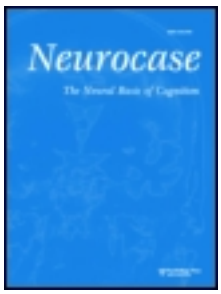
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Seeing mathematics: Perceptual experience and brain activity in acquired synesthesia

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Seeing mathematics: Perceptual experience and brain activity in acquired synesthesia

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We studied the patient JP who has exceptional abilities to draw complex geometrical images by hand and a form of acquired synesthesia for mathematical formulas and objects, which he perceives as geometrical figures. JP sees all smooth curvatures as discrete lines, similarly regardless of scale. We carried out two preliminary investigations to establish the perceptual nature of synesthetic experience and to investigate the neural basis of this phenomenon. In a functional magnetic resonance imaging (fMRI) study, image-inducing formulas produced larger fMRI responses than non-image inducing formulas in the left temporal, parietal and frontal lobes. Thus our main finding is that the activation associated with his experience of complex geometrical images emerging from mathematical formulas is restricted to the left hemisphere.

Keywords: Acquired synesthesia; fMRI; Left-hemisphere activation; Visual imagery; Mathematical.

Synesthesia is a condition in which stimulation in one sensory or cognitive stream involuntarily leads to associated internal or external experiences in an unstimulated sensory or cognitive system (Baron-Cohen, Wyke, & Binnie, 1987; Cytowic, 1989; Grossenbacher & Lovelace, 2001; Hubbard & Ramachandran, 2005; Hubbard, 2007; Ramachandran & Hubbard, 2001; Hubbard, Arman, Ramachandran, & Boynton, 2005; Sperling, Prvulovic, Linden, Singer, & Stirn, 2005; Ward & Huckstep, 2006). For example, in grapheme-color synesthesia numbers or letters are seen as colored (Baron-Cohen, Burt, Smith-Laittan, Harrison, & Bolton, 1996; Simner et al., 2006). These images are either projected onto the external world or perceived in the mind's eye (Dixon et al., 2004). Although most cases of synesthesia are developmental, acquired cases have also been reported, for example following stroke (Beauchamp & Ro, 2008) or neuropathology involving the optic nerve and/or chiasm (Afra, Funke, & Matsu, 2009). Audio-visual synesthesia has been reported to be the most common acquired type (Afra et al., 2009).

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Here we report the case of JP whose visual experiences of moving objects and mathematical formulas appear to fit the standard characterization of synesthesia. JP also appears to have savant syndrome, a condition in which a person has a talent that is so developed that he can perform what may seem like impossible mathematical, linguistic, or artistic tasks (Treffert, 2009). After a head injury in 2002 JP began to see complex geometrical figures when looking at *moving* curved, spiraling or non-solid objects, and mathematical formulas. He describes *static* objects as not having smooth boundaries (see Figure 1A, B) and reports that he sees motion in "picture frames". He describes his perception as if "someone is pressing the pause button on a video very quickly". This may be a form of akinetopsia (Zihl, Von Cramon, & Mai, 1983). JP's savant skills seem to fall into three groups: artistic, mathematical, and spatial. Despite his lack of prior training, JP is obsessed with drawing complex geometrical images using only straight lines. He appears to be able to predict the vectors for prime numbers in his drawings, and his drawing of $hf = mc^2$ (Figure 1D), which contains all the style elements of his earliest drawings, is similar to a picture of electron interference patterns, which he found several years after first drawing the pattern.

Here we aimed to identify the neural areas involved in JP's mathematical synesthesia. We were particularly interested in finding out to what extent visual areas were involved in his synesthetic experiences. We carried out a functional magnetic resonance imaging (fMRI) study to investigate the neural activation associated with the presentation of mathematical formulas which induce the experience of complex geometrical figures and contrasted this with the presentation of formulas which do not induce such percepts.

METHODS

Participant

At the time of the study, JP was a right-handed 39-year-old male with a remarkable ability to draw his synesthetic images. He was a victim of an assault in 2002, where he was hit at the back of the head, and was subsequently diagnosed with an unspecified head injury. In anatomical magnetic resonance imaging (MRI) there was no obvious damage at the time of study.

JP has been diagnosed with obsessive–compulsive disorder (OCD), a common finding in people with savant syndrome (Treffert, 2009). The DSM IV criteria for OCD include symptoms such as intruding thoughts or images that provoke anxiety (which the sufferer feels to be excessive and unreasonable), or repetitive behaviors or mental acts that help to prevent anxiety. In JP, this is reflected in his preoccupation with numbers and geometry, to which his thoughts return when trying to concentrate on something else. For example, JP sometimes finds himself counting steps or intensely studying the shapes of the leaves on a tree.

In the largest study of savant syndrome to date, 41 out 51 subjects were diagnosed with autism (Treffert, 2009). Though JP has not been tested for signs of autism, JP's OCD symptoms may indicate that he has developed an autism-like condition. The DSM IV criteria for autism require sufferers to satisfy at least one of the following conditions: (1) encompassing preoccupation with one or more stereotyped and restricted patterns of interest that is abnormal either in intensity or focus; (2) apparently inflexible adherence to specific, nonfunctional routines, or rituals; (3) stereotyped and repetitive motor mannerisms (e.g., hand or finger flapping or twisting, or complex whole-body movements); and (4) persistent preoccupation with parts of objects. JP exhibits signs that seem to satisfy 1, 2, and 4. However, he does not exhibit any signs of communication failure (either verbal or non-verbal), which is a criterion for a positive diagnosis.

After the incident JP began to see complex geometrical figures and figures with fragmented boundaries. These figures are induced by moving or static visual objects (see Figure 1A, B for examples of JP's internal images of static objects). Subsequent to the incident, JP enrolled in mathematics classes at a local community college and developed the ability to read basic mathematical formulas. While complex geometrical perceptions were induced by visual motion immediately after the injury, mathematical equations induced such percepts once JP understood their meaning. He hand-draws what he sees and is, to the best of our knowledge, the first to hand-draw complex geometrical images with pencil, compass and ruler, and does so with great precision (see Figure 1C, D). Though savant syndrome is typically accompanied by severe developmental disorders, usually autism (Snyder 2004, 2009), there are also cases in which savant syndrome occurs without any associated disability and cases in which it is acquired later in life, following central nervous

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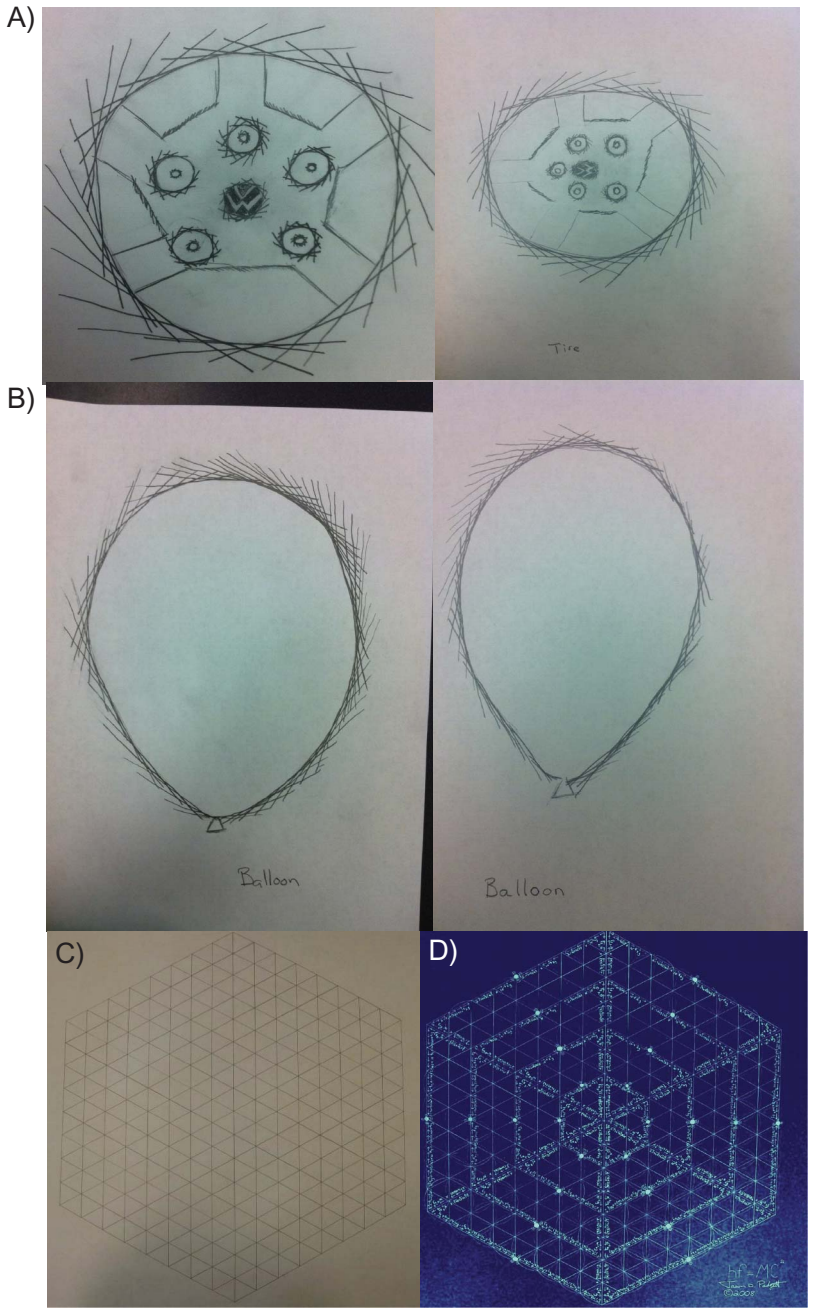


Figure 1. JP's drawings of his percepts induced by viewing (A) wheel; (B) balloon (middle); (C) the formula 2^9; (D) the formula $hf=mc^2$. (A) and (B) show first (left) and second (right) drawing of the same item, approximately 3 months apart.

system injury or disease (LaFay, 1987; Lythgoe, Pollak, Kalmas, de Hann, & Chongl, 2005; Miller et al., 1998; Sacks, 2007; Treffert, 2006, 2009). JP gave informed, written consent for participation in this study which was approved by the local research ethics committee.

Stimuli and experimental design

Synethesia tests

The most common forms of synesthesia are normally identified using the standard battery of synesthesia tests described in Eagleman, Kagan,

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Nelson, Sagaram, and Sarma (2007). These tests consist in having synesthetes choose among different representations of their synesthesia on three occasions and then testing the similarity of the chosen representations. There are also several speed recognition tests. All of these tests are available through online software (http://www.synesthete.org/index.php). The synesthesia battery, however, is not suitable for testing for unusual kinds of synesthesia like the kind that JP appears to exhibit. However, in the pre-testing phase, JP was asked to make drawings of the internal or projected images he had in response to a range of static or moving objects and mathematical formulas on two separate occasions approximately 3 months apart (see Figure 1A, B).

fMRI Study

The objective of the fMRI study was to investigate the neuronal activation associated with presentation of synesthesia-inducing mathematic formulas by contrasting these with formulas which do not induce such percepts. Prior to the experiment, a list of formulas was constructed with JP; half of these stimuli induced a geometrical percept and the other half did not. The non-inducing formulas closely resembled those which induce synesthetic experience (see Appendix). A total of 28 formulas (14 image-inducing and 14 non-inducing) were used. Some of the formulas were numbers or other mathematical expressions. Only those effective in inducing the synesthetic experience were included among the stimuli.

The fMRI study was conducted using a block design with three different types of blocks. Each fMRI run contained two image-inducing and two non-inducing blocks. In addition, two rest blocks were included during which a fixation cross was presented for the whole duration of the block. The duration of each block was 40 seconds. In each stimulation block, each of the eight formulas was presented for two seconds, followed by a blank screen for 3 seconds. The duration of this fixation period enabled sufficient time for the geometrical image to arise. Duration of each run was 4 minutes, and 7 seconds, and the whole experiment comprised 6 runs where the blocks were presented in counterbalanced order.

In addition, we carried out a motion localizer in which JP viewed low-contrast (10%) concentric expanding and contracting (7°/s) stimuli and corresponding stationary stimuli.

Data acquisition and analysis

Measurements were performed using a 3T GE Signa Excite scanner (General Electric Medical Systems) equipped with an eight-channel receiver head coil. Functional volumes were acquired with echo-planar imaging using single-shot gradient-echo sequence with the following imaging parameters: repetition time 1.8 s, 32 slices with 4.0-mm slice thickness, field of view 22.4 cm, imaging matrix 64×64, echo time 30 ms, and flip angle 60°. The duration of each run was 137 time points. In the motion localizer, the repetition time was 2.0 s, and 29 slices were acquired with 3.0-mm slice thickness, field of view was 20 cm, resulting in $3.125 \times 3.125 \times 3$ mm^3 voxel size.

Data preprocessing, estimation and visualization were done with SPM8 (http://www.fil.ion.ucl.ac.uk/spm/; Friston, Ashburner, Kiebel, Nichols, & Penny, 2007) Matlab^{TM} toolbox. In preprocessing, functional images were corrected for interleaved acquisition order and for head motion, and smoothed with 8-mm kernel. The first four images from the beginning of each run were excluded to reach stable magnetization. During the parameter estimation, the data were high-pass filtered with 128 s cutoff, and noise autocorrelation was modeled with AR(1) model. The data were coregistered to the high-resolution structural images which was standardized into MNI space using SPM8.

RESULTS

Perceptual experience

In the pre-testing phase JP was asked to make drawings of the internal or projected images he had in response to a range of moving or static objects and mathematical formulas on two separate occasions approximately 3 months apart. The drawings were compared for similarity. Examples are shown in Figures 1A, B and 2A, B. JP reports that when exposed to static objects with smooth boundaries, he experiences the boundaries in terms of small secant and tangent lines (see Figure 1A, B). JP does not see lines as smooth paths. However, it is clear that this condition is not a form of visual agnosia. In apperceptive agnosia, subjects are unable to use standard Gestalt grouping principles (e.g., similarity, continuity, or symmetry) to generate a boundary that will reveal the object's identity

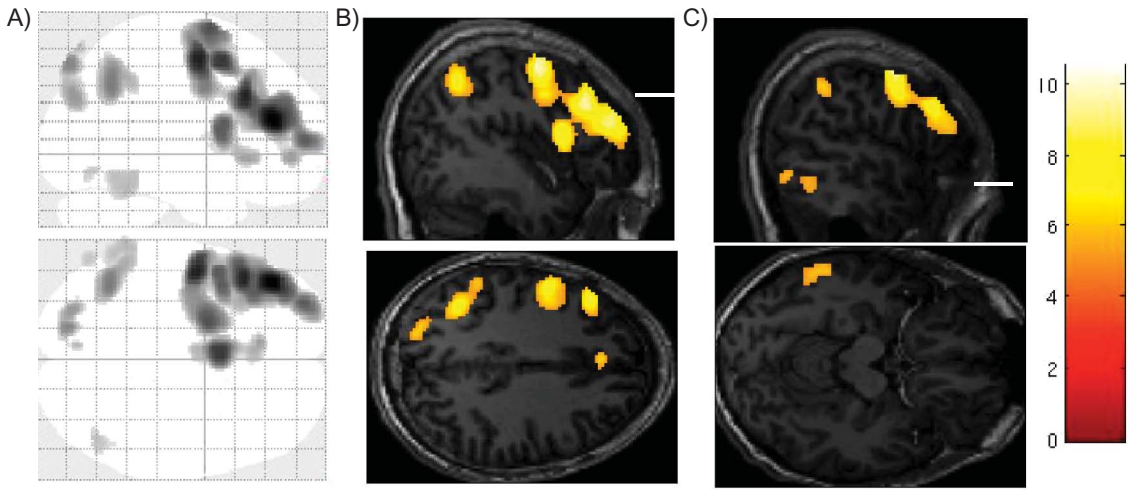


Figure 2. Activation induced by the image-inducing formulas contrasted to non-inducing formulas. The SPM(T) maps were thresholded at family-wise-error-corrected *p*-value .01 and overlaid on JP's structural T1-weighted MRI which was standardized into MNI-space using SPM8. (A) All activation viewed from sagittal (upper row) and axial (lower row) directions. (B–C) Two sagittal and axial slices. The white lines indicate the section of the other orientation.

(Karnath, Rüter, Mandler, & Himmelbach, 2009; Milner et al., 1991; McIntosh et al., 2004). Even though in JP's percept the boundaries of objects are fragmented, they stand out from the background. Furthermore, JP has normal object recognition.

JP further reports that when exposed to moving objects with smooth boundaries, he experiences visual images of complex geometrical patterns projected into real space. When he is exposed to formulas that give rise to complex geometrical images, he reports seeing the visual images "internally" or in his "mind's eye" (see Figure 1C, D). Though JP's experiences in response to moving objects and image-inducing formulas differ from more common forms of synesthetic experience, they appear to satisfy the standard characterization of synesthetic experience. There is a test–retest reliability, and in both cases, the images are automatic responses to the stimuli. He can prevent the images from appearing only by closing his eyes, attending to a different aspect of the scene or performing other distracting maneuvers.

fMRI

In the fMRI experiment, JP was presented with blocks of trials containing either image-inducing formulas, i.e., those inducing the experience of geometrical images, or non-inducing formulas, i.e., those which do not induce such percepts. After the experiment, JP confirmed having experienced geometrical patterns after the presentation of the image-inducing formulas. Figure 2 shows fMRI activations induced by the presentation of the synesthesia-inducing formulas contrasted against non-inducing formulas.

As Figure 2 shows, the image-inducing formulas (when contrasted against non-inducing formulas) are associated with the activation of the left hemisphere. Specifically, a number of regions in the temporal, frontal and parietal regions were activated by this contrast. The largest activated region in terms of number of voxels (see Table 1) encompassed the inferior frontal gyrus, middle frontal gyrus, and the precentral gyrus. In the posterior regions, significant differences were observed in the left inferior parietal lobule and precuneus and the left inferior temporal gyrus. In the right hemisphere, this contrast revealed a significant difference in the right cerebellum.

TABLE 1
List of significant clusters with their MNI coordinates

Region of activation	*Voxels*	*MNI coordinates (x, y, z)*
L middle frontal gyrus/ Inferior frontal gyrus/ precentral gyrus	6857	–44 40 20
L inferior parietal lobule	697	–42 –56 40
L parietal lobe/precuneus	414	–18 –82 52
L inferior temporal gyrus	350	–64 –46 –18
R cerebellum	38	44 –64 48

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This analysis raises the possibility that this activation pattern is not related to the experience of geometry per se, but rather reflects a general lack of responsiveness in JP's right hemisphere. We addressed this possibility by contrasting the activation induced by the image-inducing and non-inducing formulas with the activation observed during the rest blocks, where only a fixation cross was presented. These results are shown in Figure 3. Importantly, this analysis revealed activations in occipital, parietal and frontal regions in both hemispheres. The symmetric nature of the left vs. right hemisphere activation argues against the possibility that lateralized activity associated with the image-inducing formulas merely reflects reduced excitability of the right hemisphere.

In the motion localisers, JP was presented with blocks containing either a concentric expanding and contracting radial square-wave gratings or the corresponding stationary stimulus. This stimulus was used to identify motion-sensitive areas. Figure 4 shows the BOLD activations induced by the presentation of the moving stimuli contrasted against stationary ones. The results show bilateral activation in the occipital, parietal and temporal cortices, including areas which according

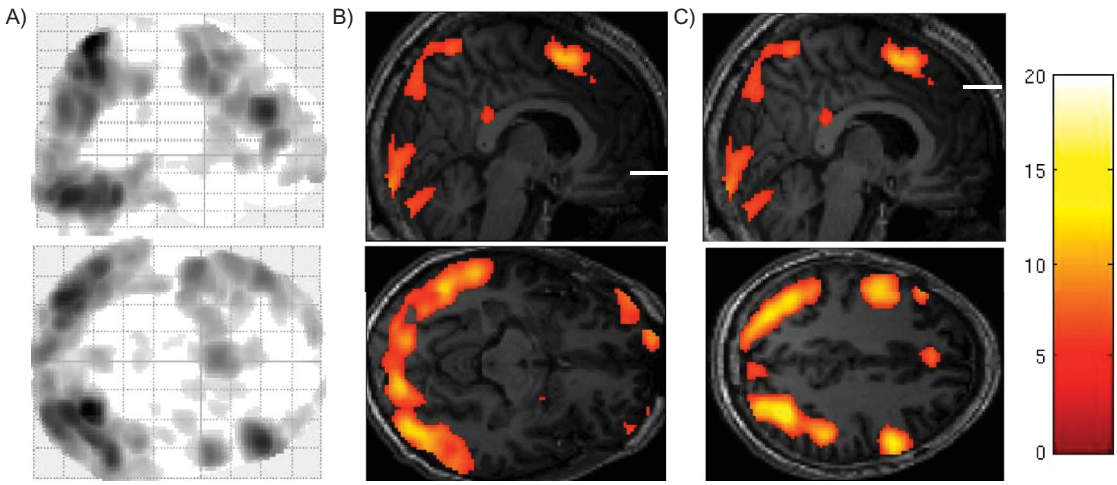


Figure 3. Activation induced by the image-inducing and non-inducing formulas against rest (in which only the fixation cross was presented). This contrast reveals JP's activation to visual stimulation in this experiment. Other details as in Figure 2.

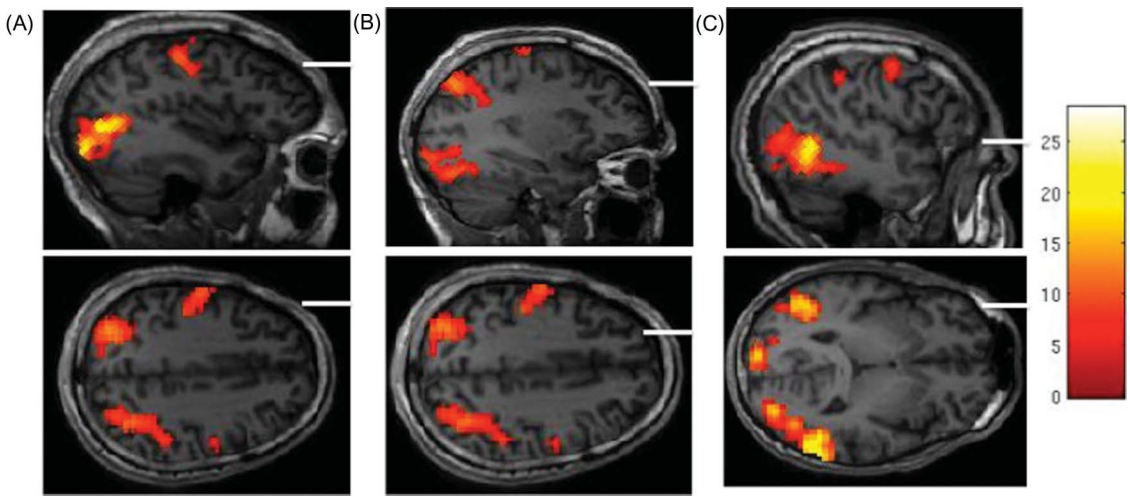


Figure 4. Activation induced by moving stimuli contrasted to stationary stimuli. The SPM(T) maps were thresholded at family-wise-error-corrected *p*-value .01. All activation viewed from sagittal (upper row) in the left hemisphere and axial (lower row) directions. Activations were observed in occipital and parietal cortices as well as in the region of precentral sulcus. The white lines indicate the section of the other orientation.

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to anatomical criteria match areas V3A (Tootell et al., 1997), V6 (Pitzalis et al., 2006), and the V5/MT complex (Watson et al., 1993), which are typically most responsive for visual motion. No clear differences were observed between the hemispheres. Of the regions in the left hemisphere associated with image-inducing formulas, motion vs. stationary contrast revealed activations in the parietal lobes and in the region of the frontal eye fields. However, these regions were activated in both hemispheres.

DISCUSSION

In this study we tested JP, a single case with acquired synesthesia and savant syndrome. After testing JP for synesthesia using the standard test–retest reliability assessment (Baron-Cohen et al., 1987; Eagleman et al., 2007), we carried out an fMRI study to compare brain activation during exposure to image-inducing formulas and non-inducing formulas. Image-generating formulas were associated with more activity in the left hemisphere (parietal, temporal, and frontal areas) compared to non-inducing formulas. Bilateral activation was observed when the presentation of the image-inducing and non-inducing formulas was contrasted with rest, indicating that the left-hemisphere lateralization associated with image-inducing formulas was not merely due to hypoexcitability of the right hemisphere. Furthermore, the motion localizer revealed no hemispheric differences in cortical sensitivity to moving stimulus.

This left-hemisphere lateralization of responses for image-inducing formulas is perhaps surprising, as most individuals with special talents that arise from a lesion or defect in brain function have had left-hemisphere damage and right-hemisphere dominance (Miller et al., 1998; Pesenti, Zago, & Crivello, 2001; Sacks, 2007; Snyder 2009; Snyder & Barlow, 1988; Snyder & Mitchell, 1999; Snyder et al. 2003; Treffert, 2005; Young, et al., 2004). Some mathematical operations, such as multiplication and integral calculus, seem to be left lateralized (Dehaene et al., 1996; Krueger et al., 2008), although most mathematical skills include a network of bilateral brain areas (Pinel & Dehaene, 2009). Against these data, JP's left lateralization is unusually strong. However, it is possible that visualizing mathematical functions is strongly left lateralized in persons who are mathematically literate for performing such task.

Yomogida et al. (2004) reported left hemisphere activation in frontal and temporal cortex in subjects instructed to imagine a novel object that does not exist in the real world, either by composing it from two visually presented words associated with a real object or two achromatic line drawings of a real object. Similar strong lateralization was found in imaging studies of visual imagery of familiar objects (D'Esposito et al., 1997; Ishai, Ungerleider, & Haxby, 2000; Ishai, Haxby, & Ungerleider, 2002). Kosslyn et al. (1995) found that the left hemisphere more effectively creates mental images by positioning parts of the image in accordance with descriptions or guidelines, whereas the right hemisphere more effectively creates mental images by arranging parts of the image at coordinates in space. We suspect that JP has developed his special skill in visualizing mathematical formulas, using the left hemisphere only. The fact that the left hemisphere was involved in visualizing the formulas suggests that synethetic experiences in associator synesthetes make use of similar neural mechanisms as novel mental image generation. One hypothesis consistent with this interpretation is that some forms of synesthesia resemble visual imagery or other forms of cognitive processing more closely than it does sensory perception (Hubbard et al., 2005; Simner & Ward, 2006).

Previous studies of synesthesia have reported increased activation in the visual areas (striate cortex and V4/V8; Aleman et al., 2001; Nunn et al., 2002). However, we did not find activity in the visual areas to be associated with the image-generating formulas relative to non-inducing formulas. This, however, is consistent with the findings of a previous study on subject DT, who has synesthesia and savant syndrome (Bor, Billington, & Baron-Cohen, 2007). Despite the fact that DT reports intensely colored synesthetic images associated with numbers, activation in DT's visual areas was not associated with these percepts. Bor et al. (2007) suggest that DT may have a different type of synesthesia than the perceptual form that is more commonly studied.

We propose that JP, like DT, has synesthetic experiences that are more conceptual than perceptual in nature and that the abstract schematic representations give rise to his exceptional visualization and drawing abilities. Our preliminary studies suggest that JP's exceptional visualization abilities relate to hyperactivity in central areas in parietal cortex and other overactivation loci and originate in his distinct form of synesthesia. The

previous study of DT also found that DT's exceptional abilities originated in his distinct form of synesthesia (Bor et al., 2007). The case of JP may be taken to be consistent with the view that synesthesia exists in everyone but is beyond conscious awareness, requiring some form of brain disturbance to become consciously accessible (Snyder & Mitchell, 1999).

Our results raise the question of how the brain activations observed in JP compare to those of trained mathematicians. If the patterns in trained mathematicians are similar to those found in JP, then we would have confirmation of the hypothesis set out by Dehaene (1999) that the difference in abilities between individuals with savant syndrome and normal individuals is a function of training and interest. According to Dehaene, what differs between individuals with savant syndrome and normal individuals is that they are more obsessed with numbers or spatial relations and devote more of their time to studying math than normal individuals.

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APPENDIX

List of formulas used in the experiment

Formulas inducing the experience of geometrical patterns in JP

1. $\mathrm{hf} = \mathrm{mc}^2$
2. $f(\mathrm{x}) = \mathrm{x} \sin (\frac{\pi}{x})$
3. $f(6) = 6 \sin (\pi/6)$
4. $6, 6^2, 6^3$
5. $\mathrm{a}^2 + \mathrm{b}^2 \Leftrightarrow \mathrm{c}^2$
6. $2 (\sin (\frac{\pi}{180})) \mathrm{r}$
7. 2^9
8. x^2
9. $8 \sin (\frac{\pi}{8}) \times \mathrm{r}^2 \times \mathrm{h}$
10. $\frac{\Delta x}{\Delta t}$, as $\Delta \mathrm{t}$ approaches $\mathrm{t_p}$
11. $2 \times \int_{-1}^{1} \sqrt{1 - x^2} - x^2$
12. $\sqrt{x}$
13. $f[\mathrm{x}]$
14. $f(\mathrm{x}) = \mathrm{x}$
15. $\frac{\pi}{x}\pi/6)\frac{\pi}{7}\frac{\pi}{8}\frac{\pi}{180}\frac{\pi}{8}\frac{\pi}{6}\frac{\Delta x}{\Delta t}\frac{\Delta y}{\Delta t}\int_{-1}^{1} 1 - x^2\sqrt{x}$

"Non-inducing" formulas (which do not induce the experience of geometrical patterns in JP)

1. $\mathrm{a} + \mathrm{b} = \mathrm{c}$
2. 10^0
3. $\mathrm{x(y)} = \int xy^2$
4. $\sin \frac{\Delta}{8} \times \mathrm{k}^5 \times \mathrm{m}$
5. $f(\sin) = \mathrm{f}$
6. $\int f(6)$
7. $5, 4, 3$
8. $\mathrm{xy} = \mathrm{xy}^2$
9. $\sin 4(6) = f(\mathrm{y})$
10. $4^{\mathrm{x,y}}$
11. $\Delta \sin(\mathrm{x}, \mathrm{y}) = \mathrm{f}$
12. $x \times \int \Delta\sqrt{\sin -4}$
13. $8^{\mathrm{y,\ sin(x)}}$
14. $\Delta^5 (f) = \sin \mathrm{r}$
15. $\int xy^2 \frac{\Delta}{8} \int f(6) \frac{\Delta 8}{\Delta 6} \frac{2}{0x} x \int \Delta\sqrt{\sin -4}$

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