritability scripts, during the first fMRI run, would be compatible with such possibility. Also, the happiness condition led to a greater engagement of the anterior insula, another brain region previously highlighted as critical to the perception of human emotional responses (1). The insula is seen as relevant to the cortical mapping of information pertaining to bodily features that accompany emotional reactions, having a specific role in the central representation of emotion-related internal visceral responses (8,29,35). The involvement of the insula in our study may have emerged in direct proportion to the degree of bodily changes associated with the script-driven emotional reactions. Taken together, the patterns of activation of our study may reflect the engagement of a neurovegetative pathway from the hypothalamus and a sensorial pathway from the thalamus to the insular and somatosensory cortices, respectively, relevant to the consciousness of autonomic changes associated with affective states (8,36).

In regard to our findings pertaining to the temporal neocortex, cognitive aspects related to recall strategies and access to semantic knowledge might also explain the activity increments elicited in midportions of the middle temporal gyrus during the happiness condition (37). Activity increases in neocortical temporal regions have been highlighted in previous studies using tasks involving autobiographical recall (7,10,37) and have been interpreted as being related to the degree of complexity and/or semantic meaning of the stimuli employed (6,32,38).

Conversely, the relative activity decrements in the left posterior temporal and visual cortices detected in the contrast between the happiness condition relative the neutral state were unpredicted; the greater degree of vividness presumably associated with the recall of happy memories would be expected to engage cortical regions involved in visual processing during the happy autobiographical memories (4). However, it has been proposed that cortical regions responsible for visual processing may be subject to top-down modulation by selective attention to emotional stimuli (6,10). Alternatively, our findings could be related to a greater degree of involvement of visual processing regions during recall of neutral situations, which were reported by subjects at post-scanning debriefing as demanding more effortful imagery (4,6,38).

In agreement with previous fMRI studies that used similar emotion-inducing paradigms (6,7), the findings of an increased BOLD signal associated with the happiness condition in our study were lateralized to the left hemisphere. Such left-lateralized findings are consistent with the recently proposed hemispheric distinction between approach and withdrawal emotions (39). According to this framework, emotions that elicit withdrawal behaviors, such as fear and disgust, are thought to be primarily processed in right anterior brain regions, while emotions driving approach behaviors, such as happiness, would be predominantly processed in left-sided brain areas.

The above interpretations should be made with caution due to the limitations of our study. These include the modest size of the sample investigated, and the variance introduced by the inclusion of both males and females in the study group (40). Another factor that may have added variability to our data was the substitution of mirror/screen for goggles in a proportion of subjects; however, it is unlikely that the latter factor confounded significantly our findings, as there was no visual stimulation during the periods of fMRI data acquisition primarily targeted in the study, namely the phases of auditory presentation of personal scripts. Lastly, additional variability may have been introduced by the relatively flexible, 6- to 12-month period of remoteness used for the selection of situations. Previous fMRI studies have demonstrated differences in the patterns of brain activity as a function of the degree of remoteness of the memories elicited during autobiographical recall (4).

In conclusion, the present fMRI investigation of happiness induction by autobiographical recall revealed the engagement of a wide network of brain regions, including structures previously shown to be involved either in the perception of emotionally salient stimuli, or in the emergence and cognitive control of emotional reactions. The use of the same uniform structure for the cueing narratives of both emotionally salient and neutral conditions may have helped to decrease the variability of our findings, but further improvements are probably needed in future studies to allow a deeper understanding of the complex results of fMRI investigations of autobiographical recall. These strategies may include the use of paradigms with a greater degree of control over the remoteness, and the sensorial, semantic and episodic components associated with the imagined situations, and the assessment of the possible influence of motivational aspects and personality traits on the patterns of brain activity changes elicited during such emotionally laden situations.

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References

1. Phan KL, Wager T, Taylor SF, Liberzon I. Functional neuroanatomy of emotion: a meta-analysis of emotion activation studies in PET and fMRI. *Neuroimage* 2002; 16: 331-348.
2. Piefke M, Weiss PH, Markowitsch HJ, Fink GR. Gender differences in the functional neuroanatomy of emotional episodic autobiographical memory. *Hum Brain Mapp* 2005; 24: 313-324.
3. Lanius RA, Frewen PA, Girotti M, Neufeld RW, Stevens TK, Densmore M. Neural correlates of trauma script-imagery in posttraumatic stress disorder with and without comorbid major depression: a functional MRI investigation. *Psychiatry Res* 2007; 155: 45-56.
4. Cabeza R, St Jacques P. Functional neuroimaging of autobiographical memory. *Trends Cogn Sci* 2007; 11: 219-227.
5. George MS, Ketter TA, Parekh PI, Herscovitch P, Post RM. Gender differences in regional cerebral blood flow during transient self-induced sadness or happiness. *Biol Psychiatry* 1996; 40: 859-871.
6. Markowitsch HJ, Vandekerckhove MM, Lanfermann H, Russ MO. Engagement of lateral and medial prefrontal areas in the ecphory of sad and happy autobiographical memories. *Cortex* 2003; 39: 643-665.
7. Piefke M, Weiss PH, Zilles K, Markowitsch HJ, Fink GR. Differential remoteness and emotional tone modulate the neural correlates of autobiographical memory. *Brain* 2003; 126: 650-668.
8. Damasio AR, Grabowski TJ, Bechara A, Damasio H, Ponto LL, Parvizi J, et al. Subcortical and cortical brain activity during the feeling of self-generated emotions. *Nat Neurosci* 2000; 3: 1049-1056.
9. George MS, Ketter TA, Parekh PI, Horwitz B, Herscovitch P, Post RM. Brain activity during transient sadness and happiness in healthy women. *Am J Psychiatry* 1995; 152: 341-351.
10. Lane RD, Reiman EM, Ahern GL, Schwartz GE, Davidson RJ. Neuroanatomical correlates of happiness, sadness, and disgust. *Am J Psychiatry* 1997; 154: 926-933.
11. Addis DR, Moscovitch M, Crawley AP, McAndrews MP. Qualities of autobiographical memory modulate hippocampal activation during retrieval: preliminary findings of an fMRI study. *Brain Cogn* 2004; 54: 145-147.
12. Oldfield RC. The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia* 1971; 9: 97-113.
13. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders (DSM-IV)*. 4th edn. Washington: American Psychiatric Press; 1994.
14. Spitzer RL, Williams JB, Gibbon M, First MB. The Structured Clinical Interview for DSM-III-R (SCID). I: History, rationale, and description. *Arch Gen Psychiatry* 1992; 49: 624-629.
15. Weissman MM, Wickramaratne P, Adams P, Wolk S, Verdeli H, Olfson M. Brief screening for family psychiatric history: the family history screen. *Arch Gen Psychiatry* 2000; 57: 675-682.
16. Campos A, Gonzalez MA, Amor A. The Spanish version of the Vividness of Visual Imagery Questionnaire: factor structure and internal consistency reliability. *Psychol Rep* 2002; 90: 503-506.
17. Snaith RP, Taylor CM. Irritability: definition, assessment and associated factors. *Br J Psychiatry* 1985; 147: 127-136.
18. Kanner AD, Coyne JC, Schaefer C, Lazarus RS. Comparison of two modes of stress measurement: daily hassles and uplifts versus major life events. *J Behav Med* 1981; 4: 1-39.
19. Buss AH, Durkee A. An inventory for assessing different kinds of hostility. *J Consult Psychol* 1957; 21: 343-349.
20. Williams LM, Phillips ML, Brammer MJ, Skerrett D, Lagopoulos J, Rennie C, et al. Arousal dissociates amygdala and hippocampal fear responses: evidence from simultaneous fMRI and skin conductance recording. *Neuroimage* 2001; 14: 1070-1079.
21. Boucsen W. *Electrodermal activity*. New York: Plenum Press; 1992.
22. Friman O, Borga M, Lundberg P, Knutsson H. Adaptive analysis of fMRI data. *Neuroimage* 2003; 19: 837-845.
23. Talairach J, Tornoux P. *Co-planar stereotaxic atlas of the human brain*. New York: Thieme Medical Publishers Inc.; 1988.
24. Bullmore E, Fadili J, Breakspear M, Salvador R, Suckling J, Brammer M. Wavelets and statistical analysis of functional magnetic resonance images of the human brain. *Stat Methods Med Res* 2003; 12: 375-399.
25. Northoff G, Heinzel A, de Greck M, Bermpohl F, Dobrowolny H, Panksepp J. Self-referential processing in our brain - a meta-analysis of imaging studies on the self. *Neuroimage*

2006; 31: 440-457.
26. Phillips ML, Drevets WC, Rauch SL, Lane R. Neurobiology of emotion perception I: The neural basis of normal emotion perception. *Biol Psychiatry* 2003; 54: 504-514.
27. Kimbrell TA, George MS, Parekh PI, Ketter TA, Podell DM, Danielson AL, et al. Regional brain activity during transient self-induced anxiety and anger in healthy adults. *Biol Psychiatry* 1999; 46: 454-465.
28. Shin LM, Dougherty DD, Orr SP, Pitman RK, Lasko M, Macklin ML, et al. Activation of anterior paralimbic structures during guilt-related script-driven imagery. *Biol Psychiatry* 2000; 48: 43-50.
29. Reiman EM, Lane RD, Ahern GL, Schwartz GE, Davidson RJ, Friston KJ, et al. Neuroanatomical correlates of externally and internally generated human emotion. *Am J Psychiatry* 1997; 154: 918-925.
30. Whalen PJ, Bush G, McNally RJ, Wilhelm S, McInerney SC, Jenike MA, et al. The emotional counting Stroop paradigm: a functional magnetic resonance imaging probe of the anterior cingulate affective division. *Biol Psychiatry* 1998; 44: 1219-1228.
31. Cabeza R, Nyberg L. Imaging cognition II: An empirical review of 275 PET and fMRI studies. *J Cogn Neurosci* 2000; 12: 1-47.
32. D'Argembeau A, Van der Linden M. Phenomenal characteristics associated with projecting oneself back into the past and forward into the future: influence of valence and temporal distance. *Conscious Cogn* 2004; 13: 844-858.
33. Schaefer A, Philippot P. Selective effects of emotion on the phenomenal characteristics of autobiographical memories. *Memory* 2005; 13: 148-160.
34. Critchley HD. Neural mechanisms of autonomic, affective, and cognitive integration. *J Comp Neurol* 2005; 493: 154-166.
35. Davidson RJ, Irwin W. The functional neuroanatomy of emotion and affective style. *Trends Cogn Sci* 1999; 3: 11-21.
36. Graham KS, Lee AC, Brett M, Patterson K. The neural basis of autobiographical and semantic memory: new evidence from three PET studies. *Cogn Affect Behav Neurosci* 2003; 3: 234-254.
37. Svoboda E, McKinnon MC, Levine B. The functional neuroanatomy of autobiographical memory: a meta-analysis. *Neuropsychologia* 2006; 44: 2189-2208.
38. Davidson RJ. Affective neuroscience and psychophysiology: toward a synthesis. *Psychophysiology* 2003; 40: 655-665.
39. Schneider F, Habel U, Kessler C, Salloum JB, Posse S. Gender differences in regional cerebral activity during sadness. *Hum Brain Mapp* 2000; 9: 226-238.
40. Bush G, Vogt BA, Holmes J, Dale AM, Greve D, Jenike MA, et al. Dorsal anterior cingulate cortex: a role in reward-based decision making. *Proc Natl Acad Sci U S A* 2002; 99: 523-528.