Chapter 6

A New Functional Transcranial Doppler Spectroscopy (fTCDS) Study of Cerebral Asymmetry During Neuro-Cognitive Functions in Men and Women

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/54877

1. Introduction

The perception of light underlies the processes of cognitive brain function. However, the characterizations of the neuroadaptational processes that relates to the physical quality of light, particularly those implicated in color processing remains largely unknown. Simultaneous color contrast and color constancy have been identified as the memory processes associated with color processing [1-8]. Simultaneous color contrast is the phenomenon that surrounding colors profoundly influence perceived color [1,9]. The mechanism implicated in simultaneous color contrast has been described as wavelength-differencing, implying the ability to differentiate the dominant wavelength of the color of light [10]. Wavelength-differencing involves wavelength-encoding main effect at subcortical peaks, and energy-encoding effects at cortical peaks [11]. On the other hand, frequency-differencing refers to the ability to differentiate the dominant frequency (the inverse of wavelength) of the color of light, and involves energy-encoding main effect at cortical and subcortical peaks [11, 12]. Genetic studies suggest gender-related differences in color vision in primates. Whereas both trichromatic and dichromatic color vision occurs among female monkeys, males appear exclusively dichromatic [13]. It was proposed that, unlike humans, squirrel monkeys have only a single photopigment locus on the X chromosome [13].

Color constancy relates to the invariance of hue, or perceived color of a surface under variation in the spectral content of illumination [3, 14, 15]. In other words, color constancy refers to the unchanging nature of the perceived color of an object despite considerable variation in the wavelength composition of the light illuminating it [16]. It has been suggested that there may exist a color space comprising chromatic axes (red-green and blue-yellow) and achromatic

(black-white) luminance axis [8]. However, the non-invasive physiologic measurements at the neural substrates to characterize the 'color space' in humans has not been feasible until now [17]. The anatomy of the main neural substrates for color processing have been characterized within the visual pathways and extrastriate cortex 'color centres' [18], which lie within the distribution territories of the posterior cerebral arteries (PCAs) [19-21] and middle cerebral arteries (MCAs) [19, 21, 22]. The superior parietal aspects of the optic radiation receive blood mainly from the MCA, whereas the inferior aspects are supplied by the PCAs [23]. The macular cortical region receives blood supply, from both the calcarine artery (a branch of the internal occipital artery of the PCA distribution), and branches of the MCA, which explains macular sparing with PCA occlusion [19]. Therefore, it is possible to characterize the 'color space' in the primary visual cortex and extrastriate areas using measurements of changes in blood flow velocity in the MCAs during color stimulation [22]. In prior studies in our laboratory for microgravity simulations, we applied non-invasive transcranial Doppler measurement of mean flow velocity (MFV) in the MCAs, to examine changes in color space in men during head-down rest, and demonstrated neuroplasticity over 25 hours of recordings [11], or more, if testing was continued. These findings have been related to formation of the phenomena of long term potentiation (LTP) and long-term depression (LTD), implicating role for NMDA receptors [11]. The phenomena of LTP [24] and LTD [25], have been applied to explain potential mechanisms of memory, primarily because they exhibit numerous properties expected of a synaptic associative memory mechanism, such as rapid induction, synapse specificity, associative interactions, persistence, and dependence on correlated synaptic activity. Given these important features, LTP and LTD remains only models of the synaptic and cellular events that may underlie memory formation.

Recently, we demonstrated using functional transcranial Doppler spectroscopy (*f*TCDS) technique, that color processing occurred within cortico-subcortical circuits [11, 12]. It was demonstrated that in men, wavelength-differencing of Yellow/Blue pairs occurred within the right hemisphere by processes of cortical long-term depression (CLTD) and subcortical long-term potentiation (SLTP). On the other hand, in women, frequency-differencing of Blue/Yellow pairs occurred within the left hemisphere by processes of cortical long-term potentiation (CLTP) and subcortical long-term depression (SLTD) [11, 12]. In both genders, there was luminance effect in the left hemisphere, while in men it was along an axis orthogonal to chromatic effect, in women it was along a parallel axis [11, 12]. It therefore, may be possible to describe mechanisms for color memory formation using *f*TCD and *f*TCDS techniques. In the present study, it was hypothesized that, the brain functionally integrates within a three-dimensional physiologic 'color space', luminance effect in the left hemisphere with wave-length-differencing activity in the right hemisphere in men, but with frequency-differencing activity in the left hemisphere in women. This functional integration in color space could be mathematically modeled and could have potential applications in the study of color memory, adaptive neuroplasticity in stroke management and rehabilitation, as well as in neurodege-nerative diseases. There has not been any in-depth characterization of the neurophysiological processes involved in wavelength-differencing. However, effort has been made to apply the new modality of *f*TCDS, based on wave propagation theory to identify the neural processes implicated in color processing. It was suggested that, simultaneous color contrast implicated

http://dx.doi.org/10.5772/54877

wavelength-differencing processes in men [11], while in women, the underlying process was characterized as frequency-differencing [12]. This is the first hint that, there may be a gender-related difference in color processing. This is a profound finding that may change our overall understanding of perceptive processes in men and women. It was therefore proposed that, the brain color processing mechanisms integrates within a three-dimensional 'color space', luminance effects in the left hemisphere, and wavelength-differencing effects in the right hemisphere in men, but frequency-differencing effects in the left hemisphere in women [17]. The latter finding led to the conclusion that, color processing followed the same rule of lateralization as other major cognitive functions, such as facial processing [26, 27] and general intelligence [30], which implicated the right hemisphere cognitive style in men, and left hemisphere cognitive style in women.

Furthermore, the functional integration in color space was mathematically modeled. It was shown that, the existence of wavelength-differencing in men and frequency-differencing in women, implemented inverse exponential and logarithmic functions, respectively. These gender-related differences that underlie cerebral asymmetry for color processing, has been hypothesized to be associated with the perception of the dual nature of light as a wave and as particulate energy referred to as quanta [11,12]. The presumed genetic and psychophysiologic effects of the physical qualities of light was the basis for the proposal of the light hypothesis of cerebral asymmetry [12]. The light hypothesis for cerebral asymmetry, posits that, the phenotypic neuroadaptation to environmental physical constraints of light as a wave and as quanta energy led to phenotypic evolution, and genetic variation of X-Y gene pairs that determine hemispheric asymmetry [12]. Hence, the evolutionary trend is towards optimization of perception of the 'whole' environment by functional coupling of the genes for complementarity of both hemispheres within self, and between both genders [12]. More specifically, the basic tenant of the Light Hypothesis for cerebral asymmetry posits that, the right hemisphere is implicated in wavelength-differencing in men and the left hemisphere, in frequency-differencing in women, with an overall gender complementarity in adaptive mechanisms for neuropsychophysiological processes. The latter has been characterized as gender-related cognitive styles designed for coupled perceptual experience of the world around us.

Overall, it has been documented that there is a gender-related difference in facial processing [26]. Facial perception occurred in the cortical region of the right hemisphere in men, but in the left in women. The results are similar to previous observations using transcranial Doppler [27], and agree with those made using electrophysiological techniques [28]. Similar gender-related hemisphere differences have been observed at the amygdale for emotionally related stimuli [29], and for performance-related processing [30-32]. Men showed a right lateralization during object processing, but women showed a right tendency or bilateral activation. The effect of perception of faces has to be examined beyond the use of colors.

One presumption about the effects of color would be that, if the neuronal assemblies processing light information shared analogous topological organization as their blood flow supply, then dark would elicit the least effect, followed by colors and other stimuli on increasing complexity. This type of summation of responses related to stimulus complexity could be presumed as evidence for topological organization of these cortical areas was observed in men [26]. It was

demonstrated that, the latter extends from the area implicated in color and object perception to a much greater area involved in facial perception. This agrees with the object form topology hypothesis proposed by Ishai and colleagues [33]. However, the relatedness of object, color and facial perception was process based, and appears to be associated with their common holistic processing strategy in the right hemisphere in men. Moreover, when the same men were presented with disarranged facial Paradigm requiring analytic processing, the left hemisphere was activated. This agrees in principle with the suggestion made by Gauthier that, the extrastriate cortex contains areas that are best suited for different computations, and described as the process-map model [34]. It has been proposed that the models of cognitive processing of colors and faces are not mutually exclusive, and this underscores the fact that color and facial processing do not impose any new constraints on the brain other than those used for other stimuli [26]. It may be suggested that each stimulus was mapped by category into color, face or non-face, and by process into holistic or analytic. Therefore, a unified category-specific process-mapping system was implemented for either right or left cognitive styles [26].

Another profound gender-related difference was related to the responsiveness to the dark condition. Studies in the dark condition were included to measure the effects of non-spectral stimuli, since it is known that, some of these can actually result in the production of color experience [35]. It was observed that, there was a tendency towards right lateralization in women but no lateralization in men in dark condition. The latter finding was difficult to interpret, and similar to observations made in previous studies [20]. These observations led to the suggestion that, scotopic visual information was processed in the right hemisphere in women [20]. However, in women data from spectral density estimates showed accentuation for dark responsiveness at the cortical (C-peaks) over those of light conditions. The latter may be an indication that greater neuronal assemblies were involved in processing scotopic vision in women compared to men. Furthermore, it was proposed that, in women the neuronal assemblies may not have the same orderly topological arrangement as in men; rather the neurons involved in processing cone and rod vision were segregated within the right hemisphere cortical region. Hence, in women the right hemisphere responded to luminance effect and object perception, but showed no category-specific face effect or color processing [12, 17, 26]. The latter arrangement explains the observed right lateralization for non-face Paradigm, but left lateralization for facial Paradigms and colors. In other words, similar to men, women employed the holistic mechanism for processing object stimulus in the right hemisphere, but preferred the analytic mechanism for facial and color perception in the left hemisphere. Therefore, one major observed gender-related difference was that, while men employed a category-specific process-mapping system for facial and color perception in the right hemisphere, women used same in the left hemisphere.

Another gender-related difference that has been consistently observed is the higher MFV in women than men [12, 17, 22, 26, 27, 36]. It is noteworthy that, the side differences appear to be related to cognitive changes rather than anatomic differences [37]. To cancel the effects of these initial variations in MFV, laterality index calculations were used [26, 27, 30]. However, if women differed from men in dark responsiveness, then LI calculations relative to dark would

http://dx.doi.org/10.5772/54877

be expected to produce differences due to initial variations. In contrast, this limitation is overcome with Fourier-derived spectral density estimates, which assessed the periodicity during each stimulus condition independently, and lacked the properties of the original MFV signals. The absolute differences in MFV values would not affect the periodicity of the time series hence the Fourier transform would be equally sensitive for both men and women.

The rationale for *f*TCDS has been discussed in detail elsewhere [26]. It has been demonstrated that, when measuring at the main stem of the middle cerebral artery (MCA) the origins of the peaks arise from a peripheral circulation reflection site such as the tip of the fingers, the terminal end of the lenticulostriate subcortical branches of the MCA and the terminal of the cortical branches of the MCA. The peaks designated as **F**- (fundamental or finger), **C**- (cortical), and **S**-(subcortical) peaks occurred at regular frequency intervals of 0.125, 0.25, and 0.375, respectively. These frequencies could be converted to cycles per second (Hz), assuming that the fundamental frequency of cardiac oscillation was the mean heart rate. The fundamental frequency *f* of the first harmonic was determined by the mean heart rate per second of for example, 74 bpm/60 seconds or 1.23 Hz. In other words, the **F**-, **C**-, and **S**-peaks occurred at multiples of the first harmonic, at second and third harmonics, respectively. The distance of the reflection site for **F**-peak could be presumed to emanate from a site at:

$$D_1 1/4\lambda \text{ or } c/4\,f, \text{ or } 6.15\ (ms^{-1})/(4*1.23\ Hz) = 125\ cm \quad (1)$$

where *c* is the assumed wave propagation velocity of the peripheral arterial tree [38]. Considering that there is vascular tortuosity, the estimated distance approximates that from the measurement site in the MCA main stem, to an imaginary site of summed reflections from the aorto-iliac junction [38] and the upper extremities, close to the finger tips when stretched sideways [26]. The **C**-peak occurred at the second harmonic, such that the estimated arterial length (using common carotid c = 5.5 ms-^{1}) [39] was given by:

$$D_2 = 1/8\lambda \text{ or } c/8 *2f, \text{ or } 28\ cm; \text{ and a frequency } f_2 \text{ of } 2.46\ Hz \quad (2)$$

This length approximates the visible arterial length from the main stem of the MCA, through vascular tortuosity and around the cerebral convexity, to the end vessels at distal cortical sites such as the occipito-temporal junction on carotid angiograms of adults [26]. The **S**-peak occurred at the third harmonic, and may have arisen from an estimated site at:

$$D_3 = 1/16\ \lambda \text{ or } c/16*3f, \text{ or } 9.3\ cm; \text{ and a frequency } f_3 \text{ of } 3.69\ Hz \quad (3)$$

The latter is about the approximate visible arterial length of the lenticulostriate vessels from the main stem of the MCA on carotid angiograms [40]. Although it is not shown, the fourth harmonic would be expected to arise from the MCA bifurcation in closest proximity to the measurement site in the main stem of the MCA. The pre-bifurcation length from the measurement point would be given by:

$$D_4 = 1/32\ \lambda \text{ or } c/32*4f, \text{ or } 3.5 \text{ cm; and a frequency } f_4 \text{ of } 4.92 \text{ Hz} \quad (4)$$

The calculated length approximates that of the segment of MCA main stem just after the carotid bifurcation, where probably the ultrasound sample volume was placed, to the MCA bifurcation or trifurcation, as the case may be. Thus, the latter estimates may approximate actual lengths. However, it has been suggested that the estimated distances may not correlate exactly with known morphometric dimensions of the arterial tree [41]. The *f*TCDS examines spectral density estimates of periodic processes induced during mental tasks, and hence offers a much more comprehensive picture of changes related to effects of a given mental stimulus. The spectral density estimates would be least affected by artifacts that lack periodicity, and filtering would reduce the effect of noise. Despite the outlined advantages of *f*TCDS, there are potential problems with the present studies which are conducted with relatively small sample size, which may create greater influence of outliers. However, statistical analysis did not reveal any extreme outliers in the present data set and exclusion of outliers did not alter the lateralization patterns. The choice of eight men and eight women for each of the two data sets for analysis, with a total of 48 points in each data set was ideal for Fourier analysis.

2. Methodological procedures

2.1. Subjects

The study included 64 (32 men and 32 women) healthy subjects, divided in four groups of comprising each 8 men of mean ± SD age of 24.6 ± 2 years, and 8 women of mean ± SD age of 24 ± 2 years, all were right handed on hand preference questionnaire [42]. All subjects had normal sight and color vision, according to testing of visual acuity by Snellen chart, color vision by Ishihara pseudoisochromatic plates and color recognition [43]. Complete physical and mental examination revealed no abnormalities and routine evaluation of the cardiovascular, neurologic and respiratory systems were unremarkable. All were placed on the usual restrictions for cognitive studies [44]. All subjects gave written informed consent according to the Declaration of Helsinki; and the Institutional Ethics Board approved the study protocol. The experimental procedure including TCD scanning was similar for cognitive studies described in detail elsewhere [17, 22, 26]. In summary, TCD studies were performed using two 2 MHz probes of a bilateral simultaneous TCD instrument (Multi-Dop T, DWL, Singen, Germany), with sample volume placed in the RMCA and LMCA main stems at a depth of 50 mm. The MCAs was chosen for measurements since it supplies about 80% of brain blood flow [45], and thus provides a global characterization of the color space than those from the PCAs. Moreover, complex processing of color occurs in the extrastriate cortex perfused by the MCAs, than in the primary visual cortex perfused by the PCAs. All participants were briefed on the protocol for the entire experiment, and all questions and practice sessions on what was required for the visual paradigms were explained prior to the start of the experimental data acquisition.

http://dx.doi.org/10.5772/54877

2.2. TCD scanning procedure

All *f*TCD procedures were performed using examination techniques previously described for cognitive studies [12, 17, 26, 27, 30, 46, 47, 48]. The *f*TCD scanning was performed using bilateral simultaneous *f*TCD instrument (Multi-Dop T, DWL, Sipplingen, Germany). *f*TCD studies were performed as follows: first, the participant was placed in a supine posture with their head up at 30 degrees (Figure 1).

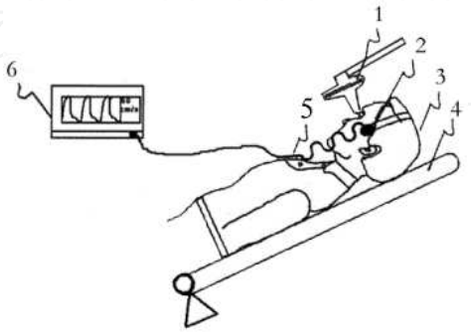

Figure 1. Shows the experimental setup with the subject supine with head-up at 30 degrees looking into the 3D-view-master for color stimulation with two 2MHz transcranial Doppler probes attached bilaterally for simultaneous measurements in both MCAs. (Source modified from Njemanze PC. United States Patent No. 8,152,727 April, 2012).

The Viewmaster *1* is placed in front of the subject where he/she could see clearly through it. The probe holder headgear *2* LAM-RAK (DWL, Sipplingen, Germany) was clamped with a base support the head *3* and on the nasal ridge, while the subject rested supine *4*. Two earplugs were affixed. Two 2-MHz probes connected via transducer cord *5* to the TCD device *6* were affixed in the probe holder and insonation was performed to determine the optimal position for continuous monitoring of both MCA main stems at 50 mm depth from the surface of the probe. The gain and power controls were kept constant for both MCAs in all participants. The headgear was placed comfortably on each participant prior to start of recording. Participants were instructed to remain mute and motionless throughout the short data acquisition time duration. They were informed that their thoughts and subjective feelings would be debriefed after the experimental data acquisition session. All participants were requested to refrain from internal or external verbalization and informed of the deleterious effects that might invalidate the data acquired. Environmental luminance was kept constant for all participants during the study. Effort was made to exclude the effects of environmental noise by sound shielding of the experimental room, and the participant wore earplugs that further reduced environmental noise levels. However, completely sensory deprivation of the participant was avoided. Vital signs were monitored using continuous recording of electrocardiography and respiration. A standard questionnaire was used for monitoring the self-perceived anxiety levels, as measured using state-trait anxiety inventory (STAI) in pre-test and posttest conditions. The STAI has been tested and validated by other investigators [49, 50]. In post-experimental debriefings was focused on what participants were ''thinking'' during task performance, and any relevance it might have to attention during the data acquisition process. The debriefings were cordial and voluntary to encourage participants to provide full disclosure of their thoughts during the

experimental data acquisition, and they were told that, there was no threat of any sanctions regardless of the outcome. Pre-experimental test runs in a different but selected group of participants provided insights into how participants understood the instructions and handled the stimulus used in the present study [22, 27]. The latter was used to modify and simplify the task design for easy comprehension and strict adherence. Baseline vital signs were recorded in full consciousness under normal resting conditions.

2.3. Recordings under dark condition

Measurements in dark condition were considered as light absent condition, as well as including background effects of scotopic vision [20, 51]. It is known that black may evoke a color experience [51]. Recording of a continuous train of velocity waveform envelopes was performed at rest with the participant mute, still, and attention-focused, in a dark visual field within a dark enclosed space with no mental or manual tasks to undertake. Although this had a similar effect to eye closure, but did not require eye muscle contractions and eye ball movements that could elicit motion artifacts. First, dark recording was obtained prior to stimuli administration for 60 seconds, and was used as reference for light stimulation conditions. An observer monitored the subject for movement artifacts, which were marked and removed from recordings.

2.4. Color stimulation recordings

The tasks were designed in our laboratory and the detailed rationale described elsewhere [22]. We have applied these tasks to show consistent and reliable recordings with TCD ultrasonography in prior studies [17, 22]. Briefly, specially adapted 3D-viewing device (Viewmaster, Portland, OR) was painted inside with black paint. The aperture on the right side of the device was closed to light, but the left side aperture was open, to be backlit from white light reflected from a remotely placed light source. In other words, there was left eye monocular vision, with light path from the left visual hemifield reaching the right side of the left eye retina, and crossing at chiasm to project contralaterally to the right visual cortex, while the light path from the right visual hemifield reaching the left side of the left eye retina, project ipsilaterally to the left visual cortex. The rationale for this design, relates to the fact that, in primates including humans, there is virtually total binocular vision; the left half of each retina project to the left visual cortex and the right half of each retina project to the right visual cortex. This means that the right visual cortex receives all its input from the left visual field and the left visual cortex receives all its inputs from the right visual field [52]. Color processing cells, receiving inputs from only one eye are grouped together within the same area of the striate cortex, extending from the upper to the lower cortical layers, and are referred to as ocular dominance columns (blobs) [15, 53, 54]. While those receiving inputs from both eyes are called hypercolumn [53, 55]. During binocular vision, there is binocular interaction due to stereopsis, the perception of depth [15]. Therefore, it is inappropriate to mix the inputs, from both retinas in a single neuron, before the information of color vision has been extracted [15]. The reflection from a light source was used, and projected onto a white surface flat screen, placed 125 cm from the lamp. The screen was positioned 80 cm from the nose ridge of the subject. The light source was a tungsten

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coil filament, of a general service lamp ran at a constant 24 V and 200 W, with a color temperature of about 2980 K and approximately 20 lumens/watt. Color stimulation was performed using optical homogenous filters placed on the reel of the Viewmaster, in the light path. Kodak Wratten filters: Deep Blue (No. 47B) with short dominant wavelength (l) of Sλ= 452.7 nm; and Deep Yellow (No. 12) with medium dominant wavelength (l) of Mλ = 510.7 nm were used. The Kodak manufacturer's manual for Wratten Filters provides the excitation purity and luminous transmittance for each filter [56]. During color stimulation the condition was identical to that of baseline, except for use of slides that were Blue, and Yellow, respectively. White light stimulation was considered as measurements with the left aperture on the reel open to white light reflected from the remote light source.

2.5. Facial stimulation recordings

Figure 2 shows that object and facial paradigms used in the present study.

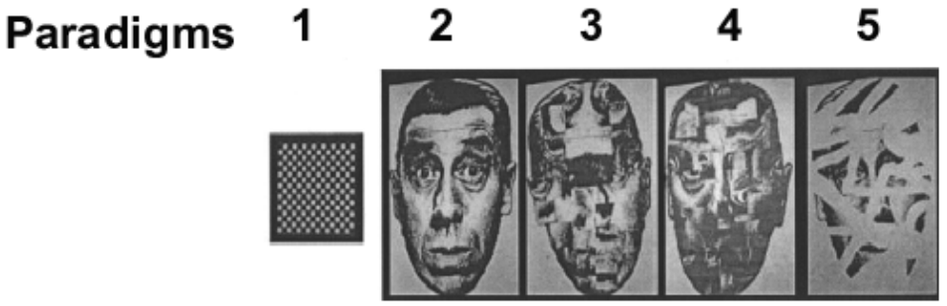

Figure 2. Shows object (Paradigm 1) and facial stimuli (Paradigms 2-5). (Source: Njemanze PC. Aviat Space Environ Med, 2004, 75:800-805).

Paradigm 1: *Object perception* - Checkerboard square paradigm. The paradigm comprised black and white chequered square of alternating black and white square dots. This was a nonverbal passive viewing task of an object foveally presented from a slide projector onto a screen placed in front of the participant, which was inclined at 30 degrees from the horizontal plane at a distance of 80 cm from the nasal ridge. During the presentation, a continuous train of velocity waveform envelopes was recorded with the participant mute, still, with fixed gaze, and attention focused on the object. There were no mental or manual tasks to perform while viewing the object. MFV measurements were made for 60 seconds.

Paradigm 2: *Face encoding task* - whole neutral face. A novel whole male face expressing a neutral emotion was presented. The participant was instructed to commit the face to memory and told that their memory would be tested later. During the presentation, MFV was recorded for 60 seconds while the participant viewed the face.

Paradigm 3: *Facial elements sorting task* – of disarranged face. This facial task comprised sorting elements of a disarranged face. Participants were instructed to sort the elements of the face and arrange them into a whole face, one element at a time, for 60 seconds. The task required a sophisticated perceptual mechanism capable of extraction of components of a face; analysis

of their width and height, distances between these elements, angles, contours, illumination, expression, hairline, hair style and so on; and constantly spatially fitting the puzzle by matching each element with that stored in memory and then proceeding to form the picture of the whole face. The task implies that, far more iterations were required to accomplish the recognition task. The rationale is based on the fact that, facial processing comprises several stages [57, 58]. However, on presentation of a face, this multi-stage processing occurs almost simultaneously [59]. The task design was an attempt to break down the processes into several iterative steps, and to exclude verbalizable features that may cause extraneous compounding effects [27]. The MFV was recorded for 60 seconds during the performance of the task.

Paradigm 4. *Facial recognition task:* This facial recognition task comprised disarranged facial elements with a part of the face left in place as a clue. Subjects were asked to recognize the face. The clues left in place were intended to introduce some measure of "automaticity" in the recognition process. In other words, the clue reduced the number of iterations required to accomplish the task.

Paradigm 5. *Facial recognition task:* This facial recognition task comprised a degraded face with missing elements of a greater level of complexity than that of Paradigm 4, but the contour and some elements were preserved in place to aid the subject to recognize the face using a 'fill-in effect' of the missing parts.

The exclusion in the task design of performance ratings by any observer and any competitive indices was done to minimize any role of anxiety. Furthermore, positively and negatively valenced pictures, culturally familiar faces, as well as female faces, were also not used in the present study. Pretest runs suggested that, the latter factors could cause emotional activation both subliminally and supraliminally, with compounding effects on autonomic responses [60]. The design rationale for this pedigree of paradigms have been described in detail elsewhere [27]. Participants were later debriefed on the sequence of task execution and the climax attained. In post-test debriefings, we focused on ''what participants were thinking'' at each stage of the task, difficulties, distractions, and any confounding experiences or thoughts. The participants described in detail the sequence and strategy used for each task execution, and how they resolved internal conflicts that arose during task performance. Their self-rating of performance on a 4-point scale (from poor to best performance) was also assessed relative to self-attained target performance for the same task during pretest runs. An observer monitored motion artifacts such as eye movements and voluntary and involuntary movements, who documented time of occurrence on the MFV train for use in later analysis.

2.6. Calculations

Artifacts were marked and removed prior to data analysis. Data averaging comprised 10-second segments of the train of velocity waveform envelopes for the dark task and each of the paradigms, respectively. For baseline and each stimulus, 60 seconds of recording resulted in six MFV values for dark and each task, respectively. These values were used for further calculations. In other words, velocity waveform envelopes for the relevant 60-s intervals were first averaged in 10-s segments, to produce six values for black and each color condition

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respectively. The resulting values were used for further computations of laterality index (LI'). Cerebral lateralization was assessed using LI' expressed as:

$$LI' = \frac{\left(\text{RMCA MFV}_{10\text{-s}} \text{ minus LMCA MFV}_{10\text{-s}}\right)}{\left(\text{RMCA MFV}_{10\text{-s}} \text{ plus LMCA MFV}_{10\text{-s}}\right)} * 100. \quad (5)$$

The relative value of lateralization (LI), for each 10-s segment for each color, was calculated as the difference between LI' values measured during the 10-s segment of the color and the corresponding 10-s segment of baseline (onset of baseline corresponds with onset of color within the 60-s segment):

$$LI = LI'\text{color}_{10\text{-s}} \text{ minus } LI'\text{ baseline}_{10\text{-s}}. \quad (6)$$

In general, positive LI values suggest right lateralization, while negative LI values suggest left lateralization. Zero LI values showed no lateralization from baseline, or possible bilateral response. LI values calculated for each 10-s segment of the MFV envelope, were used for further analysis.

2.7. Three dimensional color space

In the design of the model for three dimensional color space, it could be presumed that opponency was accomplished across two orthogonal coordinates of blue and yellow, respectively [11]. In men, wavelength-differencing activity was captured by changes in the RMCA MFV for Yellow plotted on the Y-axis, and the RMCA MFV for Blue plotted on the X-axis [11]. In women, frequency-differencing [12] was captured by changes in the LMCA MFV for Yellow plotted on the Y-axis, and the LMCA MFV for Blue plotted on the X-axis. The luminance effect on the LMCA MFV in response to White light with the highest luminous flux, was plotted on the (Z - axis), in both men and women [11]. The reconstruction of the 3D-color space plots was performed using the quadratic function [11], fitted by the procedure that has the general form:

$$Z = a_o + a_1X + a_2Y + a_3X^2 + a_4Y^2 + a_5XY \quad (7)$$

The relationships between observed variables were estimated in 3D-surface plot which offered a flexible tool for approximation. Moreover, the quadratic surface plot does not flex to accommodate local variations in data. When the overall pattern of changes in MFV dataset follows some segment of the quadratic surface, then a good fit could be achieved. The raw data spikes were displayed on the surface, to examine goodness of fit and assess the influence of outliers. The MFV gradient produced color scale sequence ranges, from minimum (green) to maximum (red) of *Z*-values of luminance effect. The color sequence ranges were used to adjudge the level of luminance effect required for wavelength-differencing activity in men, and frequency-differencing activity, in women, respectively.

2.8. Exponential function model

The 3D-graph was examined to uncover the relationship between luminance effects (*Z*-axis) and wavelength-differencing on the RMCA MFV for Yellow plotted on the *Y*-axis in men. The observation of an exponential growth suggested that, the data could be fitted to an exponential function model. The LMCA MFV for White light (*Y*-axis) and RMCA MFV for Yellow (X-axis) was fitted to an exponential function of a 2D graph, given the following:

The exponential function with positive base $b > 1$ is the function:

$$y = b^x \tag{8}$$

It is defined for every real number x for any base b.

There are two important things to note:

The y-intercept is at (0, 1). For, $b^0 = 1$.

The negative x-axis is a horizontal asymptote. For, when x is a large negative number e.g. $b^{-10,000}$ - then y is a very small positive number.

2.9. Logarithmic function model

In women, the 3D-graph was examined to uncover the relationship between luminance effects (*Z*-axis) and frequency-differencing on the LMCA MFV for Blue plotted on the *X*-axis. The observation of a logarithmic growth suggested that, the data could be fitted to a logarithmic function. The LMCA MFV for White light (*Y*-axis) and LMCA MFV for Blue (*X*-axis) was fitted to a logarithmic function of a 2D graph, given the following:

The logarithmic function with base b is the function:

$$y = log_b x \tag{9}$$

b is normally a number greater than 1 (although it need only be greater than 0 and not equal to 1). The function is defined for all $x > 0$. The negative y-axis is a vertical asymptote.

2.10. Inverse relations of exponential and logarithmic functions

The inverse of any exponential function is a logarithmic function. For, in any base b:

$$i)\ b^{log} b^x = x, \tag{10}$$

and

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$$ii)\ log_b b^x = x \tag{11}$$

Rule *i*) embodies the definition of a logarithm: $\log_b x$ is the *exponent* to which b must be raised to produce x.

Now, let:

$$\lambda(x) = b^x \text{ and } f(x) = log_b x \tag{12}$$

Then Rule *i*) is $\lambda(f(x)) = x$.

And Rule *ii*) is $f(\lambda(x)) = x$.

These rules satisfy the definition of a pair of inverse functions. Therefore for any base b, the functions:

$$\lambda(x) = b^x \text{ and } f(x) = log_b x \tag{13}$$

are inverses. This defines the well established relationship between wavelength (λ) and frequency (f), respectively, that is given by: $\lambda = c/f$.

where c is the speed of light in a vacuum and remains constant at 3.00×10^8 m/s.

2.11. Fourier analysis

The Fourier transform algorithm was applied using standard software (Time series and forecasting module, Statistica for Macintosh, StatSoft, OK, USA). The most efficient approach for Fourier algorithm requires that, the length of the input series is equal to a power of 2. If this is not the case, additional computations have to be performed. To obtain the required time series, the data were averaged in 10-second segments for one minute duration for each stimulus; yielding 6 data points for each participant and a total of 48 data points for all eight men and women, respectively. Smoothing the periodogram values was accomplished using a weighted moving average transformation. Hamming window was applied as a smoother [61, 62]. The spectral density estimates, derived from single series Fourier analysis, were plotted, and the frequency regions with the highest estimates were marked as peaks.

2.12. Other statistics

All analyses were performed using the software package Statistica (StatSoft, OK, USA). Results were given as mean±SD and plots represented as mean/SE/1.96*SE where applicable. Analysis of LI was recomputed after excluding outliers. Analysis of variance (ANOVA) was applied to spectral density estimates between two minima including the peak (as maxima) to examine the effects of paradigms on cortical and subcortical responses. The stimulus effect was assessed

by multivariant analyses of variance (MANOVA) with repeated measures applied to the MFV data set, followed by planned Scheffé contrast that compared stimulus response relative to stimulus-absent Dark condition. Analysis of covariance (ANCOVA) with repeated measures was performed to demonstrate that, the difference found during visual stimulation persists even when the differences in baseline condition were partialled out. When applicable, one-way ANOVA of paired groups was used to assess differences in spectral density estimates between two minima including the peak (as maxima), under different stimulation conditions, for the RMCA and LMCA, respectively. The determination of LUMINANCE effect was derived by comparison of Dark versus Light conditions, and the direction relative to chromatic axis was either opposite (orthogonal axis) or parallel axis. WAVELENGTH-encoding was assessed as present when the effects of longer wavelength color (Yellow) were accentuated over shorter wavelength color (Blue) [11]. Conversely, ENERGY-encoding was present when the effects of higher frequency color (Blue), was accentuated over lower frequency color (Yellow) [11]. WAVELENGTH-differencing implicated WAVELENGTH-encoding main effect at S-peaks, and at least a tendency for ENERGY-encoding at C-peaks [11]. The pre-condition for WAVELENGTH-differencing requires that, a chromatic contrast detector sub-serving one area of chromatic space, excite a chromatic detector of opposite type and/or inhibit a chromatic detector of the same type in neighboring areas of chromatic space [11, 15]. On the other hand, FREQUENCY-differencing involved ENERGY-encoding main effect at C-peaks, and at least a tendency at S-peaks. CLTP process accentuated C-peaks over S-peaks due to prevailing SLTD. Conversely, SLTP process accentuated S-peaks over C-peaks, due to prevailing CLTD. The latter was followed by planned contrasts to examine luminance effect (dark versus Paradigm 1), discrimination of face from non-face or category-specific face effect (Paradigm 1 versus Paradigm 2), and face-processing strategy effect (Paradigm 2 versus Paradigm 3). The Paradigms 4 and 5 were used only in the *f*TCD analysis but not in the further, *f*TCDS analysis. The level of significance was at p=0.05.

3. Results

3.1. Gender-related asymmetry during color processing by *f*TCD

The gender-related asymmetry for color processing is shown in Figure 3, that displays the box and whiskers plot of the MFV data obtained for all subjects under all conditions. Overall, MFV for women were higher than that for men. The plot shows the five-number summary (the minimum, first quartile, median, third quartile, and maximum) of the distribution of the observations of the MFV data set, and showed a more symmetric distribution during color stimulations (Blue, Yellow, and Red) in men, compared to greater dispersion in women. Table 1A shows the mean ± SE of MFV for men, and the planned contrast (Scheffé P-value) variation from Dark condition. In men, the RMCA MFV increased significantly in response to Light (2.6%), Blue (4.3%), Yellow (2.5%) and Red (2.8%). While LMCA MFV increased only to Blue (2.6%) stimulation. Table 1B shows the mean ± SE of MFV for women. In women, only Blue stimulation evoked increase in MFV in the RMCA (2.6%) and LMCA (2.2%).

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Stimulations	RMCA (cm/s)	Scheffé *P* (cm/s)	LMCA	Scheffé P
Dark	64±1.26	-63.9±1.8		
Light	65.7±1.2	*<0.05*	64.2±1.67	*NS*
Blue	66.8±1.28	*<0.0001*	65.6±1.8	*<0.01*
Yellow	65.6±1.26	*<0.05*	64.4±1.7	*NS*
Red	65.8±1.27	*<0.01*	64.4±1.6	*NS*
A				
Stimulations	**RMCA (cm/s)**	**Scheffé *P* (cm/s)**	**LMCA**	**Scheffé P**
Dark	81.6±2	-	80.7±1.8	-
Light	82.3±2	*NS*	81.26±1.7	*NS*
Blue	83.8±1.9	*<0.0001*	81.6±1.77	*<0.01*
Yellow	82.57±1.86	*NS*	81.3±1.6	*NS*
Red	82.1±1.9	*NS*	80.7±1.68	*NS*
B				

Table 1. A. Mean±SE and Planned Contrasts of MFV Changes during Visual Stimulations from Dark Baseline in Men; B. Mean±SE and Planned Contrasts of MFV Changes during Visual Stimulations from Dark Baseline in Women

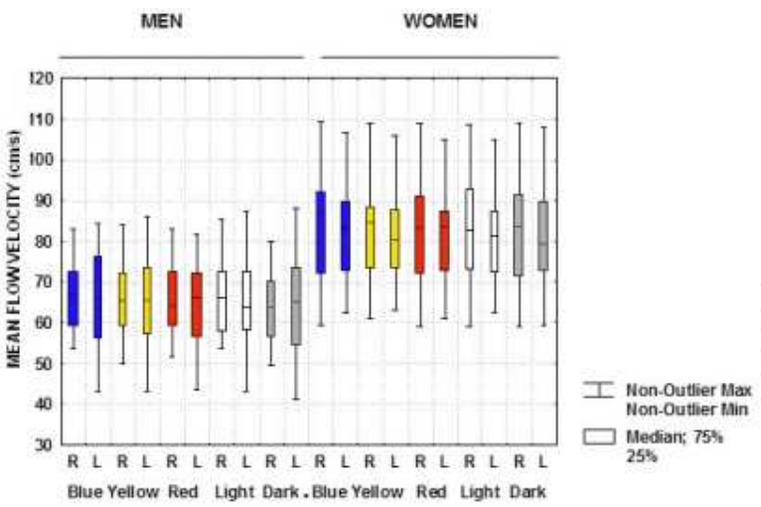

Figure 3. Box and whiskers plots of mean/SE /1.96*SE of MFV (in cm/s) during dark and color stimulation in men and women. (Source modified from: Njemanze PC. Exp Transl Stroke Med 2010, 2:21-27.).

To assess the overall gender-related differences in MFV during color stimulation, a MANOVA test was applied to MFV data set to assess differences between measurements in the RMCA and LMCA in men and women, with a 2 × 5 × 2 design: two levels of GENDER (Men and Women), five levels of STIMULATIONS, (Dark, Light, Blue, Yellow, and Red), and two levels

of ARTERY (RMCA and LMCA). The MFV was analyzed as the dependent variable. There was a main effect of GENDER, $F(1,94) = 65.4$, MSE = 68166, $p < 0.0001$. There was a main effect of STIMULATIONS, $F(4,376) = 5.6$, MSE = 111.7, $P < 0.001$. There was no main effect of ARTERY, P = NS. However, there was STIMULATION × ARTERY interaction, $F(4,376) = 3.3$, MSE = 5.96, $P < 0.05$.

The 3D surface quadratic plots of MFV changes in color space are shown in Figures 4(A-B) for men (Figure 4A) and women (Figure 4B), respectively. The male 3D surface quadratic plot (Figure 4A) was 'funnel shaped', indicating overall that, wavelength-differencing activity was narrowed at low luminance effect, but broadened with increasing luminance effect. In men, there was an exponential relationship (Figure 5A) between right hemisphere wavelength-differencing and contralateral left hemisphere luminance effect, as demonstrated in the 2D graph (Figure 5B), showing all subjects within the 95% confidence band. The exponential function model in men (Figure 5B) indicated that brain functional integration of luminance effects and wavelength-differencing activities was maintained within a 'narrow physiologic range' of MFV of 50 to 85 cm/s in the RMCA and LMCA. On the other hand, in women, the 3D-surface quadratic plot was the mirror-image of that observed in men, showing a closed 'cone shape' with a widespread base (Figure 4B). The base of the cone shape suggests that at very low luminance effect on LMCA MFV, frequency-differencing activity occurred over a very wide range. However, with increasing luminance effect, frequency-differencing activity narrowed. In women, there was a logarithmic relationship between ipsilateral left hemisphere frequency-differencing and luminance effect, as demonstrated in the 2D graph of logarithmic function (Figure 5C), showing all subjects but two, within the 95% confidence band. The logarithmic function model in women (Figure 5D) indicates that, brain functional integration of luminance effect and frequency-differencing activities was maintained within a 'narrow physiologic range' of MFV of 60 to 106 cm/s in the LMCA, however, somewhat wider than that for men. In both, men (Figure 5C) and women (Figure 5D), respectively, there appears to be a high level of scatter. However, in men (Figure 5C) it is more disperse than in women (Figure 5D), which may suggest as greater sensitivity to luminance in men (see Figure 4A), than in women (see Figure 4B).

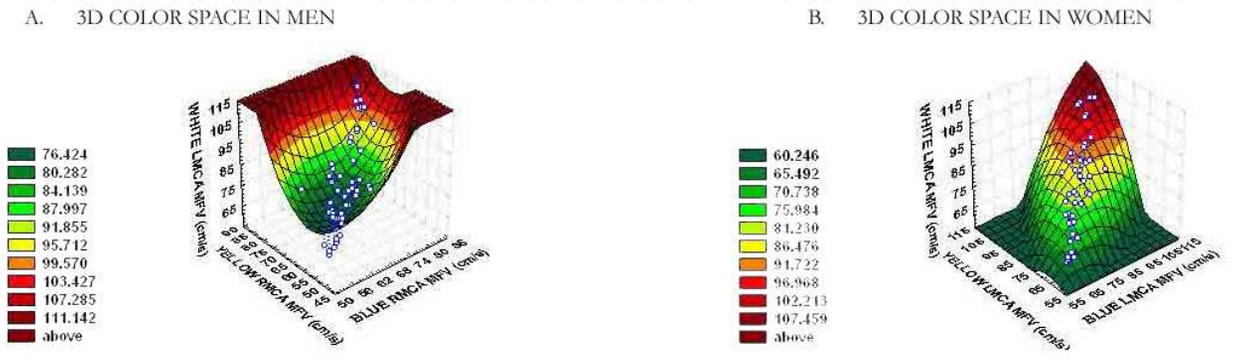

Figure 4. A-B). Shows the 3D surface quadratic plots of MFV changes in color space for men (Figure 4A) and women (Figure 4B), respectively. (Source modified from: Njemanze PC. Exp Transl Stroke Med 2011, 3:1-8.).

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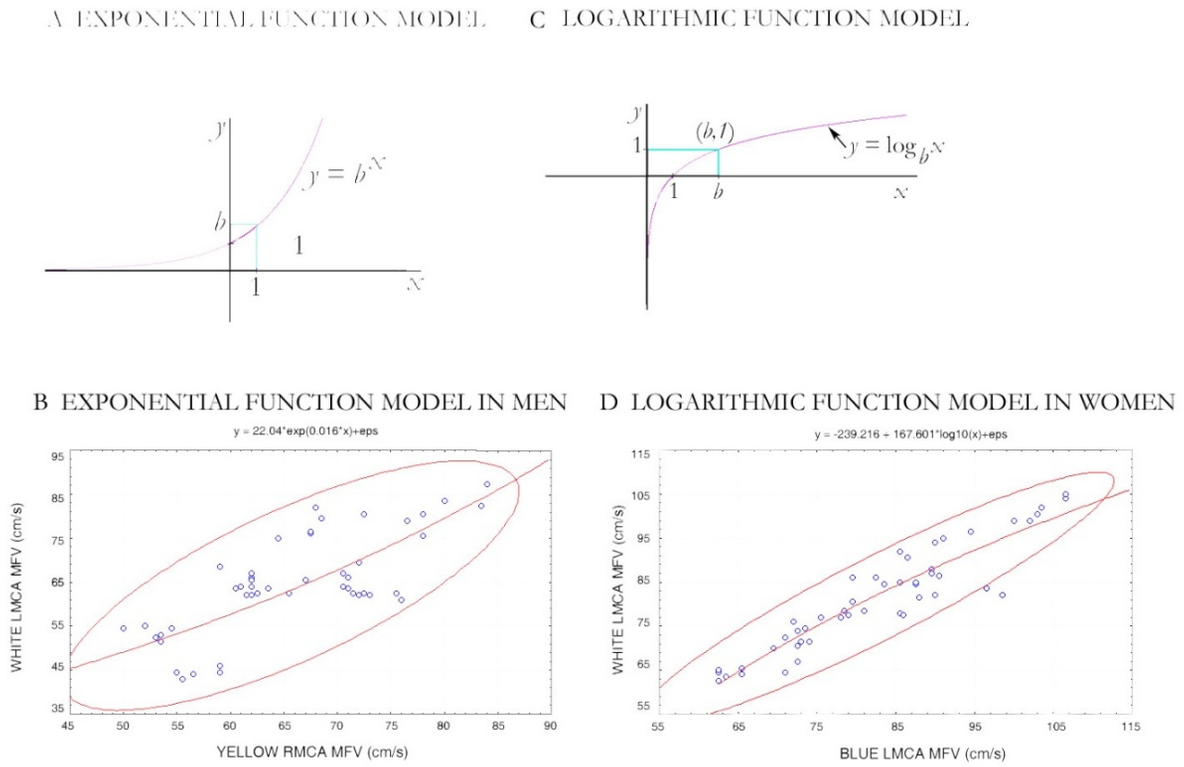

Figure 5. A-D). Shows the exponential function curve used for any base *b* (Figure 5A) that was used for the exponential function model fitted to the data in men (Figure 5B); in contrast, to the logarithmic function curve used for any base *b* (Figure 5C) that was used for the logarithmic function model fitted to the data in women (Figure 5D). All subjects were plotted with the 95% confidence band shown. (Source modified from: Njemanze PC. Exp Transl Stroke Med 2011, 3:1-8.).

3.2. Gender-related asymmetry for color processing by *f*TCDS

Figures 6 (A-D) demonstrates the conventional spectral density plots for each artery during Dark, Light, Blue and Yellow stimulations in men (Figures 6A-B) and women (Figures 6C-D), respectively.

In general, for all stimulations in both men and women there were three peaks designated as fundamental (F-peak), cortical (C-peak), and subcortical (S-peak), which occurred at regular frequency intervals of the first (0.125 Hz), second (0.25 Hz), and third (0.375 Hz) harmonics, respectively. Given the differential MFV response in men and women, the spectral density estimates for men and women were analyzed separately, to uncover changes at cortical and subcortical peaks. A MANOVA with repeated measures was applied to spectral density estimates in a 2 × 5 × 2 design: two levels of REGIONS (Cortical, Subcortical), five levels of STIMULATIONS (Dark, Light, Blue, Yellow and Red) and two levels of ARTERIES (RMCA and LMCA). In men, there was no main effect of REGIONS, p = NS, but there was a tendency for subcortical peaks to be higher than cortical peaks in men. There was a main effect of STIMULATIONS, $F(4,24) = 4.2$, MSE = 11586, $p < 0.01$. There was no main effect of ARTERIES, p = NS. There was a REGIONS × STIMULATIONS interaction, $F(4,24) = 4.8$, MSE = 31945, $p < 0.01$. There was no REGIONS × ARTERIES interaction, p = NS. There was a STIMULATIONS × ARTERIES interaction, $F(4,24) = 4.7$, MSE = 7397, $p < 0.01$. There was a three-way interaction,

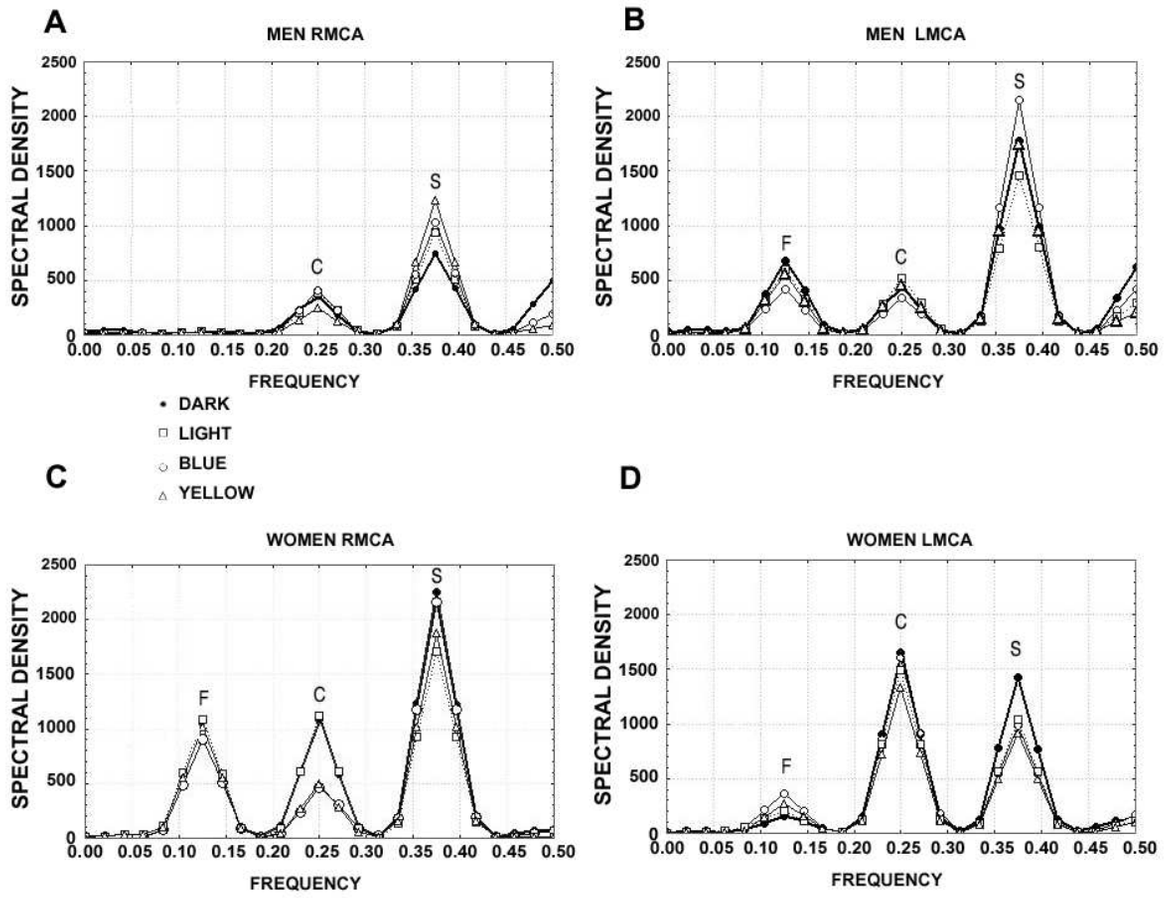

Figure 6. A-D). Shows the plots of spectral density estimates for dark, light and color stimuli (blue, yellow) for the RMCA in men (Figure 6A), for the LMCA in men (Figure 6B); for the RMCA in women (Figure 6C) and LMCA in women (Figure 6D). (Source modified from: Njemanze PC. Exp Transl Stroke Med 2010, 2:21-27.).

REGIONS × STIMULATIONS × ARTERIES, $F(4,24) = 4.76$, $MSE = 25392$, $p < 0.01$. An analysis of covariance (ANCOVA) with repeated measures was applied to demonstrate that the difference found during color stimulation persists even when the difference due to baseline condition was partialled out. In men, there was significant increase in MFV produced by luminance, hence WAVELENGTH-encoding activity could only be adjudged after partialling out the changes under Dark and Light conditions as changing covariates. Conversely, in women, there was no change in MFV associated with luminance, and hence only baseline Dark condition was used as a covariate.

In men, in the RMCA, at C-peaks, there was a tendency for ENERGY-encoding, $F(1,5) = 5.95$, $MSE = 10315$, $p = 0.058$. However, at S-peaks, there was a significant main effect of WAVELENGTH-encoding, $F(1,5) = 9.98$, $MSE = 1016.8$, $p < 0.05$. This may suggest that, there was WAVELENGTH-differencing in the right hemisphere in men. There was no luminance effect in the RMCA territory, p = NS. However, in the LMCA, there was an orthogonal LUMINANCE effect, $F(1,5) = 6.27$, $MSE = 6834.6$, $p < 0.05$. Figure 6A shows that the RMCA S-peaks were 'topologically' separated, achromatic from chromatic peaks, and between the latter, short

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wavelength (Blue) from long wavelength (Yellow and Red). There was a reverse tendency at the C-peaks. Overall, in men, wavelength-differencing in the right hemisphere (Figure 6A), and luminance effect in the left hemisphere (Figure 6B), occurred by processes of CLTD and SLTP. In women, in the RMCA, the C-peaks were unremarkable, p = NS. However, at S-peaks, there was some residual tendency for ENERGY-encoding effect, $F(1,6) = 5.65$, MSE = 31823, $p = 0.054$, and LUMINANCE sensitivity, $F(1,6) = 5.52$, MSE = 58620.5, $p = 0.057$. On the other hand, in the LMCA, a main effect for ENERGY-encoding occurred at C-peaks, $F(1,6) = 6.35$, MSE = 34730, $p < 0.05$, as well as at S-peaks, $F(1,6) = 7.5$, MSE = 2197.7, $p < 0.05$. This may suggest that in women, FREQUENCY-differencing occurred in the left hemisphere. A parallel LUMINANCE main effect, occurred at C-peaks, $F(1,6) = 6.27$, MSE = 10461.6, $p < 0.05$, but showed a tendency at S-peaks, $F(1,6) = 5.5$, MSE = 58620, $p = 0.057$. In women, both frequency-differencing and luminance effect responsiveness in the left hemisphere (Figure 6D), occurred by processes of CLTP and SLTD.

3.3. Gender-related asymmetry during facial processing by *f*TCD

The LI for men is displayed in Figure 7A, and for women in Figure 7B, respectively.

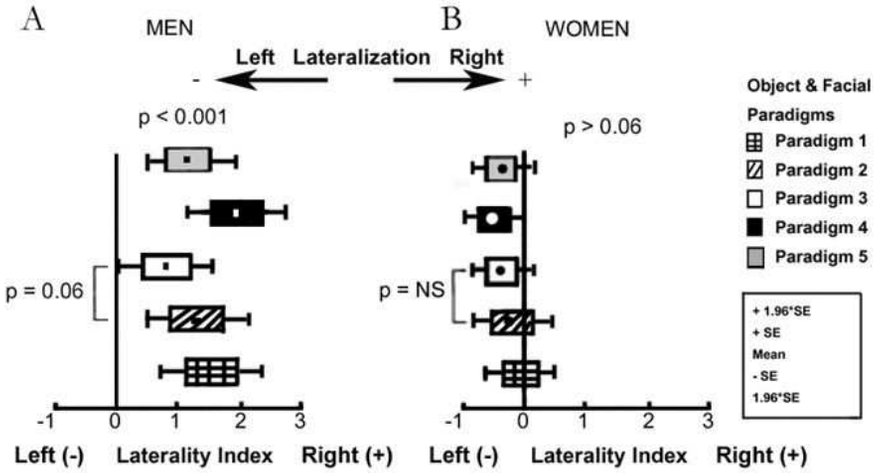

Figure 7. A-B). Shows the box and whiskers plot of mean/SE /1.96*SE of LI during object (Paradigm 1) and facial (Paradigms 2-5) stimulation in men (Figure 7A) and women (Figure 7B).

Overall, men were right lateralized for facial Paradigms 2-5 as well as non-face object Paradigm 1. On the other hand, women were left lateralized for facial Paradigms 2-5, but right lateralized for object Paradigm 1. However, on exclusion of outliers, women showed no lateralization with zero LI value or bilateral activation during object processing. In men, at baseline MFV in dark condition did not differ between RMCA and LMCA. Paradigms 1–5 induced significant variation in MBFV in the RMCA ($p < 0.01$) and LMCA ($p < 0.001$), that resulted in right lateralization for all tasks. There was a marginal difference between Paradigm 2 and Paradigm 3 ($p = 0.06$), due to more pronounced activation in the LMCA ($p < 0.01$) than RMCA ($p = 0.053$) (Figure 7A) during Paradigm 3. Overall, tasks were right lateralized ($p < 0.001$), showing stimulus-specific effect in lateralization. The LI for women is displayed in Figure 7B. At

baseline MFV in dark condition was higher in LMCA than R-MCA, and Paradigms 1–5 induced significantly greater attenuation of MFV in the RMCA ($p < 0.05$) than in the L-MCA ($p < 0.001$). As a result, there was left lateralization for all Paradigms 1-5 (Figure 7B). There was no difference between Paradigm 2 and Paradigm 3. In other words, in women, stimulus-specific effects did not yield lateralization of MFV. Given the observed marginal tendencies for changes between Paradigms 1-3, the *f*TCDS analysis was carried out for dark and Paradigms 1-3 effects.

3.4. Gender-related asymmetry during facial processing by *f*TCDS

The spectral density plots for each artery during all study conditions in Figures 8 A-D, in men (Figure 8 A-B) and women (Figure 8 C-D), respectively.

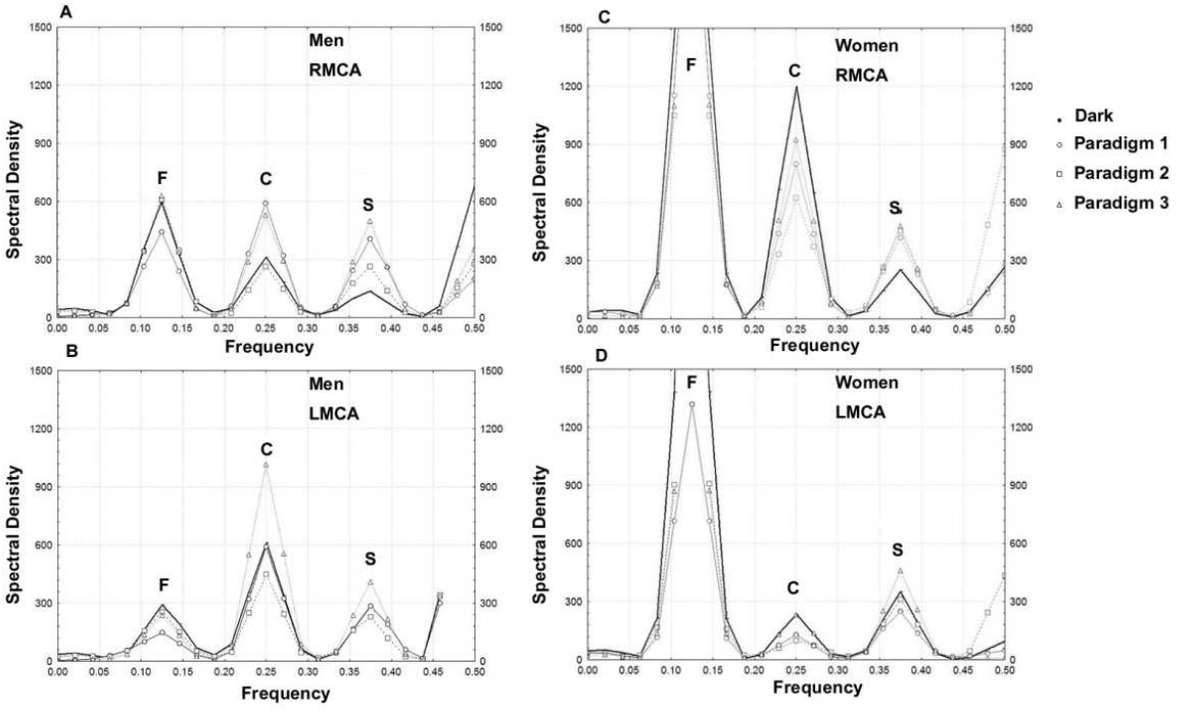

Figure 8. A-D). Shows the plots of spectral density estimates for dark, object (Paradigm 1) and facial (Paradigms 2-3) stimulation for the RMCA in men (Figure 8A), for the LMCA in men (Figure 8B); for the RMCA in women (Figure 8C) and LMCA in women (Figure 8D). (Source modified from: Njemanze PC. Laterality 2007, 12:31-49.).

In general, for all stimulations in both men and women there were three peaks designated as **F**-, **C**-, and **S**-peaks, representing the fundamental, cortical, and subcortical peaks, which occurred at regular frequency intervals of 0.125, 0.25, and 0.375, respectively. The spectral density peaks were analyzed for each gender separately to examine the effect of dark and stimulations at **C**- and **S**-peaks for the RMCA and LMCA, respectively. A one-way ANOVA with repeated measures for all four levels of STIMULATION (Dark, Paradigms 1-3) was used. This was followed by planned contrasts. In men, in the RMCA at C-peaks, there was a main effect of STIMULATION, $F(3, 18) = 4.2$, $MSE = 16804.3$, $p = 0.05$. Planned contrast revealed a category-specific face effect, $p = 0.05$, (Figure 8A). However, at the S-peaks there was only a

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marginal tendency for luminance effect. In men, in the LMCA at C-peaks, there was a main effect of STIMULATION, $F(3, 18) = 4.4$, MSE = 39947, $p = 0.05$. Planned contrast revealed a facial processing strategy effect, $p = 0.05$, (Figure 8B). However, at S-peaks there was no main effect of STIMULATION. In women, in the RMCA at C-peaks, there was a main effect of STIMULATION, $F(3, 18) = 4.2$, MSE = 38441.9, $p = 0.05$. Planned contrast revealed a luminance effect, $p = 0.05$ (Figure 8C). Similarly, at the S-peaks there was a marginal tendency for luminance effect. In women, in the LMCA at C-peaks, there was a main effect of STIMULATION, $F(3, 18) = 3.2$, MSE = 2791.4, $p = 0.05$. Planned contrast revealed a facial processing strategy effect, $p = 0.05$ (Figure 8D). However, at S-peaks there was no main effect of STIMULATION.

3.5. Confounding effects

The cardiovascular measures that could cause confounding effects were assessed using one-way analysis of variance (ANOVA). In men the heart rate during Paradigm 1 (71.9±10.6 bpm), Paradigm 2 (69.6±11 bpm), and Paradigm 3 (70.5±5 bpm) did not differ from resting baseline (67.5±9 bpm), ($p = 0.05$). Similarly, in women the heart rate during Paradigm 1 (76.9±9.8 bpm), Paradigm 2 (78.9±12 bpm), and Paradigm 3 (79.3±13.8 bpm) did not differ from resting baseline (76.9±9.6 bpm), ($p = 0.05$). In men the respiratory rate during Paradigm 1 (17.3±3.5 per minute), Paradigm 2 (19.9±5.7 per minute), and Paradigm 3 (16.9±3.7 per minute) did not differ from resting baseline (17.9±2.5 per minute), ($p=0.05$). Similarly, in women the respiratory rate during Paradigm 1 (19±4.5 per minute), Paradigm 2 (21±5 per minute), and Paradigm 3 (21±6 per minute) did not differ from resting baseline (19.3±6.4 per minute), ($p > 0.05$). The overall mean heart rate was 74 bpm and respiratory rate was 19 per minute. There was no significant difference between pre-test and post-test blood pressure, ($p > 0.05$). Similarly, there were no significant differences between the stimuli for heart rate, respiratory rate, and anxiety scores ($p > 0.05$). In other words, there were no changes in cardiovascular parameters and anxiety scores during the study. In post-test debriefings, participants described their initial condition as ''blank'', unaware of subtle emotional state, as they tried to focus attention on the imagery spot within the dark visual field. Women described the paradigms in greater detail than men. For example, on first prompt for description, most men described Paradigm 1 simply as a draught board or chess board, while most women described it as alternating black and white squares within a cube. For execution of Paradigm 3, both men and women reported sorting one part of the face at a time into place before proceeding to the next part, in other words, all followed a step-by-step approach. All rated themselves as not being anxious, and assessed themselves as having good performance, with no difficulty with task execution.

4. Discussion

4.1. Gender-related asymmetry during color processing

Overall, the gender-related differences could be summarized as follows: (1) in men, wavelength-differencing activity was enhanced at high luminance effect, conversely, in women, frequency-differencing activity was enhanced at low luminance effect. (2) In men, luminance

effect varied exponentially with wavelength-differencing activity, while in women, luminance effect varied logarithmically with frequency-differencing activity. (3) The physiologic range of MFV in the MCA territories for the relationship between luminance effect and wavelength-differencing activity in men, was narrower than that for frequency-differencing activity in women. The gender-related differences in color processing, which comprised right hemisphere wavelength-differencing in men, but left hemisphere frequency-differencing in women, suggest that, color processing followed the same rule of lateralization as other major cognitive functions, such as facial processing [26, 27] and general intelligence [30], which implicated the right hemisphere cognitive style in men, and left hemisphere cognitive style in women. Prior studies have suggested that, the right hemisphere was implicated in color processing [20, 21, 22] and the left hemisphere in color memory [61, 62]. Functional magnetic resonance studies demonstrated that memory for colors activated the same cortical regions associated with color perception in the left fusiform gyrus [63, 64]. This has led some investigators to suggest that, color memory is a constructive process reflecting the synthesis of features each of which are processed in the different cortical regions [65-67]. The functional integration of color processing and luminance effect could provide a model for the study of the functional integration of color processing and color memory within the color space.

However, the reason for gender-related cerebral asymmetry for color processing remains to be elucidated. It was suggested that, the neuroadaptation to the physical qualities of light as a wave and as quanta energy, pre-conditioned the right hemisphere for wavelength-differencing and left hemisphere for frequency-differencing, respectively. A light hypothesis for cerebral asymmetry was postulated, to infer that, the phenotypic neuroadaptation to the environmental physical constraints of light, led to phenotypic evolution and genetic variation of X-Y gene pairs that determined hemispheric asymmetry [12, 17]. The evolutionary trend is towards optimization of perception of the 'whole' environment by functional coupling of the genes for complementarity of both hemispheres within self, and between both genders [12, 17, 26]. The contralateral hemisphere processing of wavelength-differencing and frequency-differencing was as a result of the inverse relationship between wavelength and frequency. The results further demonstrate that, color processing was organized within cortico-subcortical circuits [11]. It could be presumed that, the neuronal assemblies processing light information as well as their blood flow supply, share analogous topological organization [26]. In men, the distribution of the S-peaks showed that dark elicited the least effect followed by White, Blue, Yellow and Red. This type of summation of responses, with distinction between achromatic and chromatic contrasts along orthogonal axis, on one hand, and between short wavelength and long wavelength on the other, could be presumed to be evidence for stimulus complexity topological organization based on wavelength, in the right hemisphere in men [12, 17, 26]. The latter extends from an area implicated in luminance processing to a much greater area for wavelength-differencing. Similar stimulus complexity topological organization, has been observed in studies involving facial and object stimuli in the right hemisphere in men [26]. In other words, there is a topological organization, based on category-specific stimulus complexity of the functions, located within the ventral temporal cortex of the right hemisphere in men. The latter would be compatible with the findings that thin stripes in V2 contain functional maps where the color of a stimulus is represented by the location of its response

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activation peak [52, 53]. Conversely, in the left hemisphere in women, at **C**-peaks, frequency-differencing separated the peak for high frequency color (Blue) from low frequency color (Yellow), but was parallel to the luminance axis. Hence, the differentiation was process-mapped only to frequency. Similar process-map model has been proposed for facial processing [26, 34]. It could be suggested that in the left hemisphere in women, there is a category-specific process-mapping system for retrieving color from memory. The latter would be consonant to the proposed distinct map for representation of color in memory [66, 67].

The present work may offer some indication on the neurophysiologic mechanisms underlying vasomotor changes during color processing, which have remained largely unknown until now. The cerebral arteries are innervated by postganglionic nitrergic nerves, originating from the ipsilateral pterygopalatine ganglion, that tonically dilate cerebral arteries in the resting condition [70]. The observed changes in MFV in response to visual stimulations have been related to imbalance between sympathetic vasoconstrictor traffic and vasodilator effects of nitric oxide (NO) [11, 22, 71]. The NO released postsynaptically, diffuses back across the synaptic cleft, to act on the presynaptic terminals, causing increases in presynaptic glutamate release [70, 72], which could account for ipsilateral LTP [11, 72]. Others contend that LTP induced in the visual cortex in animal models is NO dependent [72]. The LTP and LTD recorded non-invasively using *f*TCDS, have shown neuroplasticity during color processing over several hours [11], and hence could be applied to the study of stroke rehabilitation and monitoring of drug effects on N-Methyl- D-aspartate (NMDA) receptors.

Presuming that these mechanisms are present, it could be proposed that in men, wavelength-differencing within the right hemisphere by processes of cortical long-term depression (CLTD) and subcortical long-term potentiation (SLTP) [12, 17], occurred simultaneously with contralateral cortical short-term depression (CSTD) and subcortical short-term potentiation (SSTP) in the left hemisphere, marked by exponential decaying increase in synaptic strength that appears to involve NMDA receptors as well [12, 17, 73, 74], but decays after reaching the asymptotic levels of MFV (Figure 5A-B). Thus, it could be postulated that in men, in the contralateral left hemisphere, memory activation implicated 'exponential expansion' by CSTD and SSTP processes. On the other hand, in women, frequency-differencing within the left hemisphere occurred by processes of cortical long-term potentiation (CLTP) and subcortical long-term depression (SLTD) [11, 12, 17], concurrently, with ipsilateral cortical short-term potentiation (CSTP) and subcortical short-term depression (SSTD) in a selective area of the left hemisphere [11, 12, 17], characterized by logarithmic decaying decrease in synaptic strength that may also involve NMDA receptors, but decays after reaching the asymptotic levels of MFV (Figure 5C). Thus, in women, in the ipsilateral left hemisphere memory activation involved 'logarithmic compression' by CSTP and SSTD processes. Analogous synaptic and cellular activities have been observed in animal experiments [73, 74].

The clinical relevance of the observed profound gender-related differences in cortico-subcortical activation during color stimulation is yet to be fully realized. The plausible implications of the result that, in men, in the right hemisphere, SLTP and CLTD occurred with wavelength-differencing, and conversely, in women in the left hemisphere, CLTP and SLTD occurred with frequency-differencing, is not known. It could be suggested that, there could be a gender-

related difference in the effects of brain lesions in men and women. While in men, subcortical lesions of the right hemisphere may be associated with severe color deficits because of impaired SLTP processes for wavelength-differencing, in women, cortical lesions of the left hemisphere could result in more severe deficits due to inability to form CLTP processes for frequency-differencing. The onset of memory deficits may be characterized by loss of the capability to perform 'exponential expansion' in the memory area of the left hemisphere in men, or 'logarithmic compression' in the selective memory area of the left hemisphere in women. The latter may open the possibility of use of *f*TCD and *f*TCDS to determine early onset of memory deficits in patients with neurodegenerative disorders. Another practical clinical implication of the findings is that, in the structuring of tests of color vision, one eye has to be tested at a time, since binocular interaction may inhibit the responses from color processing neurons due to multiplexing responses in ocular dominance hypercolumns, rather than responses evoked from ocular dominance columns (blobs) [15].

In conclusion, gender differences in color processing implicated right hemisphere wavelength-differencing in men, but left hemisphere frequency-differencing in women. Future research using *f*TCDS technique should explore clinical applications of color processing in stroke rehabilitation, and monitoring of drug effects. Genetic and comparative animal experiments, as well as brain lesion studies are needed to further elucidate mechanisms of gender differences in color processing.

4.2. Gender-related asymmetry during facial processing

Facial perception occurred in the cortical region of the right hemisphere in men, but in the left in women. Similar observations have been made using transcranial Doppler [27], and electro-physiological techniques [28]. Similar gender-related hemisphere differences have been observed at the amygdale for emotionally related stimuli [29], and for performance-related processing [30-32]. Men showed a right lateralization during object processing, but women showed a right tendency or bilateral activation. The observed category-specific face effect was consistent with the concept of category-specific model, which posits a neural module for face category as distinct from non-face [59, 75, 76, 77]. However, others have advocated the existence of alternative models [33, 34].

The *f*TCD technique presumes that, the neuronal assemblies processing light information share analogous topological organization as their blood flow supply, then dark would elicit the least effect, followed by Paradigm 1, Paradigm 2, and Paradigm 3. This type of summation of responses related to stimulus complexity could be presumed as evidence for topological organization of these cortical areas in men. It has been posited that the latter extends from the area implicated in object perception to a much greater area involved in facial perception [26]. This agrees with the object form topology hypothesis proposed by Ishai and colleagues [33]. However, the relatedness of object and facial perception was process-based, and appears to be associated with their common holistic processing strategy in the right hemisphere. Moreover, when the same men were presented with facial Paradigm 3 requiring analytic processing, the left hemisphere was activated. This agrees in principle with the suggestion made by Gauthier that the extrastriate cortex contains areas that are best suited for different computations, and

described as the process-map model [34]. Therefore, the proposed models are not mutually exclusive, and this underscores the fact that facial processing does not impose any new constraints on the brain other than those used for other stimuli. It may be suggested that each stimulus was mapped by category into face or non-face, and by process into holistic or analytic. Therefore, a unified category-specific process-mapping system was implemented for either right or left cognitive styles.

Furthermore, in women, the neuronal assemblies may not have the same orderly topological arrangement as in men; rather the neurons involved in processing cone and rod vision were segregated within the right hemisphere cortical region. Hence, in women the right hemisphere responded to luminance effect and object perception, but showed no category-specific face effect. The latter arrangement explains the observed right lateralization for non-face Paradigm 1, but left lateralization for facial Paradigms 2 and 3. In other words, similar to men, women showed a tendency for holistic mechanism for processing object stimulus in the right hemisphere, but in contrast to men, they preferred the analytic mechanism for facial perception in the left hemisphere. Therefore, one major observed gender-related difference was that, while men employed a category-specific process-mapping system for facial processing in the right hemisphere, women used a category-specific process-mapping system for facial processing in the left hemisphere. In conclusion, it could be said that men and women use different hemispheres with complimentary mechanisms to perceive the essence of facial expressions that we come across in our daily life.

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