right insula ($F_{1,13} = 6.948$, $P = 0.021$) and left primary motor cortex ($F_{2,26} = 7.894$, $P = 0.002$), a significant RT effect in left GP ($F_{1,13} = 1.573$, $P < 0.0001$), right GP ($F_{1,13} = 37.957$, $P < 0.0001$), right insula ($F_{1,13} = 6.948$, $P = 0.021$), left putamen ($F_{1,13} = 45.757$, $P < 0.0001$), right putamen ($F_{1,13} = 13.968$, $P = 0.002$), right NAcc ($F_{1,13} = 5.755$ $P = 0.032$), left caudate ($F_{1,13} = 10.553$, $P = 0.006$), left DLPFC ($F_{1,13} = 10.568$, $P = 0.006$) and left primary motor cortex ($F_{1,13} = 38.179$, $P < 0.0001$).

Post hoc analysis with Bonferroni correction showed there were significant differences between paroxetine and placebo in only the left primary motor cortex, Pslow and Sslow ($P = 0.003$), Pfast and Sfast ($P = 0.008$), in which the activations were greater under placebo treatment (Fig. 1j). In the absence of drug or placebo treatment, the fast RT trials (Nfast) showed significantly higher activation than the fast RT trials of paroxetine condition (Sfast) in left GP ($P = 0.023$), left insula ($P = 0.008$), right insula ($P = 0.007$), right putamen ($P = 0.008$), left DLPFC ($P = 0.022$) and left primary motor cortex ($P = 0.003$) (Fig. 1a,c,d,f,i,j), which was not shown in comparison between the slow RT trials. There were no significant differences between placebo and no drug in any of the ROI.

Considering the way the ROI were defined, it was natural that there were significant differences between Nslow and Nfast in all the ROI. In paroxetine conditions, Sfast was significantly more activated than Sslow in only the left primary motor cortex (Fig. 1j). When subjects were given placebo, Pfast activation was greater than Pslow only in the left GP ($P = 0.045$), left putamen ($P = 0.007$) and left primary motor cortex ($P = 0.042$) (Fig. 1a,e,j).

DISCUSSION

Disturbances in motivation and motor activity are seen in MDD and these symptoms are sometimes exacerbated by SSRI in some patients. To investigate this paradoxical effect, we wish to use fMRI to monitor affected patients in response to drug therapy. However, as a first step, we studied normal subjects following a single dose of the SSRI paroxetine.

In this collection of normal subjects, there were no differences among the three drug conditions within each of the average RT of the whole, no incentive, incentive and subdivided RT trials. Thus, paroxetine administration did not affect subject behavior or performance globally. The average RT of no incentive and incentive trials showed no significance, which might be induced by the instruction for the subjects to press the button within the short duration of 500 ms even when the cue was no incentive.

Then, we investigated brain activations between the slow RT and the fast RT trials, which were behaviorally subdivided with significance, within treatment groups. The fast RT trials recruited greater activation in the GP, insula, putamen, NAcc, DLPFC, caudate and primary motor cortex than slow RT trials under no drug treatment. Under placebo conditions, the fast RT trials recruited greater activation in the GP, putamen and primary motor cortex. However, the paroxetine condition showed greater activations in the fast RT trials compared to the slow RT trials only in the primary motor cortex. These results indicated paroxetine desensitized RT influence on reward-anticipation-related brain activity, meanwhile no drug and placebo conditions reflected RT influence fully or partially in the reward-related areas.

In the next step, we looked into the activation differences in the same RT (slow or fast) group among the different drug conditions. Paroxetine significantly suppressed activation in the left GP, bilateral insula, right putamen and left DLPFC as reward-anticipation-related areas compared to no drug in the fast RT trials reflecting higher motivation, not in the slow RT trials reflecting lower motivation.

In the primary motor cortex, the activation under paroxetine administration was significantly weaker than no drug in the fast RT trials only, but weaker than placebo in both fast and slow RT trials. Besides, the fast RT trials were activated greater than the slow RT trials in all three drug conditions. Thus, the characteristics shown in the reward-related areas collapsed in the primary motor cortex, although paroxetine reduced activation compared to no drug and placebo in any case.

Taken together, paroxetine attenuated the brain activity in the reward-anticipation-related areas between the subdivided RT groups and compared to no drug in the more motivated fast RT trials. When anhedonia, one of the major symptoms of MDD, is considered as decreased motivation and sensitivity to rewarding experiences, our results suggest that a single dose of paroxetine may create a relatively anhedonic state in healthy subjects.

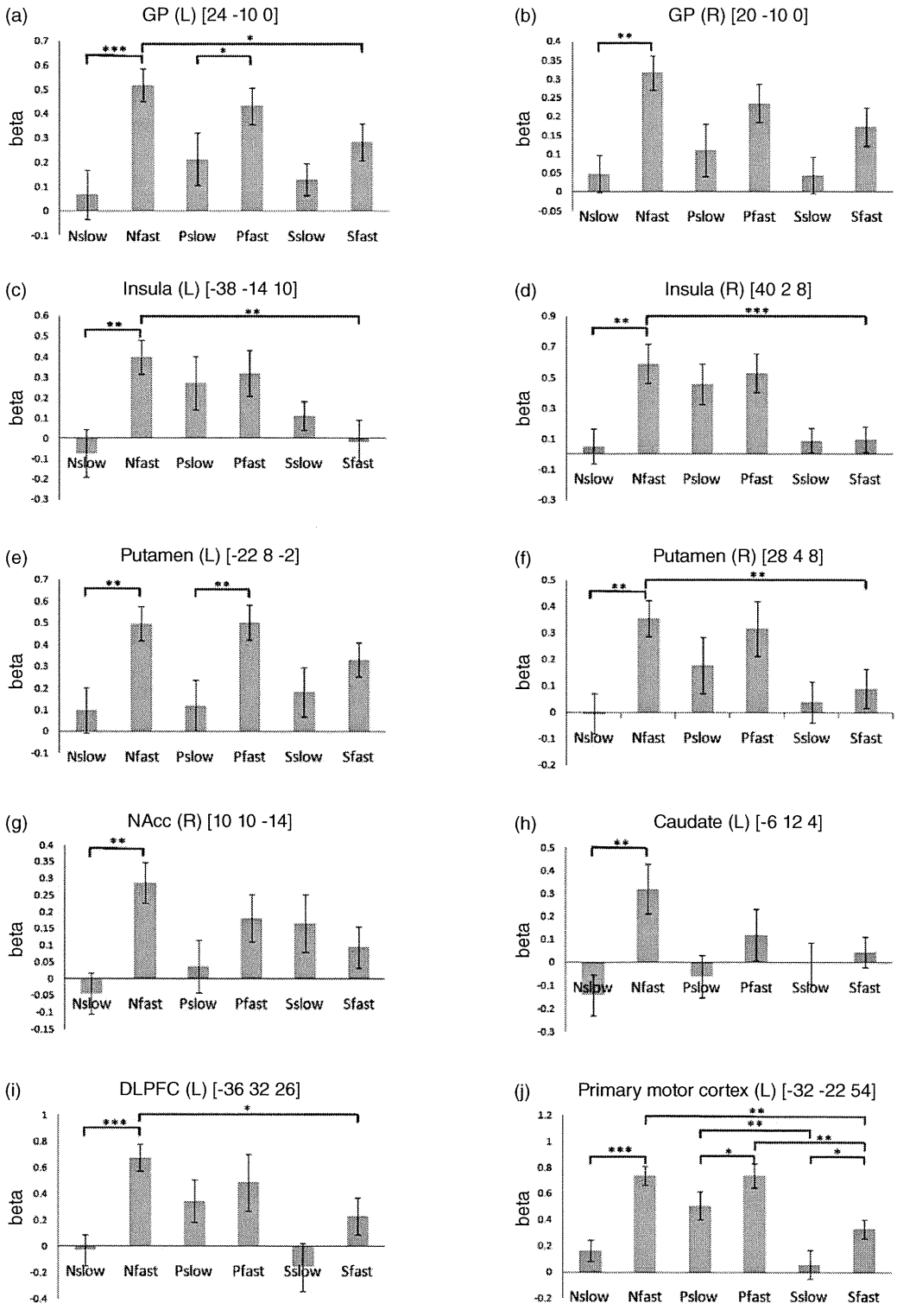

Figure 1. The mean beta values for the peak activation categorized by drug and reaction time type for the defined regions-of-interest. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$. Error bars show SEM. DLPFC, dorsolateral prefrontal cortex; GP, globus pallidus; L, left; NAcc, nucleus accumbens; R, right.

These results might partly come from the duration of drug administration because sufficient antidepressive effects of SSRI are not apparent normally until after 3–6 weeks of treatment. The increase in 5-HT produced by a single administration of SSRI not only stimulates the postsynaptic 5-HT receptors but also stimulates the somatodendritic inhibitory 5-HT_{1A} autoreceptors and presynaptic 5-HT_{1B} and 5-HT_{1D} autoreceptors. This varied activity could produce a net reduction in the activity of the 5-HT system.[32] Long-term treatment with SSRI induces desensitization/internalization of 5-HT autoreceptors, and this could lead to the downregulation of some postsynaptic receptors, such as the 5-HT_{2A} and 5-HT_{2C} subtypes. The end result of this process is thought to be a net activation of the 5-HT system.[32] Our results may partly arise from a net reduction of serotonin function by 5-HT autoreceptors produced by acute paroxetine administration.

We should briefly mention a relatively strong affinity of paroxetine for the norepinephrine transporter, $K_D = 40 \pm 2$ nmol[23] and muscarine receptor, $K_i = 72 \pm 3$ nmol/L,[22] but it is beyond the scope of the present study to examine the effects of paroxetine on these pathways.

In conclusion, paroxetine single acute administration diminished brain activity induced by motivation in healthy subjects. Our results may partially explain clinically observed decreased motivation seen in patients with relatively mild symptoms taking an initial paroxetine tablet dose of 10 or 20 mg for the first time. Further research is needed to clarify the effects of SSRI on brain activity with respect to cognitive and motor functions.

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Eye Gaze during Observation of Static Faces in Deaf People

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Abstract

Knowing where people look when viewing faces provides an objective measure into the part of information entering the visual system as well as into the cognitive strategy involved in facial perception. In the present study, we recorded the eye movements of 20 congenitally deaf (10 male and 10 female) and 23 (11 male and 12 female) normal-hearing Japanese participants while they evaluated the emotional valence of static face stimuli. While no difference was found in the evaluation scores, the eye movements during facial observations differed among participant groups. The deaf group looked at the eyes more frequently and for longer duration than the nose whereas the hearing group focused on the nose (or the central region of face) more than the eyes. These results suggest that the strategy employed to extract visual information when viewing static faces may differ between deaf and hearing people.

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Introduction

It has been hypothesized that deaf people may explore and see the visual world differently from hearing people because of their adaptation to hearing loss and/or consequential changes in communication strategy. Some studies have supported altered visual functions in deaf people, especially in the distribution and processes of visual attention [1]–[6].

Facial processing is considered to be one of the fundamental visual processes necessary for successful social interaction. This is because, for sighted people, facial processing constitutes a basic skill for detecting and recognizing other people's emotional states. A few studies have shown that facial processing in deaf people might differ from that of hearing people. For example, McCullough & Emmorey [7] showed that American deaf people are better at detecting subtle differences in facial features (particularly around the eyes and mouth) and suggested that long-term experience in discriminating grammatical facial expressions used with American Sign Language (ASL) and lip-reading may contribute to enhanced detection of nuances in relevant facial features (see also [8],[9]).

Since high spatial resolution visual processes are possible only at the fovea, humans produce a series of foveal fixations to extract visual information [10], which are closely linked with overt visual attention [11]. With regard to facial processing, studies investigating eye movements have consistently found a systematic fixation sequence in which the eyes are not directed equally to all regions of a face but only to selected parts; i.e., mainly the eyes and mouth [12]–[16].

Several studies that examined the eye movements of deaf people have found that they tend to look at facial regions in a similar magnitude as do hearing people [17]–[19]. For example, Muir & Richardson [17] conducted gaze-tracking experiments with deaf people watching sign language video clips and found that participants fixated mostly on the facial regions rather than on the hand movements of the signer, presumably to detect facial movements related to expression. In addition, Emmorey et al. [19] compared eye movements of beginning signers with experienced signers of ASL during ASL comprehension and found differences in fixation patterns: Beginning signers looked at facial regions around the signer's mouth while native signers fixated more on the areas around the eyes. Although these previous studies showed that there are minor differences in fixation patterns between certain groups, the sequence of fixation on the eyes and mouth has been considered to be a universal information extraction pattern.

Nevertheless, the idea of strictly universal facial processing has recently been challenged by several studies that investigated cultural influences on eye movements [20],[21]. Blais et al. [20] showed that Western Caucasian observers consistently fixated on the eye region and partially on the mouth area, confirming the triangular fixation pattern, whereas East Asian observers fixated more on the central region of the face (i.e., around the nose region). These results were interpreted by the authors in the context of cultural influences on visual environment affordance (analytic versus holistic processes [22]) and indicate that, even for face processing, strategies employed to extract visual information are shaped by experience (see also [23]–[27]).

Since hearing loss imposes significant constraints on everyday life, it is possible that deaf people use a visual strategy that is different from that used by hearing people, which might lead to differences in scan paths. The triangular pattern of scan path during observations of faces has not been examined quantitatively in deaf people. The purpose of the current study was therefore to report differential scan paths between deaf and hearing people. We chose an emotional valence evaluation task with static faces because it was easy to understand and perform by both deaf and hearing participants.

Because our participants were Japanese (i.e., East Asian), we expected to observe the generally dominant fixations on the central region of the face (i.e., around the nose region) [20]. Then, there were several possibilities, besides that of no difference in eye movement pattern between deaf and hearing participants. Firstly, since deaf people communicate with sign languages, manually signed languages, and/or lip-reading, the mouth region would be of importance for deaf people and therefore fixated more during face observation. Secondly, eye contact is an imperative component of communication and this is more so in a deaf community [28]. Hence, fixations in the eye region might be more pronounced in deaf people. Thirdly, visual processing in deaf individuals exhibit more emphasis on the peripheral visual field [2]–[6]. Therefore, in addition to the general tendency toward the nose region [20] [21], deaf individuals might make more eye movements in the parafoveal and peripheral regions, irrespective of whether the region is the main parts of faces (eyes and mouth) or not.

Methods

Ethics Statement

The procedures were approved by the internal review board of the Tsukuba University of Technology, and written informed consent was obtained from all participants prior to the testing.

Participants

We recruited 24 congenitally deaf Japanese people and 29 Japanese people with normal hearing function. Due to procedural failures during the experiment and/or spontaneous withdrawal from the study, data from 10 participants were excluded. The remaining participants comprised 20 congenitally deaf Japanese people (10 males and 10 females; mean age = 21.7 years, standard deviation = 0.75) and 23 Japanese people with normal hearing function (11 males and 12 females; mean age = 24.6 years, standard deviation = 3.11). All deaf participants were undergraduate students at Tsukuba University of Technology, where one of the entrance criteria is hearing loss of 60 dB or more. The deaf participants typically used manually signed Japanese and/or lip-reading for communication. None of the hearing participants were practiced in sign languages, manually signed languages, or lip-reading.

Stimuli

Stimuli were obtained from a commercially available database (the ATR face database DV99; ATR-Promotions, Inc.) and consisted of 4 male and 4 female Japanese identities expressing 10 different expressions (neutral [NE], fear [FE], happiness with the mouth opened [HO], happiness with the mouth closed [HC], sadness [SD], surprise [SP], anger with the mouth opened [AO], anger with the mouth closed [AC], disgust [DI], and contempt [CT]). The images were displayed on a 17-inch LCD monitor and viewed at a distance of about 55 cm, subtending 20 degrees of visual angle (27 cm) vertically and 36 degrees of visual angle (54 cm) horizontally. Each face image was centrally located and about 20 cm in height, which represents the size of a real face. Approximate positions of the eyes and mouth were aligned. Presentation of stimuli was controlled by Tobii Studio software (ver. 2.1.12, Tobii Technology, Stockholm, Sweden).

Eye tracking

Eye movements were recorded at a sampling rate of 60 Hz with the Tobii T-60 eye-tracker (Tobii Technology), which has an average gaze position error of 0.5 degrees and near-linear output over the range of the monitor used. Only the dominant eye of each participant was tracked although viewing was binocular. A manual calibration of eye fixations was conducted at the beginning of each session using a 9-point fixation procedure as implemented in the Tobii Studio software, and drift correction was performed for each trial.

Procedure

Participants were informed that they would be presented with a series of face pictures in order to evaluate the emotional valence of each face stimulus shown. Before each trial, participants were instructed to fixate on a cross at the center of the screen to perform an automatic drift correction. The participant initiated each trial by pressing a space bar. After a 2-s fixation period, a face was presented for 3 s. Then, the evaluation display appeared, and the participants used a computer mouse to click on the emotional valence of the face in the picture (out of a 7-point positive-negative scale with 1 being most positive). Evaluation was not speeded. Upon the participant's click of the mouse, the next trial began. A session consisted of 3 training trials with neutral expressions followed by 144 test trials. For the test trials, each combination of 8 identities and 9 expressions (except for NE) was presented once (72 trials), and each neutral expression of 8 identities was repeated 9 times (72 trials). The presentation of face stimuli was randomized.

Data analysis

The rating scores of emotional valence were first averaged for each expression by each participant. The mean rating scores were then grouped by the combination of hearing loss and participants' gender. A 3-way analysis of variance (ANOVA) was conducted to assess statistical significance, with hearing loss (deaf versus hearing) and participants' gender (male versus female) as between-group factors and facial expression of the stimulus as a within-group factor.

For each participant, we calculated the time that they fixated (fixation duration) and the number of fixations (fixation frequency) on the following areas of interests (AOIs): the eyes, the nose, and the mouth. AOIs were defined for each face (Figure 1). To control for differences in the sizes of AOIs, we normalized the fixation duration by the area of the AOI so that the sum of relative fixation duration would be 1 for each trial (relative fixation duration). The same normalization was performed for fixation frequency to calculate relative fixation frequency. Relative fixation duration and relative fixation frequency on the different AOIs were averaged separately for expressions within each participant. The averages were then grouped by combining hearing loss and participants' gender separately for AOIs. The relative fixation duration on AOIs was entered into a 4-way ANOVA, with hearing loss and participants' gender as between-group factors and facial expression and AOIs as within-group factors. The same ANOVA was conducted on the relative fixation frequency.

Results

Evaluation of emotional valence

The averaged rating scores of emotional valence are shown in Figure 2. Face stimuli with happy expressions (HO and HC) were

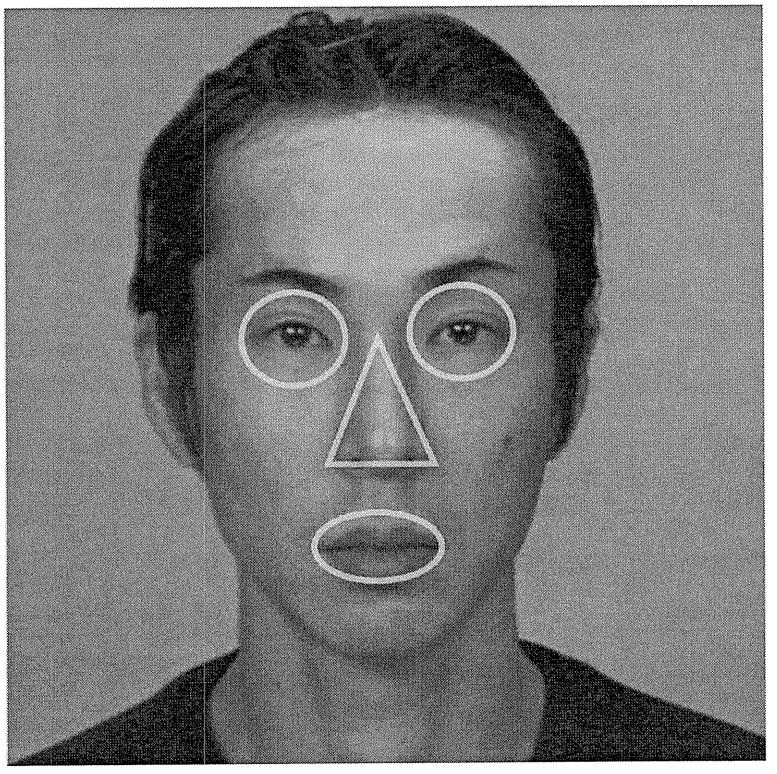

Figure 1. Example of areas of interest (AOIs). For each face stimulus, we defined AOIs: the eyes, nose, and mouth. In order to control for differences in sizes of AOIs, the fixation duration and fixation frequency were normalized by the AOI (relative fixation duration and relative fixation frequency) so that the sum of fixation duration and that of fixation frequency would be 1 for each trial.
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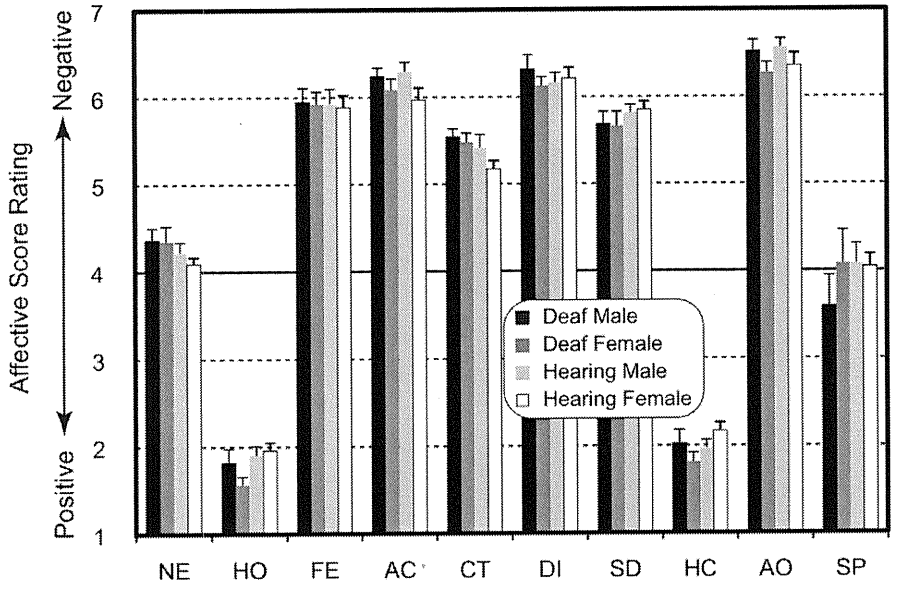

Figure 2. Mean rating scores of emotional valence as a function of expression in face stimuli. The face stimuli with happy expressions (HO and HC) were evaluated positively while the face stimuli with sad (SD), angry (AO and AC), disgust (DI), and contempt (CT) expressions were rated negatively. The faces with neutral (NE) and surprised (SP) expressions were evaluated neither positively nor negatively. NE = neutral; HO = happiness with the mouth opened; FE = fear, AC = anger with the mouth closed; CT = contempt; DI = disgust; SD = sadness; HC = happiness with the mouth closed; AO = anger with the mouth opened; and SP = surprise.
doi:10.1371/journal.pone.0016919.g002

evaluated positively while face stimuli with fear (FE), sad (SD), angry (AO and AC), disgust (DI), and contempt (CT) expressions tended to be rated negatively. Faces with neutral (NE) and surprised (SP) expressions were evaluated, on average, neither positively nor negatively. Three-way ANOVA showed that a main effect of expression ($F(9,351) = 597.7$, $P<0.001$) was significant while the main effects of hearing loss and participants' gender were not significant ($F(1,39 = 0.3$, $P = 0.60$, $F(1,39) = 1.2$, $P = 0.29$, respectively). No interaction reached a significant level ($F<1.3$, $P>0.23$). These results suggest that the participants evaluated the emotional valence of the faces presented as stimuli consistently, irrespective of hearing loss and participants' gender.

Eye movements

Data from trials where no gazes were directed at AOIs (i.e., the eyes, nose, or mouth) were excluded from the following analysis, which were 0.8%, 0.4%, 0.4%, and 0.5%, for deaf male, deaf female, hearing male, and hearing female groups, respectively. There was no significant difference in the number of discarded trials (Fisher exact test; $P = 0.32$). Figure 3 depicts the relative fixation duration mapped onto an example image of neutral face separately summed for deaf participants (Figure 3a), normal-hearing participants (Figure 3b), female participants (Figure 3c), and male participants (Figure 3d). This figure suggests that the gaze patterns differed among the participant groups.

Figure 4a shows relative fixation duration as a function of AOI, averaged over all facial expressions within different combinations of participant groups. In general, participants tended to fixate on the eyes and nose longer than on the mouth. In addition, deaf participants looked at the eyes longer than the nose whereas normal-hearing participants gazed at the nose longer than the eyes (Figure 4b). The tendency to fixate longer on the eyes appeared to be stronger in females compared with male participants (Figure 4c). Figure 5 shows the relative fixation duration for the different AOIs as a function of facial expression averaged over all participants. The differential relative fixation durations for different AOIs were apparent; i.e., fixation duration on the eyes and the nose was longer than on the mouth. In addition, the pictures of faces with neutral expressions appeared to lead to longer fixation on the eyes in exchange for shorter fixation duration on the mouth.

Four-way ANOVA revealed significant main effects of participants' gender ($F(1,39) = 8.7$, $P<0.01$; female > male), AOI ($F(2,78) = 26.8$, $P<0.001$; post hoc Ryan's method, eyes = nose > mouth, $P<0.001$), and expression ($F(9,351) = 5.6$, $P<0.001$).

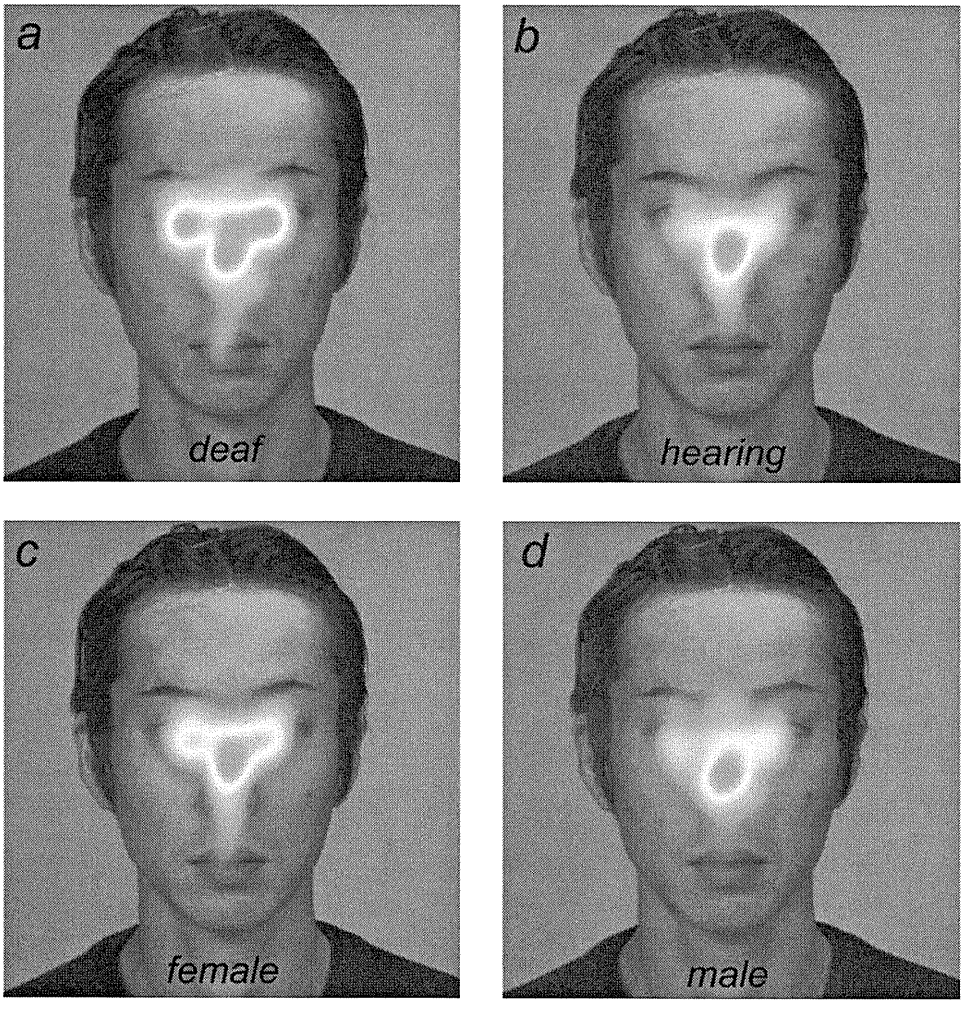

Figure 3. Total fixation duration mapped onto an example face image: (a) deaf participants, (b) hearing participants, (c) female participants, and (d) male participants. Red regions represent the places where the participants' eyes stayed longer. The fixation patters differed among the participant groups.
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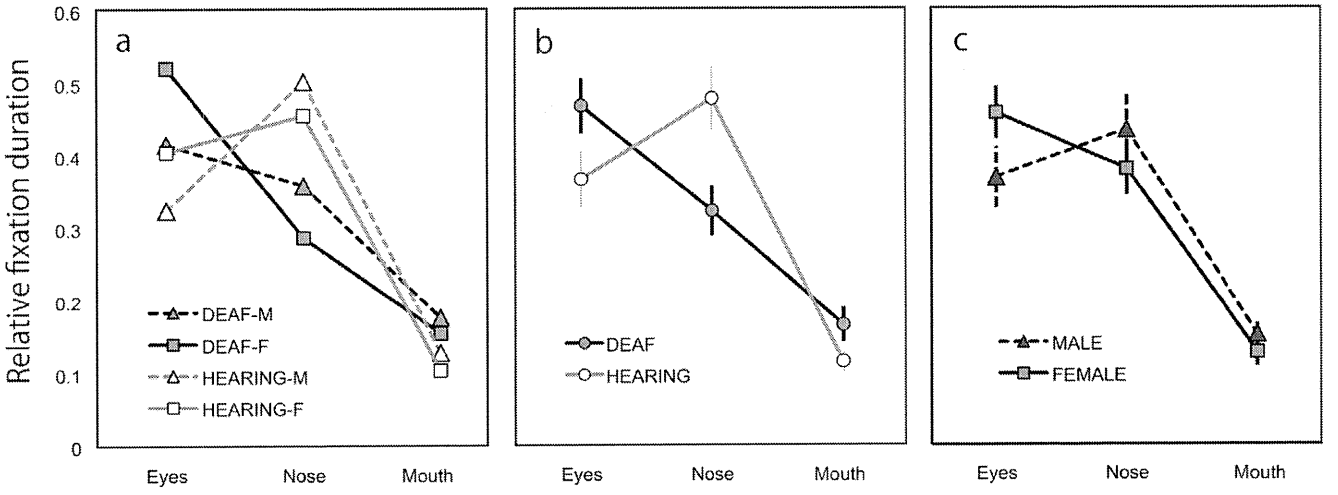

Figure 4. Relative fixation duration. (**a**) Relative fixation duration as a function of area of interest averaged over all facial expressions within different combinations of participant groups. Participants tended to fixate on the eyes and nose longer than on the mouth. (**b**) Relative fixation duration compared between deaf and hearing participants. The deaf participants looked at the eyes longer than the nose whereas the hearing participants gazed at the nose longer than the eyes. (**c**) Relative fixation duration compared between female and male participants. The female participants tended to fixate on the eyes longer than did the male participants.
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A significant interaction between hearing loss and AOI ($F(2,78) = 5.3$, $P<0.01$) and between expression and AOI ($F(18,702) = 2.8$, $P<0.001$) were found. There were also significant interactions between hearing loss and expression ($F(9, 351) = 2.0$, $P<0.05$) and among participants' gender, expression, and AOI ($F(18, 702) = 1.7$, $P<0.05$). Analyses of simple main effect indicated that the normal-hearing group looked at the nose longer than the eyes whereas the deaf group tended to look at the eyes more than the nose ($P<0.05$). The interaction between expression and AOI was mainly due to the fact that participants fixated longer on the eyes in pictures of neutral faces than in pictures of faces with other expressions ($P<0.05$). The data of relative fixation frequency corroborated the results of relative fixation duration (Figures 6 and 7).

An additional analysis was performed to test whether the fixation duration and fixation frequency outside the AOIs differ among participant groups. Whereas significant main effects of participants' gender were found (male > female; fixation duration, $F(1,39) = 13.6$, $P<0.01$; fixation frequency, $F(1,39) = 15.1$, $P<0.01$), no statistical difference was observed between deaf and hearing participants (fixation duration, $F(1,39) = 0.14$, $P = 0.7$; fixation frequency, $F(1,39) = 1.14$, $P = 0.29$), corroborating the results of 4-way ANOVA.

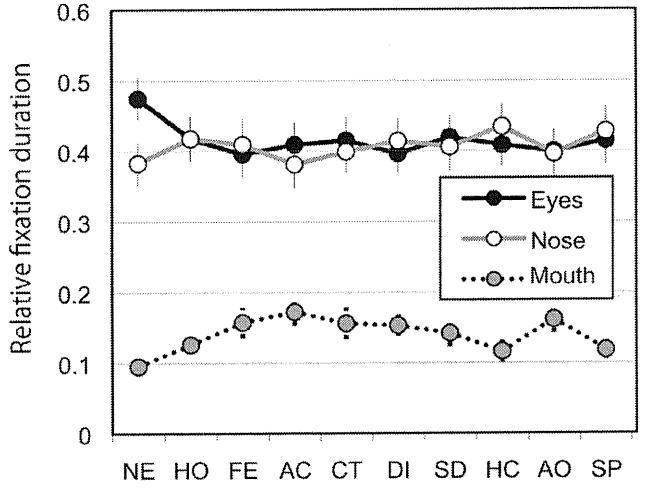

Figure 5. Relative fixation duration for the different areas of interest as a function of facial expression, averaged over all the participants. The faces with neutral expression led to longer fixation duration on the eyes. NE = neutral; HO = happiness with the mouth opened; FE = fear, AC = anger with the mouth closed; CT = contempt; DI = disgust; SD = sadness; HC = happiness with the mouth closed; AO = anger with the mouth opened; and SP = surprise.
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Discussion

In the present study we examined the possible difference in the pattern of eye movements between congenitally deaf and normal-hearing Japanese individuals while they evaluated the emotional valence of static faces. The results can be summarized as follows: (1) The emotional valence of face stimuli were evaluated consistently irrespective of hearing loss and participants' gender; (2) participants fixated (in terms of frequently and duration) on the eyes and nose more than on the mouth (the main effect of AOI), confirming overall fixation dominance on the eyes; (3) female participants tended to look at the main facial parts (i.e., the eyes, nose, and mouth) more than did male participants (the main effect of participant's gender); (4) faces with neutral expressions induced fixations on the eyes more than did faces with other expressions (the interaction between expression and AOI); and (5) deaf participants looked at the eyes more than the nose whereas normal-hearing participants tended to look more at the nose (the interaction between hearing loss and AOI).

It has been reported that females have an advantage in decoding nonverbal emotion [29]–[35] and that females look more at the main parts of the face than do males, with particular emphasis on the eyes [34],[35]. The main effects of participant's gender supported this notion. Although the interaction between participants' gender and AOI and the interaction among participants' gender, hearing loss, and AOI did not reach a significant level, our data clearly showed a tendency in the female

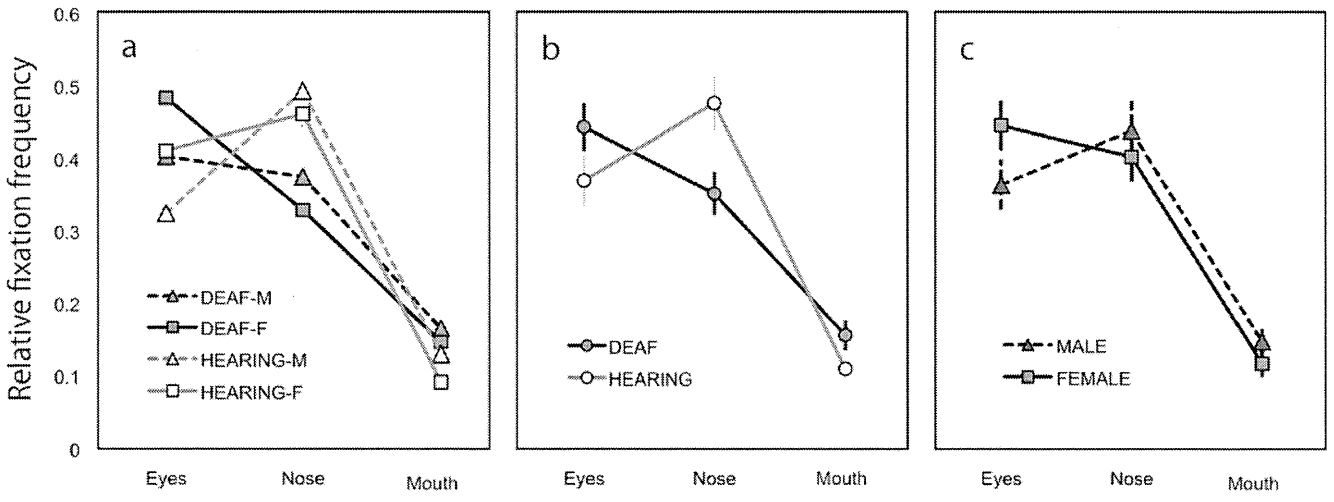

Figure 6. Relative fixation frequency. (**a**) Relative fixation frequency as a function of area of interest averaged over all facial expressions within different combinations of participant groups. (**b**) Relative fixation frequency compared between deaf and hearing participants. (**c**) Relative fixation frequency compared between female and male participants. The results for fixation frequency corroborated those of fixation duration.
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participants to fixate on the eyes (Figure 4c and Figure 6c). Thus, the present results may be taken as evidence supporting a gender difference in fixation pattern for faces with emotional expressions [34],[35].

Irrespective of participant group, faces with neutral expressions tended to produce more fixations on the eyes than did faces showing other expressions. Faces with emotional expressions have distinct features that help observers to interpret the expression. On the other hand, neutral faces are ambiguous and lack the visual cues for comprehension of emotion. It has been suggested that understanding and communication of emotion depends greatly on the visual processing of the eye region [36]–[39]. Therefore, it is possible that people fixate more on the eyes of ambiguous neutral faces in an attempt to discern emotional clues. However, it should

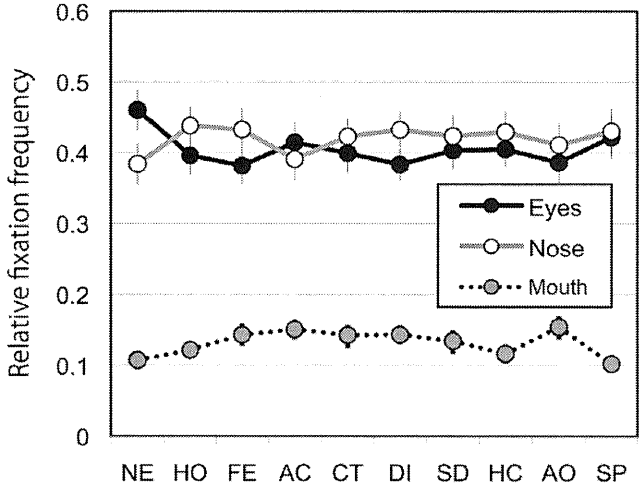

Figure 7. Relative fixation frequency for the different areas of interest as a function of facial expression averaged over all the participants. The results for fixation frequency corroborated those of fixation duration. NE = neutral; HO = happiness with the mouth opened; FE = fear, AC = anger with the mouth closed; CT = contempt; DI = disgust; SD = sadness; HC = happiness with the mouth closed; AO = anger with the mouth opened; and SP = surprise.
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be stated that there was a possible confound in the present experiment that the neutral faces were repeated 9 times while the others were presented once and the interaction between expression and AOI may be due to repetition rather than expression. Further investigations are warranted to examine whether less emotional facial expressions indeed lead to more fixation on the eye region. Specifically, a future study should avoid the possible confound between viewing less emotional face expressions and repeated viewing.

The main focus of the present study was to investigate potential differences in fixation patterns between deaf and hearing participants. The hearing participants in the present study looked at the nose (i.e., central) region most rather than at the eye region. Since all the participants in the current study were Japanese, this may be attributed to a cultural influence on eye movement. Blais et al. [20] reported that Western Caucasian observers consistently fixated the eye region, and partially the mouth, whereas East Asian observers fixated more on the central region of the face to extract information from faces. They hypothesized that this difference is due to the social norm in East Asian cultures that direct or excessive eye contact may be considered rude [40] and to the difference in cognitive strategy (holistic/analytic approach to visual information: [22],[41]). On the other hand, our Japanese deaf participants looked at the eye region most, closer to the fixation pattern of Western Caucasians in Blais et al [20]. It has been reported that in a deaf community, eye contact is vital for communication because avoiding eye contact disrupts communication more profoundly than it does in sighted communities [28]; this holds true for a Japanese deaf community. Therefore, it is possible that the increased fixation on the eye region in our Japanese deaf participants may reflect their communication strategy. In this sense, the present study may be taken as an extension of Blais et al. [20], showing that living in a specific community (more specifically, deaf community in Tsukuba University of Technology in Japan) might alter how we look at faces (also see [23]–[27]).

The underling mechanism for differential scan paths between deaf and hearing individuals remains to be clarified. However, one possible mechanism is the altered distribution and processes of visual attention [2]–[5]. Deaf individuals are more distracted by

visual information in the parafovea and periphery [5]. Since there was no difference in fixation duration and frequency outside the AOIs and no increase of fixation in the mouth region, the present finding cannot be explained solely by the attention emphasis on the peripheral processing. However, it is still possible that altered peripheral visual attention and scrutinizing strategy for faces may interact to produce the differential scan paths.

Limitations of the present study

Although the difference in fixation pattern was clear, it should be noted that the present study has considerable limitations. One limitation is that the stimuli used in the present study were static, rather than dynamic, stimuli. Many studies of emotional expression have used static face stimuli. Yet, facial expressions are highly dynamic, and thus, static stimuli represent unnatural snapshots of them. Recent studies on dynamic facial expressions have shown that visual processes for facial expressions are essentially tuned to dynamic information [36],[42],[43]. Evidence supporting this notion comes from facilitative effects of dynamic presentation on facial processing [44]–[50] and enhanced neural activities for dynamic, as opposed to static, face stimuli [51]–[53]. Therefore, it is likely that the pattern of results would be different if dynamic stimuli were used. In particular, the relatively less fixations in the mouth region might be due to the use of the static face stimuli. It has been shown that the mouth region conveys useful information for emotion discrimination [54]–[58], and this seems to be more so with dynamic face stimuli, e.g., [59].

Another limitation stems from the use of the evaluation task of emotional valence. Many previous studies have examined the scan paths during emotion discrimination and identification (e.g., [56],[57]) but little study has employed an evaluation task of emotional valence. Therefore, the present results may not be compared directly with those of the previous studies. Also, in order to elucidate the mechanism for valence evaluation and emotional processes, it is important to consider the relation between the time-course of evaluation processes and eye movement. The face stimuli used in the present study included some variations in visual information for emotional valence evaluation, which in turn would lead to different demands for different face stimuli. Since the decision was not timed, we did not know when the participants reached their decisions. Therefore, the eye movement pattern may reflect either pre-decision or post-decision processes or both.

The final limitation is the demographic peculiarity of the participants. It is possible that the use of sign language (Japanese Sign Language; JSL) leads to enhanced attention to the eye region because changes in eye configurations convey various syntactic distinctions and grammatical information in JSL as in ASL [60],[61]. However, until around 2002, most Japanese schools for the deaf emphasized oral education; i.e., teaching through lip-reading. Although manually signed Japanese (which is a signed form of the Japanese language) has recently started to be used in schools for the deaf, even now Japanese sign language is not officially taught. Therefore, it is difficult to infer whether the difference in fixation pattern is due to the hearing loss itself, to the extended use of sign language, and/or to the specific historical situation of Japanese deaf education.

Despite the above limitations, the present study showed the differential scan paths during observation of static face stimuli between deaf and hearing participants. Further investigations, preferably with speeded response or confidence/difficulty rating of decision, with dynamic stimuli, and with cross-cultural comparisons, will shed light on how and to what extent hearing loss influences how we look at faces and interpret others.

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Author Contributions

Conceived and designed the experiments: KW TM MN. Performed the experiments: MN. Analyzed the data: KW TN MN. Contributed reagents/materials/analysis tools: TM TN. Wrote the manuscript: KW MN.

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Neural circuits in the brain that are activated when mitigating criminal sentences

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In sentencing guilty defendants, jurors and judges weigh 'mitigating circumstances', which create sympathy for a defendant. Here we use functional magnetic resonance imaging to measure neural activity in ordinary citizens who are potential jurors, as they decide on mitigation of punishment for murder. We found that sympathy activated regions associated with mentalising and moral conflict (dorsomedial prefrontal cortex, precuneus and temporo-parietal junction). Sentencing also activated precuneus and anterior cingulate cortex, suggesting that mitigation is based on negative affective responses to murder, sympathy for mitigating circumstances and cognitive control to choose numerical punishments. Individual differences on the inclination to mitigate, the sentence reduction per unit of judged sympathy, correlated with activity in the right middle insula, an area known to represent interoception of visceral states. These results could help the legal system understand how potential jurors actually decide, and contribute to growing knowledge about whether emotion and cognition are integrated sensibly in difficult judgments.

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Philosophers, psychologists and legal scholars have long debated whether mercy, sympathy and compassion should reduce moral culpability of legal defendants. People do have negative emotional responses to a wide range of situational factors that are not normatively justifiable because they are not considered evidence, or appeal to 'prejudices and sympathy', which jurors are typically instructed to ignore, for example, gruesome crime scene pictures lead to more mock jury convictions when they are in colour (compared with black and white[1]). Other studies show that evidence that provides negative emotions leads to more punitive judgments[2]. A mock trial study reported that jurors found a defendant less guilty when they heard a defense attorney urging sympathy for the defendant[3].

Studies of moral cognition in hypothetical non-legal scenarios have revealed the increased activity in emotion-related brain regions (that is, insula, amygdala and orbitofrontal cortex) and decreased activity in cognitive processes (that is, dorsolateral prefrontal and parietal areas) when participants contemplated morally charged actions, such as a trolley dilemma involving killing lives of some people to save others[4]. Other studies indicate that people do sometimes punish norm violators in non-legal or legal situations, driven by moral judgments in which negative emotional reactions have a critical role[5,6]. Prosocial emotions, such as sympathy, also influence decision making (for example, charitable giving)[3]; however, there is currently no direct cognitive and neural evidence for how sympathy is translated into legal outcomes.

All these studies raise an important question of whether moral judgments and accompanying emotions are used reasonably (as legal rules require) or not. Neuroscience is now entering this debate about defendants, but very little is known about whether mental activity of juries and judges conforms to legal principles. The case we explore here is 'mitigating circumstances', a rare case where emotions, such as sympathy, are allowed to influence juror judgment.

The legal domain is unusual because it may be especially challenging to map emotions into numerical legal outcomes. This difficulty is found in studies of hypothetical punitive damages in tort cases, which not only show that jurors typically agree on moral outrageousness of actions, but also show large disagreement about how outrage is mapped to punitive dollar awards[7,8].

Weighing mitigation puts an unusual burden on people (*qua* jurors) to have appropriate emotional sympathetic reactions, then encode their emotions into prison years. Uncovering the cognitive and neural mechanisms of sympathy that motivate mitigation will inform the role of emotion in jurors' decision process, and perhaps the ultimate policy issue of what role emotional evidence can and should have in trials. Understanding the neuroscientific basis of legal mitigation adds to a basic understanding of moral neuroscience. Neural evidence could also advance theory and practice of law, as so little is known about whether the mental activity of juries and judges conforms to normative legal principles[9].

In summary, our results revealed that sympathy activated brain regions associated with mentalising and moral conflict, including dorsomedial prefrontal cortex (DMPFC), precuneus and temporoparietal junction (TPJ). Sentence mitigation also recruited these sympathy regions, uncovering neural evidence for a close relationship between sympathy and mitigation. Furthermore, individual differences on the inclination to mitigate were reflected in differential middle insula activity. These findings do not just contribute to the field of neuroscience, but could help lawmakers to understand jurors' decision making and their individual differences in trials.

Results

Sympathy and no-sympathy scenarios. We measured brain activity using functional magnetic resonance imaging (fMRI) while subjects are making hypothetical sentence reduction decisions, in dramatic scenarios adapted from actual murder cases. Sympathy-related brain activity was collected during reading circumstances pertaining to defendants' crimes (Fig. 1a). Only actual Japanese murders were used, so the crime was serious, uniform across trials and lifelike. This simple design was chosen to generate engagement and limit nuisance brain activity due to subtle differences in crimes and plausibility of artificially created scenarios.

Mitigating circumstances were of two types: those that would induce sympathy and those that would not. The sympathy scenarios included desperate situations of defendants suffering from domestic violence, disease or poverty. Figure 1a gives one example of each type. The intentionality and severity of the murders were matched between conditions (see Supplementary Methods). After reading about the circumstances, subjects decided how much they would change the sentence given for the defendant (initially 20 years) if they were on a jury. After scanning, subjects were again presented with the same scenarios and asked to rate how much sympathy they felt for the defendant, using a visual analogue scale.

Sympathy and punishment ratings. The sympathy manipulation is internally valid because participants gave significantly higher sympathy ratings to those defendants with sympathy circumstances compared with those with no-sympathy circumstances (n = 22, paired t-test, $t_{21} = -18.94$, $P<0.001$, Fig. 1b). They also reduced sentences much more in sympathy circumstances (n = 22, paired t-test, $t_{21} = 11.82$, $P<0.001$, Fig. 1c). Unsurprisingly, sympathy and punishment (sentence length) were highly negatively correlated (n = 32 stories, linear regression analysis, $P < 0.001$, $R^2 = 0.97$, Fig. 1d).

fMRI results were analysed using standard generalized linear model regression techniques (see Methods). A short block design was used where regressors were included for the various events of the trials (Fig. 1a). Interaction terms corresponding to punishment and sympathy ratings interacted with trial onsets that were added as parametric regressors.

Brain regions associated with sympathy scenarios. We first analysed brain areas exhibiting a stronger response in sympathy scenarios than no-sympathy scenarios. Precuneus, left TPJ and DMPFC showed larger activities for sympathy than for no-sympathy scenarios (n = 22, one-sample t-test, Table 1). These regions are related to mentalization and sympathy as discussed below in detail, which confirms that the experimental manipulation of sympathy produced results consistent with the sympathy ratings data.

Brain regions associated with punishment and sympathy. We then searched for brain regions that responded, during the description, to the subjects' trial-by-trial ratings of sympathy and their amounts of punishment reduction. Activity in precuneus, DMPFC and left TPJ were correlated with sympathy ($P<0.05$, small-volume-corrected, Fig. 2, Supplementary Table S1). Signal increase in precuneus and DMPFC were also associated with the reduction of punishment ($P<0.05$, small-volume-corrected, Fig. 2: note that a small TPJ region was also activated in sentence reduction, but only with $k=6$ voxels). Thus, precuneus and DMPFC were commonly activated by both sympathy and reduction of punishment. Sentence reduction was also associated with activity in anterior cingulate cortex (ACC). All regions showing a whole-brain correlation at $P<0.001$ are listed in Supplementary Tables S1 and S2.

Brain regions associated with an inclination to mitigate. Next, we constructed an individual-specific measure of an inclination to mitigate, by reducing sentences, as a function of sympathy. This measure comes from a simple linear regression on each individual's decisions: punishment = $b_0 + b_1$*sympathy + error[10]. A measure of an inclination to mitigate, the reduction in sentence per unit of sympathy, was given by the b_1 coefficient of the regression. This number represents a complex mapping from an emotional response to a number representing prison time for a defendant (a years-per-emotion coefficient).

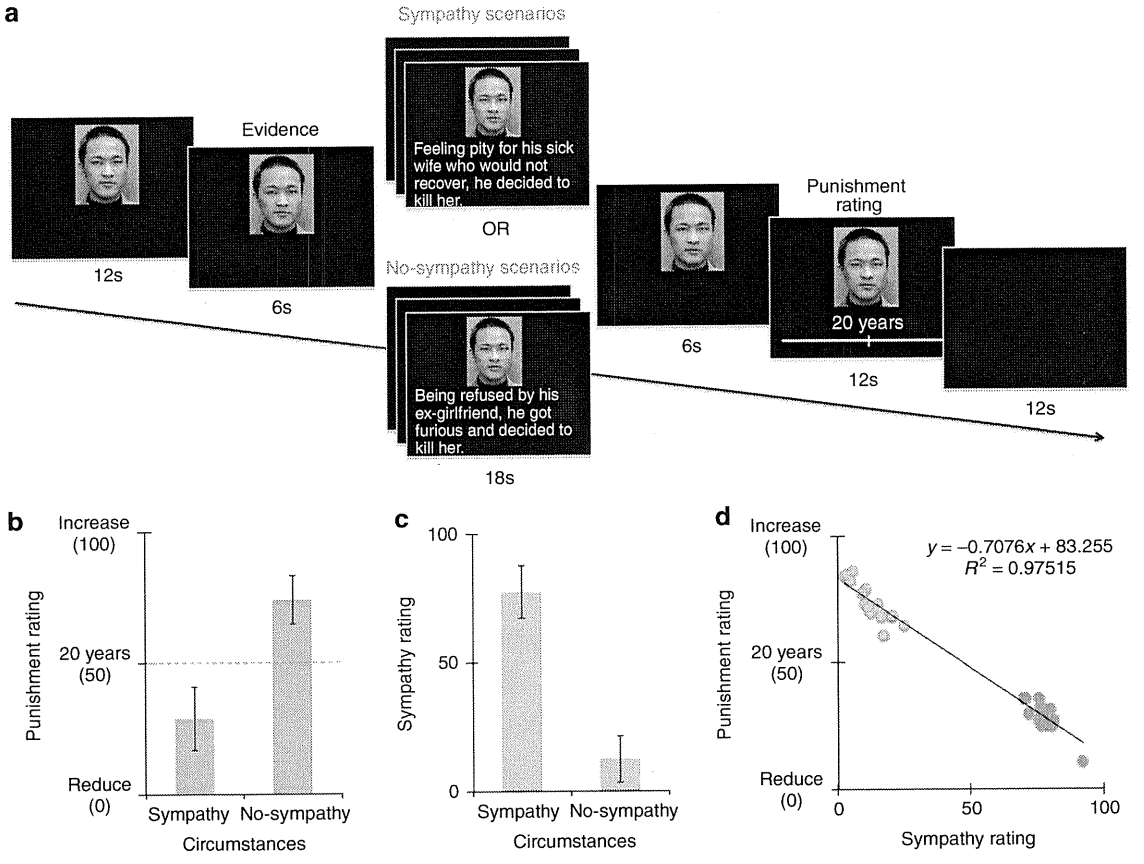

Figure 1 | Task design and behavioural performance. (**a**) Study paradigm. (**b**) Mean punishment ratings for sympathy and no-sympathy trials (n = 22, paired t-test, t_{21} = −18.94, P<0.001). (**c**) Mean sympathy ratings for sympathy and no-sympathy trials (n = 22, paired t-test, t_{21}=11.82, P<0.001). (**d**) Correlation between sympathy and punishment ratings for sympathy stories (red circles) and no-sympathy stories (green circles). Error bars indicate s.d.

These b_1 coefficients were negative for all subjects (mean= −6.5±0.2, linear regression analysis, all P<0.001), indicating that the feeling of sympathy did correlate with reduction of punishment, but to different degrees across subjects. A negative linear regression between the individual-specific b_1 coefficient and blood oxygenation level-dependent responses in sympathy minus no-sympathy trials found activity in the right middle insula (P<0.05, small-volume-corrected, Fig. 3). Individuals who had larger activities in the insula when reading circumstances showed higher tendencies to mitigate, reducing sentencing years more as their sympathy increased.

Discussion

Comparison of activity during judgments of sympathy, and sentence reduction, suggest that activity in DMPFC (also known as paracingulate), precuneus (also known as posterior cingulate) and TPJ reflect a judgment-action circuit, which is illustrated in Fig. 2. Strength of sympathy judgments is associated with activity in DMPFC, precuneus and TPJ. DMPFC is involved in general mentalising[11] and is active when empathizing[12] or sympathizing[13] with others in pain. Precuneus has been linked to subjective perspective taking[14–16]. TPJ is also commonly identified as a part of a theory-of-mind circuit[17], including mentalising about intentions[18], and was activated in one study on judging innocence of intentions of people who caused harm[19]. This suggests that the sympathy judgment is an engagement with a reasoned simulation of what the defendant was thinking when committing the crime or how most people would judge the normative basis for mitigation. Note that although precuneus and TPJ can each be activated by non-social demands as well (for example, attention reorienting[20]), they are rarely co-activated as a group unless social cognitive demands are present.

Regions activated by the punishment reduction judgment include a large region of precuneus and smaller regions in DMPFC and ACC. As noted, precuneus has been linked to simulation on the self to understand others, and is also active when compassionating[21] and forgiving others[22]. The activation in this area is correlated with more iterated steps[23] and higher-value[24] strategic thinking in game theory tasks. Note that both feelings of sympathy and judged mitigation of punishment were encoded in activity in precuneus. This overlapping activity suggests that the precuneus may be a region that accepts emotional judgment input and maps it into concrete punishment actions.

ACC is a region now thought to be activated by negative affect[25,26], positive reward[27] and cognitive control[26,28]. In our context, mapping emotional sympathy into numerical sentencing requires high-level executive function by weighing negative affective reaction to murder, positive sympathy for the murder's mitigating circumstances and exerting cognitive control to choose numerical punishments that weigh these emotions consistently.

Smaller regions in caudate also showed differential activation in response to punishment reduction (Supplementary Table S2). Caudate activity is consistent with the hypothesis that sentence reduction is encoded as a special kind of prosocial 'charity' (as mitigation is like giving to charity[29]), as other prosocial choices activate the caudate too[30].

One fMRI study elicited punishment judgments in artificial scenarios varying offender culpability[6] and reports right DLPFC activity associated with responsibility judgments. We speculate that the absence of right DLPFC activation in our study is because there is no doubt about the defendants' guilt, so the most morally burdensome question of guilt versus innocence is resolved (right DLPFC is discharged from jury duty, so to speak). Activity then shifts to

Table 1 | Areas exhibiting a stronger response in sympathy scenarios.

Region	*Side*	*MNI coordinates*			*Z*	*k*	*SVC*
Posterior cingulate cortex	**R**	**2**	**−50**	**28**	**4.05**	**2946**	**0.001**
Precuneus	**L**	**−2**	**−68**	**42**	**3.85**		
Precuneus	**R**	**0**	**−18**	**28**	**3.73**		
Middle frontal gyrus	R	36	16	60	4.11	1501	
Superior frontal gyrus	R	20	32	58	4.08		
Superior frontal gyrus	L	−18	24	64	4.06		
Temporo-parietal junction (middle temporal gyrus)	**L**	**−50**	**−72**	**20**	**4.15**	**535**	**0.001**
Temporo-parietal junction (angular gyrus)	**L**	**−46**	**−64**	**34**	**3.58**		
Inferior frontal gyrus (p. orbitalis)	L	−40	34	−14	4.37	296	
Inferior frontal gyrus (p. triangularis)	L	−50	36	18	3.62		
Inferior frontal gyrus (p. triangularis)	L	−42	34	0	3.54		
Dorsomedial prefrontal cortex (superior medial gyrus)	**L**	**−4**	**44**	**22**	**3.50**	**217**	**0.008**
Dorsomedial prefrontal cortex (superior medial gyrus)	**L**	**−4**	**54**	**28**	**3.49**		
Superior frontal gyrus	**L**	**−12**	**52**	**34**	**3.33**		
Caudate nucleus	R	12	18	8	3.82	179	
Hippocampus	R	26	−32	−8	3.47	151	
Parahippocampal gyrus	R	28	−24	−22	3.43		
Caudate nucleus	L	−8	18	2	3.53	101	
Caudate nucleus	L	−12	14	10	3.37		
Middle temporal gyrus	L	−52	4	−32	3.72	81	
Lingual gyrus	R	16	−44	−8	3.50	59	
Parahippocampal gyrus	R	26	10	−30	3.68	48	
Dorsomedial prefrontal cortex (superior medial gyrus)	**R**	**10**	**44**	**50**	**3.37**	**23**	**0.011**
Superior frontal gyrus	**R**	**16**	**16**	**46**	**44**		
Inferior frontal gyrus (p. orbitalis)	L	−26	26	−26	3.56	22	
Temporal pole	L	−36	22	−32	3.19		
Medial temporal pole	R	44	16	−38	3.37	13	
Inferior frontal gyrus (p. orbitalis)	R	38	28	−12	3.22	13	
Temporal pole	L	−34	6	−20	3.17	12	

Abbreviation: SVC, small volume correction.
A priori regions of interest are in bold ($P<0.001$, $k>10$).

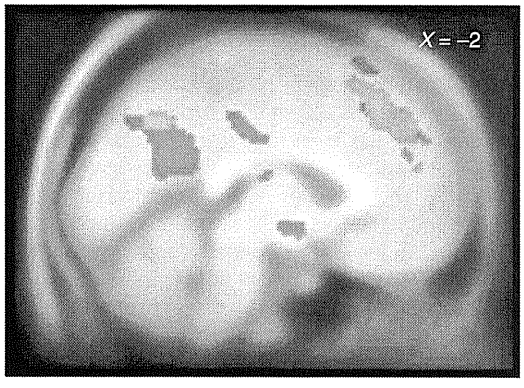

Figure 2 | Brain regions activated during trial-by-trial sympathy and punishment reduction. Regions in which activity correlated with parametric regressors of increasing sympathy (green) and reduced punishment (red). Common areas were found in precuneus (yellow). The image is shown at $P<0.001$ (uncorrected; $n = 22$, one-sample t-tests).

areas generally associated with moral and cognitive conflicts instead (DMPFC, precuneus and ACC).

The individual difference analysis showed that activity in the right mid-insula was related to the individual differences on the inclination to mitigate (mapping sympathy to sentences). Middle/posterior insula has been suggested to encode economic inequity[31], norm violation[32], somatosensory representation[33], monitoring internal states[34] and heart rate during a compassionate state[35]. These types of interoceptive processing in middle insula suggest that it is sensitive to emotions linked to sociality. Our study provides unusual evidence of this processing associated with a unique high-impact social judgment that affects others.

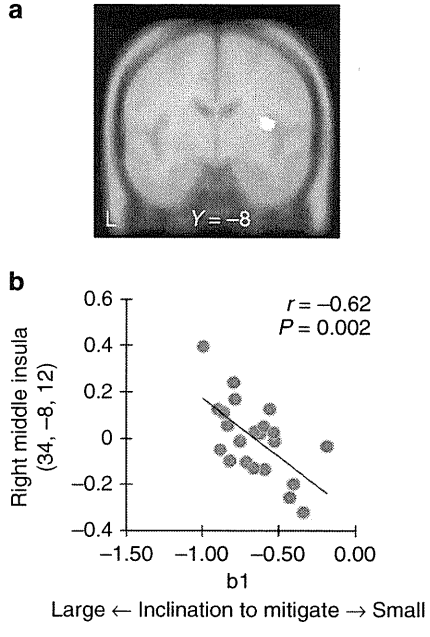

Figure 3 | Individual differences in inclination towards mitigation. Activation in right middle insula in the contrast sympathy minus no-sympathy trials (**a**, MNI 34/−8/12; $n = 22$, one-sample t-test, $P = 0.023$, small-volume-corrected) correlated with participant-wise coefficient of mitigation (**b**, $n = 22$, Pearson $r = -0.62$, $P = 0.002$).

The identified brain activity provides new insight into the capacity of the average brain to translate sympathetic feelings into appropriate legal action. A plausible neuro-legal standard is that the influence

of sympathetic reaction on difficult sentencing should recruit brain areas that process sympathy judgments in general, as well as areas that encode difficult decision conflict. Activity in these 'sympathy' regions is evident in our study when judging sympathy alone, and in choosing sentence mitigation. However, not every brain maps sympathy to prison sentences in the same numerical way (as reflected in differential mid-insula activity). Differences in these brain circuits between individuals, suggest that differential juror responses might need to be considered unequally. There is also mixed evidence about the normative basis of legal judgment, including a recent finding that judges' decisions are affected by timing of meals[36].

The current finding would also contribute to the attribution literature on situational correction, as there has not been any fMRI work on this. People often attribute behaviour to the corresponding personal disposition, which is, yet, corrected based on situational inducements too[37]. This is an apt psychological function behind mitigating circumstances that is to make someone less culpable, and the revealed brain activity might be associated with this type of situational correction.

Finally, we note that many legal principles treat emotional responses as likely to be prejudicial and prone to inflammatory manipulation (that is, an ideal juror would suppress them and legal rules limit their influence). Weighing mitigating circumstances during sentencing (*after* a verdict) represents an unusual case in which emotional sympathy judgment is actually required. Japanese criminal law, for example, requires that the decision among these sentences be based on mitigating circumstances[38].

Ironically, the fact that sympathy is clearly evident in brain activity, and influences sentence mitigation (as it should), raises interest in the opposite question: can people also suspend emotions when the law instructs them to? More generally, a deeper understanding of the brain could help figure out how highly evolved brain structures, which were sculpted to maintain order in small-scale ancestral societies, can be put to work under modern legal rules in much more challenging cases to create modern justice.

Methods

Participants. A total of 26 right-handed healthy subjects (12 males; mean age = 21.5±1.8 (s.d.) years) participated in the study. All subjects had normal or corrected-to-normal vision, no history of neurological or psychiatric disorder and were not taking medications that interfere with the performance of fMRI. The study was approved by the Ethics and Radiation Safety Committee of the National Institute of Radiological Sciences (Chiba, Japan). Data from four participants were discarded owing to excessive movement (three subjects) and sleep (one subject). The data from 22 subjects (11 males; mean age = 21.5±1.9 (s.d.) years) were included and analysed.

Stimuli and the task. A total of 32 faces of defendants and criminal acts were prepared in the study. Faces were drawn from a set of Asian face stimuli developed by CAS-PEAL face database[39]. Pilot participants (n = 30) rated attractiveness for each faces using an 11-point scale of −5 (not attractive at all) to +5 (very attractive). The average attractiveness for 32 faces was 0.15±0.70.

All criminal acts were the pure murder cases, which were modified from real stories taken from a precedent search engine provided by Supreme Court of Japan (www.courts.go.jp) and from news articles on the web. We prepared 32 scenarios and consulted a judicial expert for advice on how externally valid the scenarios were. Each scenario composed of the fact (when, where and to whom) and the circumstance (why the defendant committed the murder). Half of the scenarios would induce sympathy for the defendants who suffer from domestic violence, death to disease or poverty (sympathy scenarios), and the other half that would not (no-sympathy scenarios). Responsibility, intentionality and severity of crime were matched between scenarios (see Supplementary Methods for all scenarios used in the study).

Subjects were instructed to judge crimes as if they were jurors (lay judges). Before entering the scanner, subjects read each criminal case and were asked to indicate if they have known them through media. The aim of this session was to ensure and ease comprehension in the scanner that constrain duration of presenting each scenario. During the fMRI task, subjects read each scenario and rated how much they would like to reduce or increment the sentence (all 20 years) given for the defendant using a VAS (with scores ranging from 0 = reduce as much as possible to 100 = increment as much as possible, and 50 = given sentence of 20 years; Fig. 1a). We chose a sentence of 20 years as a reference point, based on a sentencing guideline in Japan that gives 20 years in prison to a person who commits murder. Defendants' faces were presented together with the scenarios in order to make the experimental setting more realistic and to help participants to dedicate to the study. They completed two sessions, and each session contained 8 sympathy and 8 no-sympathy scenarios, 16 trials in total. The presentation of each scenario within a session was pseudorandomized. The order of sessions and the combination of faces and circumstance types were counterbalanced between subjects.

After the scan, subjects were shown the same scenarios again to rate how much they felt sympathy for the defendants using a VAS (with scores ranging from 0 = having no sympathy to 100 = having sympathy very much). They were also asked to fill out Interpersonal Reactivity Index (IRI), a self-report measure of dispositional empathy.

fMRI data acquisition. The functional imaging was conducted using a GE 3.0 Tesla Excite system to acquire gradient echo T2*-weighted echoplanar images with blood oxygenation level-dependent contrast. Each volume comprised 35 transaxial contiguous slices with a slice thickness of 3.8 mm to cover almost the whole brain (flip angle, 75; echo time, 25 ms; repetition time, 2000 ms; matrix, 64*64; and field of view, 24×24 cm^2).

fMRI data preprocessing. Image analysis was performed using SPM8 (Wellcome Department of Imaging Neuroscience, Institute of Neurology, London, UK), except for the overlay image shown in Fig. 2 that was created using the MRIcron software (http://www.sph.sc.edu/comd/rorden/mricron/). All volumes were realigned to the first volume of each session to correct for subject motion and were spatially normalised to the standard space defined by the Montreal Neurological Institute (MNI) template. After normalisation, images were spatially smoothed using a Gaussian kernel with a full-width-at-half-maximum of 8 mm. Intensity normalisation and high-pass temporal filtering (using a filter width of 128 s) were also applied to the data.

Generalized linear model. For the primary whole-brain analyses, two modelling approaches were used. In the first approach, trials from each of the sympathy and no-sympathy circumstances were modelled as separate conditions. This allowed separate estimation of the evoked response for each of the conditions at each voxel. The model also included regressors for face, criminal evidence, punishment, and fixation, as well as six head-motion parameters as regressors of no interest. We first calculated a first-level single-subject contrast for reading sympathy minus no-sympathy circumstances. Then, we calculated a second-level group contrasts using a one-sample t-test. In the second approach, all trials from reading circumstances modelled using a single condition (that is, overall task-related activation), and two additional orthogonal parametric regressors were included representing (a) the amount of reducing punishment and (b) the level of sympathy rating. We first calculated first-level single-subject contrasts for reading circumstances modulated by reducing punishment and for reading circumstances modulated by sympathy rating. Then, we calculated second-level group contrasts using one-sample t tests on the single-subject contrasts to identify brain regions whose activation correlated with the amount of reducing punishment and the sympathy rating.

A statistical threshold of $P < 0.05$ corrected for multiple spatial comparisons across the whole brain at cluster level was used, except for a priori hypothesized regions that were voxel thresholded at $P < 0.001$ uncorrected (only clusters involving $k > 10$ or more contiguous voxels were reported[40]). Small volume correction (a 10-mm radius sphere) was used on a priori regions of interest: DMPFC/ACC, precuneus/posterior cingulate cortex, TPJ and the insula.

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Author contributions

M.Y. and H.T. designed the experiment. M.Y. and F.S. prepared and conducted the experiment. M.Y. analysed the data and wrote the paper. C.F.C. edited the manuscript. H.T. coordinated subject recruitment. All authors discussed the results.

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Effectiveness of Pramipexole, a Dopamine Agonist, on Rapid Eye Movement Sleep Behavior Disorder

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Rapid eye movement (REM) sleep behavior disorder (RBD) is parasomnia characterized by REM sleep without atonia (RWA) and elaborate motor activity in association with dream mentation. Periodic leg movement during sleep (PLMS) is observed in a large share of patients with RBD, suggesting a common pathology: dopaminergic dysfunction. This study was undertaken to evaluate the effectiveness and mechanism of action of pramipexole, a dopamine agonist, on RBD symptoms. Fifteen patients (57-75 years old) with RBD with a PLMS index of more than 15 events/h shown by nocturnal polysomnography were enrolled. Sleep variables, the score of severity for RBD symptoms, REM density, and PLM index were compared before and after one month or more of consecutive pramipexole treatment. Correlation analysis was conducted between the rate of change in RBD symptoms and the rate of reduction of REM density. Fourteen patients with RBD (80.0%) achieved symptomatic improvement of RBD with pramipexole treatment, which reduced REM density and PLM index during non-REM sleep despite the unchanged amount of RWA. The rate of change in RBD symptoms correlated positively with the rate of REM density reduction. Significant reduction of the PLM index was observed in non-REM sleep but not in REM sleep. Pramipexole can improve RBD symptoms, possibly because of changes in dream contents or its amount manifested as the reduction of REM density. The restricted influence of pramipexole on PLMS only during non-REM sleep suggests that other factors may affect the pathophysiology of PLMS during the REM sleep period in RBD.

Keywords: dopaminergic function; periodic leg movements; pramipexole; REM sleep behavior disorder; REM sleep without atonia
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Rapid eye movement (REM) sleep behavior disorder (RBD) is a parasomnia characterized by dream-enacting behavior associated with REM sleep without atonia (RWA). Although the pathogenesis of RBD remains unclear, RBD is frequently associated with α-synucleinopathies including Parkinson disease (PD), dementia with Lewy bodies, and multiple system atrophy. It has been widely accepted that RBD represents a prodromal phase of these diseases (Olson et al. 2000; Boeve and Saper 2006; Iranzo et al. 2006; Postuma et al. 2006).

Periodic leg movement during sleep (PLMS) is often comorbid with RBD, suggesting a common pathogenesis of the two disorders. Its frequency in RBD is higher than that seen in the normal population, especially during the REM sleep period (Fantini et al. 2002). Although two previous case series investigated the effectiveness of pramipexole on RBD symptoms (Fantini et al. 2003; Schmidt et al. 2006), these studies did not respectively examine the effect of pramipexole on PLMS during non-REM (NREM) and REM sleep periods. Moreover, the pathophysiology of PLMS in idiopathic RBD remains unsolved.

Episodes of violent behavior in RBD are mostly associated with nightmares. However, no report describes the effectiveness of pramipexole for alleviating nightmares in RBD or its relation to REM density, which possibly triggers dream imagery (Ogawa et al. 2005).

To elucidate the mechanism of pramipexole action on the pathogenesis of RBD, we investigated its effects on RBD symptoms, with particular attention to REM-related parameters and PLMS in this pilot study.

Methods

Subjects

This study was approved by the ethical committee of the Neuropsychiatric Research Institute. During August 2006 - December 2008, 15 consecutive patients (man : woman = 8 : 7, age [range] = 65.7 [57-75] years), who were diagnosed with idiopathic RBD according to the International Classification of Sleep Disorders sec-

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ond edition (ICSD-2) published by the American Academy of Sleep Medicine (AASM 2005) and who showed a PLMS index of more than 15 events/h on nocturnal polysomnography (n-PSG), were enrolled in this study. All patients had no other sleep disorder or symptom suggestive of neurodegenerative disorder and/or dementia. After diagnosis with PSGs and clinical interviews, the patients began treatment with pramipexole and underwent a second n-PSG more than 3 months after starting the treatment. All the patient subjects were drug naïve before starting the treatment for RBD. All patients who had taken any concomitant treatments other than pramipexole were excluded from this study.

PSG variables

Sleep stages were scored according to criteria set by Rechtschaffen and Kales. The RWA and REM density were scored according to a previously described method (Consens et al. 2005). REM density was defined as the ratio of the number of 3-s epochs of REM sleep with at least 1 REM divided by the total number of all 3-s epochs with REM sleep. The reduction rate of REM density with the treatment was calculated by dividing the difference in the REM densities measured before and after medication by the value of REM density before medication. The severity of RBD symptoms was assessed according to criteria explained in the revised edition of ICSD-1 (AASM 2001) based on reports of the frequency and intensity of vocalization or dream enactment behavior obtained from patients or their family members. Additionally, we assessed the subjective frequency of nightmares based on their reports. The rate of reduction of RBD symptoms was calculated by taking the difference in the scores of RBD symptoms obtained before and after medication and dividing that difference by the score before medication. PLMS was scored according to the criteria set by AASM (AASM 2007). PLMS was distinguished carefully from phasic EMG activity on the anterior tibialis muscle during stage REM by consideration of the periodicity or amplitude of leg movements.

Statistical analysis

Using Wilcoxon signed rank tests, scores of RBD symptoms and sleep variables before and after treatment were compared. Correlation between the rate of change of the RBD symptoms and the rate of reduction of REM density was investigated using Spearman's rank correlation coefficient.

Results

Kolmogorov-Smirnov tests revealed that the sleep variables were not normally distributed. Table 1 shows that the mean dosage of pramipexole was 0.21 ± 0.09 mg/day. The mean duration of the treatment before the second n-PSG was 9.1 ± 7.1 months. Subjective assessment revealed that 12 patients (80%) achieved clear improvement with the pramipexole treatment: 50% reduction in the score for severity of RBD symptoms. The scores of severity for RBD symptoms after pramipexole treatment were significantly lower than those before the treatment ($Z = -3.376$,

Table 1. RBD symptoms before and after treatment with pramipexole.

Patient no.	Age	Sex	Dosage of pramipexole (mg/day)	Length of treatment (months)	Score of severity for RBD symptoms[1)]		Disappearance of nightmares after treatment	Improvement of nightmares[2)] after treatment
					before treatment	after treatment		
1	69	M	0.125	8	2	1		+
2	72	F	0.250	4	2	2		
3	63	F	0.375	21	3	1	+	
4	57	M	0.250	25	3	1	+	
5	61	F	0.250	17	3	1		+
6	64	F	0.375	13	3	1		+
7	75	M	0.250	4	3	1		+
8	75	M	0.250	6	3	2		
9	64	F	0.125	3	3	1		
10	63	M	0.125	4	3	2		+
11	63	F	0.125	5	3	1	+	
12	69	M	0.125	5	3	1		
13	67	F	0.125	3	2	1		+
14	59	M	0.250	3	3	0	+	
15	69	M	0.125	6	3	0	+	
	66.5 ± 5.2	M:F = 8:7	0.2 ± 0.1	8.0 ± 7.0	2.8 ± 0.4	1.1 ± 0.6*		

RBD, REM sleep behavior disorder.

*$p < 0.01$ compared to the score of severity of RBD symptoms before treatment.

[1)]Severity of RBD symptoms are scored for 0 = none; 1 = REM sleep behavior occurs less than once per month and causes only mild discomfort for the patient or bed-partner, 2 = REM sleep behavior occurs more than once per month but less than once per week and is usually associated with physical discomfort to the patient or bed-partner, 3 = REM sleep behavior occurs more than once per week and is associated with physical injury to the patient or bed-partner.

[2)]Improvement of nightmares means 50% or more reduction of frequency of nightmare.