Imaging the passionate stage of romantic love by dopamine dynamics

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Using [11C]raclopride, a dopamine D2/D3 receptor antagonist, we undertook a positron emission tomography (PET) study to investigate the involvement of the dopaminergic neurotransmitter system when subjects viewed the pictures of partners to whom they were romantically attached. Ten subjects viewed pictures of their romantic partners and, as a control, of friends of the same sex for whom they had neutral feelings during the PET study. We administered [11C]raclopride to subjects using a timing for injecting the antagonist which had been determined in previous studies to be optimal for detecting increases in the amount of dopamine released by stimulation. The results demonstrated statistically significant activation of the dopaminergic system in two regions, the medial orbitofrontal cortex (mOFC) and medial prefrontal cortex, the former of which has been strongly implicated in a variety of rewarding experiences, including that of beauty and love. A positive correlation was obtained in mOFC between excitement levels and dopaminergic activation only in the love but not in the control condition.

Keywords: dopamine, orbitofrontal cortex, medial prefrontal cortex, positron emission tomography (PET), romantic love

Introduction

Love, especially during its passionate phase, is an all-encompassing experience which, despite its disorienting effects, is regarded as a highly pleasurable and rewarding one by most. The experience of love when viewing the face of a loved partner, whether of the opposite or the same sex, correlates with activity in a small number of distinct cortical and subcortical areas of the brain (Bartels and Zeki, 2000; Fisher et al., 2005; Zeki and Romaya, 2010), which is not to say that these areas act in isolation but only that they are especially prominently engaged during such experiences. This restriction in the number of areas prominently engaged is surprising, given the all-embracing nature of romantic love. Yet it is also an advantage for it limits the areas to be explored for other neural characteristics that correlate with the experience of love—at least in initial exploratory studies. The relatively small number of areas involved encouraged us to extend earlier brain imaging studies and enquire whether there is any particular neurotransmitter activity that is especially prominent in them under similar conditions. The obvious choice in this initial study was dopamine, partly because it has been found to be critical for pair-bonding in voles ( rodents) (Young and Wang, 2004; Mcgraw and Young, 2010), even if it does not act in isolation but as part of a critical...
neurotransmitter circuit that also includes oxytocin and vaso-
pressin, and partly because it has been closely associated with
reward (Schultz, 2001; Jonasson et al., 2014).

Our aim was to learn whether there is any increase in
dopamine release during phases of romantic love in humans,
and whether the increase could be localized to specific areas of
the brain. Although dopamine neurons are located in the ven-
tral tegmental area (VTA), nucleus accumbens and other parts of
the midbrain and brain stem, the dopaminergic system has rich
connections with a number of subcortical and cortical terminals,
including the orbitofrontal cortex (OFC) of the forebrain. Any
of the many areas that are rich in dopaminergic activity could
therefore be involved. The medial orbito-frontal (mOFC) cortex
was especially interesting since it is active in conditions in
which maternal love is expressed (Bartels and Zeki, 2004), when sexu-
ally attractive faces are viewed (Ishai, 2007) and, more generally,
during rewarding experiences (Schultz, 2001). We were particu-
larly interested in D2 receptors because their activation has been
reported to accelerate rewarding experiences, at least in voles,
one of the most intensively studied species in terms of social
and pair-bonding (Young and Wang, 2004). Mating in them
results in an increase in extracellular dopamine in the nucleus
accumbens while administration of dopamine antagonists blocks
mating preferences. This made it plausible to suppose that, like-
wise in humans, the rewarding experience of viewing pictures of
loved partners will similarly result in increased dopaminergic D2
receptor activity.

Materials and Methods

Subjects

We recruited 13 healthy volunteers who were in the early stages of
romantic heterosexual relationships; all had normal or corrected-
to-normal visual acuity, were right-handed according to the
Edinburgh handedness inventory (Oldfield, 1971) and had no
history of medical illness. They all gave written informed con-
sent. Three male subjects were subsequently excluded from the
analysis because two moved during the scanning experiments
and there was a failure in the synthesis of the PET tracer in one.
Thus, the total number of subjects was 10 (6 females and 4 males,
with an average age of 27.4 ± 4.3 years). The durations of the
partnerships were in the range of 2–125 months (median = 17
months).

During a first visit to the laboratory, some 2 weeks prior to
scanning, each subject provided 8 picture portraits of their part-
ner, taken from different angles, and a similar number of por-
traits of other friends of the same sex as their partner, whom
they had known for equivalent periods but toward whom they
had neutral feelings. All pictures were matched as far as possible
for expression and general appearance. The experiment was
explained to the subjects, who viewed a sample stimulus of a ran-
don anonymous face. Each subject completed a Passionate Love
Scale (PLS) (Hatfield and Sprecher, 1986; Hanari and Kawano,
2012) questionnaire, to attempt to quantify their feelings about
their partner as far as possible. Age and length of relationship
were recorded for each subject. After the PET scan, subjects
recorded their subjective sensation of excitation on a visual ana-
log scale (VAS) from 0 (no excitation) to 100 (most excitation),
in order to ascertain the intensity of their feeling immediately
after the scans. The entire protocol was approved by the Ethics
Committee of the Osaka City University Graduate School of
Medicine.

Experimental Design and Positron Emission
Tomography (PET)

The time schedule of experiments is shown in Figure 1A.
Two PET scans were performed to measure the availability of
dopamine D2/D3 receptors in the brain during the experience
of love (i.e., while watching the partner’s pictures) and during
the control condition (while watching friends’ pictures). Subjects
viewed stimuli corresponding to one condition in the morning
and to the other in the afternoon, the conditions being coun-
terbalanced across subjects. Subjects were positioned in the PET
scanner (Biograph-16, Siemens, resolution 4.6 × 4.6 × 5.1 mm)
with their heads tilted slightly upwards and fixed to enable them
to view comfortably the monitor used for presenting the stimuli;
the heads were lightly tied with bandages to minimize movement
during the scans.

![Figure 1](Image)
Subjects were required to press a key each time a picture appeared on the monitor screen, to ensure consistent attention over the duration of the experiment. Before the emission scans, CT scans were performed for head positioning and attenuation correction. The PET scan procedure followed a previous study aimed at detecting dopamine turnover during the aesthetic experience of music (Salimpoor et al., 2011); briefly, in order to allow for release and accumulation of endogenous dopamine, the visual stimuli (pictures) were presented 15 min before the administration of the dopamine antagonist, \(^{11}\)C]raclopride, and lasted for 30 min.

**Stimuli:** Visual stimuli were created by clipping the outlines of the face and body in the original photographs, as described by each subject, and replacing background details with a flat mid-gray tone (Zeki and Romaya, 2010). In the love condition, subjects viewed their partners’ picture, in random order, for 15 s; this was followed by a baseline blank epoch for 15 s (Figure 1B). For the control condition, they viewed the pictures of friends, presented again in random order. Each scanning session consisted of 60-pictures and 60-blank epochs, over a total period of 30 min. Subjects closed their eyes while remaining awake for 45 min after the presentation of the visual stimuli.

\(^{11}\)C]Raclopride was synthesized at Osaka City University Hospital by methylation using desmethyl raclopride, as described previously (Langer et al., 1999). The identity and concentration of \(^{11}\)C]raclopride were assessed using high-performance liquid chromatography. The purified fraction was evaporated and reconstituted with approximately 5 mL of saline containing 100 mg ascorbic acid. The radiochemical purity was more than 99%, and the specific radioactivity was 16.7 ± 9.7 GBq/µmol at the administration. The dose of administered \(^{11}\)C]raclopride was 5.4 ± 1.5 MBq/kg B.W. At the start of the emission scan, \(^{11}\)C]raclopride was intravenously administered for ca. 30 s, and the catheter line was flushed with 15–20 mL saline to prevent radiotracer retention. Serial PET scanning of the brain was performed for 60 min in the 3-dimensional dynamic mode, in the following frames: 6 × 10 s, 6 × 30 s, 11 × 60 s, and 15 × 180 s.

**Magnetic Resonance (MR) Image**

Fine structural whole-brain T1-weighted magnetic resonance anatomical images were acquired at the end of the experimental session for each subject, using the Philips Achieva 3.0 TX (Royal Philips Electronics). (Echo time, 2.48 ms; repeat time, TR = 1900 ms; TE = 4.62 ms; flip angle of 15°; FOV = 256 mm; one slab with number of 176 slices per slab; voxel dimensions, 1.0 × 1.0 × 1.0 mm)

**Analysis of PET Data**

PMOD software Version 3.5 (PMOD Technologies Ltd.) was used for quantitative analysis of PET data. PET and structural MR images were co-registered. The binding potential (BP\(_{ND}\)) was calculated using the simplified reference model 2 (Wu and Carson, 2002), with the cerebellum as the reference region. Using Statistical Parametric Mapping 8 software (SPM8, Wellcome Department of Imaging Neuroscience), whole-head structural images were then normalized to the Montreal Neurological Institute (MNI) T1 image template, with the same parameters applied to the BP\(_{ND}\) image. BP\(_{ND}\) images were resampled to a voxel size of 2.0 × 2.0 × 2.0 mm, using SPM8. The between-condition comparison (love vs. control) of the BP\(_{ND}\) was performed on a voxel-by-voxel basis using t-statistics, with the statistical threshold set at \(P < 0.001\) at the voxel level and more than 20 voxels at the cluster level for the entire brain. The co-ordinate of each brain region was defined by using the Wake Forest University Pick-atlas (Maldjian et al., 2003).

**Physiological Responses**

Objective measures of physiological responses indicative of excitation were collected during the experiments with the Procom Infinity biofeedback system by Thought Technology (Montreal, Canada). Participants’ right hands were attached to the recording equipment to monitor heart and respiration rates, skin conductance and temperature, blood volume pulse (BVP) amplitude, and body temperature, as described previously (Salimpoor et al., 2011). In order to evaluate sympathetic and parasympathetic activity, low frequency (LF), and high-frequency (HF) components of the pulse-interval variation of the BVP (which reflect sympathetic and parasympathetic nerve activities, respectively, Malliani et al., 1991), were analyzed with fast Fourier transform. The LF power was calculated as the power within a frequency range of 0.04–0.15 Hz, and the HF one as that within a frequency range of 0.15–0.4 Hz. We analyzed averaged values for each physiological indicator for a 15 min period, starting from the beginning of the PET scan to the end of the stimulus presentation. Data for physiological responses were not obtained in one subject due to the failure of the measuring equipment.

**Statistical Analysis**

Differences between conditions for VAS parameters, physiological responses and BP\(_{ND}\) (plots) were analyzed using a paired t-test. Pearson’s correlation analysis was also performed between these parameters. All \(P\)-values were two-tailed, and \(P\) values less than 0.05 were considered significant. These analyses were performed with the IBM SPSS 20.0 software package (IBM Corp., Armonk, NY).

**Results**

**Subjective Excitation and Physiological Response**

We undertook scanning experiments, using PET to detect the activation of dopaminergic system, while 10 subjects, with an average score of 201.9 ± 33.7 on the PLS (Hatfield and Sprecher, 1986; Hanari and Kawano, 2012), viewed pictures of their romantic partners and, as a control condition, pictures of friends of the same gender as their partner but for whom they had neutral feelings (Figure 1). The results of the VAS, which is a measure of excitement levels when viewing pictures of romantic partners and friends, are summarized in Table 1, as are physiological responses that give objective measures of excitation. VAS value for excitation during the love condition was significantly higher (\(P < 0.001\)) than that of the control condition. In order
TABLE 1 | Subjective excitation and physiological responses.

|                  | Love          | Control       | p-value |
|------------------|---------------|---------------|---------|
| VAS for excitation, score | 55.3 ± 17.4   | 14.8 ± 9.6    | < 0.001 |
| LF, ms²          | 60.9 ± 17.0   | 48.1 ± 21.0   | 0.033   |
| HF, ms²          | 71.8 ± 24.4   | 62.8 ± 23.4   | 0.249   |
| Skin temperature, °C | 32.9 ± 2.6    | 34.2 ± 1.3    | 0.114   |
| Skin conductance, µS | 1.7 ± 1.0     | 1.8 ± 0.9     | 0.662   |
| Heart rate, beats/min | 61.7 ± 6.9    | 63.1 ± 8.2    | 0.254   |
| Respiration rate, breath/min | 7.0 ± 0.8     | 6.9 ± 0.8     | 0.699   |

VAS, visual analog scale; LF, low frequency power; HF, High frequency power. Values are presented as mean ± SD.

We found a convincing difference in dopaminergic activity within the mOFC and mPFC between the control and love conditions. OfC is part of the emotional brain and has been implicated in a variety of emotional conditions, including the experience of beauty in general (Kawabata and Zeki, 2004; Ishizu and Zeki, 2011) beauty in a face (Ishai, 2007), maternal love (Bartels and Zeki, 2004), and aesthetic judgment (Ishizu and Zeki, 2013). It has also been repeatedly shown to be engaged during reward experiences (Gottfried et al., 2003). The part of the mOFC implicated in the present study corresponds closely to the part that was engaged during experiences of beauty and of maternal love, suggesting that the dopaminergic activity there may not be related uniquely to romantic love but may be more related to rewarding experiences, of which romantic love is one example. There could, nevertheless, be further subdivisions within the mOFC that are active during different types of reward. We were however interested to observe that, although both regions showed more dopaminergic activity, the correlation between VAS value and BPND was observed in the mOFC alone, suggesting a difference in the role of the two areas within the context of our experiment. The involvement of two distinct regions of the frontal cortex in our study, in one of which (mOFC) there was a (negative) correlation with VAS values while in the other there was none, may be indicative of a much wider functional sub-specialization within the OFC. Izuma et al. (2008), likewise found that the activity in mPFC was not graded in a self-evaluation paradigm, unlike activity in the striatum which correlated with reward level.
FIGURE 2 | Decreased BP_{ND} by viewing loved partners’ pictures. Statistical parametric maps of BP_{ND} in the medial orbitofrontal cortex (mOFC) and medial prefrontal cortex (mPFC) in the love condition (Control minus Love) (A) and graphs to show the peak value of the binding potential within the cluster (BP_{ND}) in these regions of each subject (B). The mean and standard deviation is shown in (B) and the P values resulted from statistical analysis by two-tailed paired t-test.

FIGURE 3 | Correlation between subjective excitement levels and BP_{ND}. Correlation between visual analog scale (VAS) values for excitation produced by viewing partners’ (left) and friends’ (right) pictures, and the BP_{ND} in the OFC during the love and control condition, respectively. Pearson’s coefficient value and P value are shown. Note the absence of a correlation in the right panel.
Thus, this first PET study of neurotransmitter activity during the experience of romantic love not only revealed specific areas of the brain where the dopaminergic system is activated during the experience, but additionally showed that different subdivisions within the frontal cortex may use this heightened release in different ways. Future studies should determine whether this specific pattern of dopaminergic activation in the mOFC is unique to romantic love or whether it is a more general pattern that correlates with other intense, and rewarding, emotional experiences. It would, as well, be interesting to determine the relationship between dopamine release in the OFC and dopaminergic activity elsewhere in the brain, particularly in areas of the sub cortex that have been implicated in the experience of romantic love.

Acknowledgments

We would like to thank Drs. Yasuhiro Nakatomi, Yasunori Tokuda, Kazuhiro Takahashi, Mr. Hideki Kawahata, and Mses. Hisako Kobata and Kayo Onoe for help with the PET experiments and data analyses. In addition, we would also like to thank Mr. Atsushi Ikemoto for MRI scan. Semir Zeki’s laboratory is supported by the Wellcome Trust, London.

Supplementary Material

The Supplementary Material for this article can be found online at: http://www.frontiersin.org/journal/10.3389/fnhum. 2015.00191/abstract

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