Effects of pathway-specific visual stimulation on perception

Ph.D. Thesis

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Contents

Publications related to the thesis

Kaposvári P, Bognár A, Csibri P, Utassy G, Sáry G.
Fusion and fission in the visual pathways.
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Transcranial stimulation of the orbitofrontal cortex affects processing of magnocellular information.
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Publications not directly related to the thesis

Csete G, Bognár A, Csibri P, Kaposvári P, Sáry G.
Aging alters visual processing of objects and shapes in inferotemporal cortex in monkeys. Brain Res Bull. 2015 Jan;110:76-83

Kaposvári P, Csete G, Bognár A, Csibri P, Tóth E, Szabó N, Vécsei L, Sáry G, Kincses TZ.
Audio-visual integration through the parallel visual pathways.
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Visual pathways

Our visual system analyses several aspects of our surrounding, the contrast and rapid changes in illumination, motion, form, depth and colour information. These features are processed by parallel visual pathways which originate from the parallel networks of retinal cells.

Here we give only a brief review of the major components of the human visual system. In the human retina two types of photoreceptors are responsible for vision, the rods and the cones. The rods contain only one type of pigment so they provide achromatic information for the visual system. These receptors are located in the parafoveal-peripheral part of the retina and play an important role in night vision; they have a very high sensitivity to light, these receptors can be activated by a single photon. Except for a few cases three type of cones can be found in the retina. The information collected by the cones play an important role in daytime vision. Each type has a different pigment which is sensitive to different parts of the visible light spectrum, thus the cones give the input for colour vision. The location of the cones is different from that of the rods, they are concentrated in the fovea where an approximately 1° area, the rod-free zone can be found.

The output of the retina is conveyed by the ganglion cells. Between the photoreceptors and the ganglion cells the retinal interneurons combine signals from several photoreceptors, but the electrical responses of ganglion cells depend critically on the precise spatial and temporal patterns of the light that reached the retina.

The parallel processing of the different visual features begins in the retina with parallel networks of ganglion cells. The most studied cell types are the magnocellular (M) ganglion cells and parvocellular (P) ganglion cells, however the function of the koniocellular and melanopsin containing ganglion cells is also important. The M can respond very rapidly to the stimulation. Because of their thicker axons and more myelin, the action potential conductance of these cells is really fast. The P ganglion cells have a relatively slow conductance speed (Callaway EM 2005). Another type of ganglion cells is the koniocellular cells. These cells are smaller than the P cells and their functions is not well known, but their play a role probably in colour constancy mechanism (Zaidi Q et al. 1997). The function of the melanopsin containing cells is outside of the scope of vision, they are playing an essential role in synchronizing the circadian rhythm and seasonal mood change (Hattar S et al. 2002; Paul KN et al. 2009). The M cells project to the deep two “M” layers, while the P ganglion cells project to the upper four “P” layers of the lateral geniculate nucleus (LGN)(Kaplan E et al. 1990). The koniocellular cells project to thin layers of the LGN in between the M and P layers (Hendry SH and RC

Reid 2000). Since the koniocellular cells are a heterogeneous group and the presented studies focus on the two other pathways there is no detailed description given of this population in this thesis. According to the projection layers of the LGN we call these parallel networks as M and P pathways. The cells in M layers are not able to respond to colour contrast, but are very sensitive to luminance differences. As low as 2% of luminance contrast can be perceived by the M cells, while the P layers have high colour contrast sensitivity, but start to respond over 10% of luminance contrast (Plainis S and IJ Murray 2005). There are also differences in the coding of spatial and temporal information. This is important since different spatial frequencies carry different aspects of the visual stimuli. The M has good temporal resolution, while the P pathway is responsible for the transmission of the fine details of visual information which build up from the high spatial frequency (HSF) elements, but is not sensitive to the information having high temporal resolution (Livingstone MS and DH Hubel 1987). While the P cells get information from the central visual field, the M cells are more sensitive to the stimuli presented at the periphery (Shapley R and VH Perry 1986). As mentioned earlier, another important difference between the two pathways is the speed of their transmission. The fast information conductance of the M pathway is the basis of detecting changes with high temporal frequencies, quick changes in the positions of objects and motion (Nassi JJ and EM Callaway 2009; Pokorny J 2011). Differences in conduction speed between the two pathways can be demonstrated as early as the LGN: information arriving via P has a 20 ms delay as compared to M, and this difference persists also in V1 (Maunsell JH and WT Newsome 1987; Nowak L et al. 1995; Schmolesky MT et al. 1998). The axons of the two pathways terminate in different sublaminas of the primary visual cortex. The axons of M cells reach sublamina 4Cα while the axons of P cells terminate in sublamina 4Cβ. The information from the above pathways feed into the extrastriate pathways, the dorsal and ventral pathway, respectively which convey information to the higher-order visual areas.

The dorsal pathway originates from layer 4B of the primary visual cortex and it reaches the middle temporal area (MT) in the parietal cortex directly or through the thick stripes of V2 and V3 (Dow BM 1974; Maunsell J and DC van Essen 1983; Livingstone MS and DH Hubel 1984). The cells of the blob and interblob areas of the primary visual cortex project also to V2, but to the thin stripes and interstripe areas. The cells of the ventral pathway project to the anterior part of inferotemporal area through several synapses in the V4. The function of these pathways was described as a “What/Where” model based largely on lesion studies of non-human primates and human subjects (Mishkin M and LG Ungerleider 1982). According to this model the ventral stream is responsible for object vision, colour perception

and the dorsal stream for spatial vision and action (Goodale MA and AD Milner 1992). The ventral stream is sampling the foveal and parafoveal inputs with high resolution and the cells of ventral or "What?" pathway are sensitive to increasingly more complex physical features of objects built up from the fine details of the visual stimulus. Cells in the inferotemporal cortex (IT), the final unimodal stage of the visual stream respond to complex, colourful stimuli (Desimone R et al. 1984). In the anterior portions of IT, in area TE, the complexity of the critical stimulus features further increases (Gross CG et al. 1972).These cells might be selective to shapes, i.e., they respond to, or rather respond more strongly to some shapes than to others (Gross CG et al. 1972; Desimone R et al. 1984; Tanaka K et al. 1991) and code object identity with strong invariance; despite changes in illumination, retinal position, viewing angle, size and other modifications of stimuli the pattern of activity in IT cortex is the same (Sáry G et al. 1993). It is also known that IT cells that respond to common visual features are grouped together into cortical columns (Tanaka K 1996).

M is regarded as the main input to the dorsal or "Where?" pathway that processes visuo-spatial information, motion and serves spatial attention (Goodale MA and AD Milner 1992; Mishkin M and LG Ungerleider 1982). The middle temporal areas (MT), medial superior temporal area (MST) and additional areas in the inferior parietal cortex respond selectively to spatial aspects of stimuli, such as the direction and speed of a moving stimulus. In the MT over 80% of the cells are directionally selective, the single cell activity can be linked to the motion and the lesions of the MT cause deficit in motion discrimination (Albright TD et al. 1984; Pasternak T and WH Merigan 1994; Britten KH et al. 1996). The cells in these areas also respond when the animal visually tracks a moving target and have an important role in guidance of grasping actions. For the dorsal pathway M provides very fast input: 6-9 ms after responses in V1, cellular activity can be detected in V3, in the MT, in the MST and in the frontal eye field (FEF) (Schmolesky MT et al. 1998).

Although the basis of the existence of the What? and Where? pathways is strongly supported by track-tracing and electrophysiological recordings investigating the selectivity of the neurons (Baizer JS et al. 1991; Kaas JH and DC Lyon 2007), nowadays more and more scientific results prove that the dissociation of the two pathways is not absolute; there are direct connections between the different stages of this parallel system (Van Essen DC 2005; Nassi JJ and EM Callaway 2009; Rosa MG et al. 2009). There are common target regions for both streams; visual signals processed in the dorsal stream might modulate activity in the ventral stream through feed-forward, lateral or feed-back connections (Distler C et al. 1993; Nowak LG and J Bullier 1997; Zhong Y-M and KS Rockland 2003; Rosa MG et al. 2009).

Direct connections to the inferior temporal area from the MT, MST, lateral intraparietal (LIP), orbitofrontal (OFC) areas were mapped (Distler C et al. 1993; Webster MJ et al. 1994), furthermore projections from the ventral stream to the dorsal are also known. There are direct projections from the V4 to the LIP and MT (Ungerleider LG et al. 2007). The complexity is further increased by the observed reciprocal connections between the two pathways, not only feedforward, but feedback connections running parallel with the feed-forward connections (Felleman DJ and DE Van 1991; Rosa MG el al. 2009; Pollen DA 2011). Furthermore, there are regions receiving converging inputs from the two pathways, for example the sulcus temporalis superior (STS) and also share regions in the prefrontal cortex (Pollen DA 2011; Distler C et al. 1993). These interactions between the two pathways are essential, although the dorsal pathway can independently execute simple visuomotor functions, the schematic information coded by the ventral pathway is essential for complex behavioural responses (Creem SH and DR Proffitt 2001). The interactions of the two pathways can explain those psychophysical results which prove the importance of the dorsal pathway in those functions which were solely connected to the ventral pathway, like object recognition and categorization. When rapid information acquisition is needed or the environmental conditions are not optimal for the stimulation of the ventral pathway (e.g., thick fog) the sharing of global information processed by the dorsal pathway can be essential. This is supported by those studies which prove that the achromatic, low spatial frequency (LSF) images with low contrast content and images projected on the peripheral part of the retina, which cannot activate the cone system sufficiently, can be as well categorized as images optimally stimulating the neuronal network of the ventral stream (Tootell RB et al. 1988; Fabre-Thorpe M et al. 2001; Macé MJM et al. 2005; Delorme A et al. 2010; Macé MJ-M et al. 2010). Electrophysiological results show that the first part of the activity of IT cells reflect global features (Sugase Y et al. 1999; Tamura H and K Tanaka 2001) and only the later part of the responses, after ~50 ms, carries information about fine details (SugaseY et al. 1999).

It seems to be clear that the different stimulus aspects can be processed in different parts of the visual system and these interactions can improve our perception. To clearly understand the interactions between the parallel pathways and their role in the integration of other modalities in order to provide a stable representation of our surrounding, however, we have to stimulate the pathways selectively.

Selective stimulation of visual pathways

We know the function of the visual pathways from lesion studies using non-human primates (Mishkin M and KH Pribram 1954; Schiller PH 1993; Behrmann M and R Kimchi 2003). The investigations on human subject with lesions in the temporal and parietal areas and later healthy subjects using imaging techniques confirmed that this organization also exists in the human visual system (McNeil and Warrington 1993; Goodale MA et al. 1994; Moscovitch M et al. 1997). For testing the detailed function of the pathways we have to segregate them. There are different techniques to stimulate selectively the M and P pathways, since the two pathway are sensitive for different features of the stimulus.

As it was described in the introduction the M pathway is sensitive to achromatic differences in luminance and these cells can detect the LSF information with low contrast content. Furthermore, images projected to the peripheral retina almost exclusively stimulate the rod system. The P pathway is sensitive to the colour contrast and HSF -this information is collected from the central visual field.

The two pathways can be segregated by modulating the aforementioned parameters of the presented stimuli. An achromatic image containing only HSF information will stimulate the P system (Ferrera VP et al. 1992), while if this high spatial information is filtered out from the achromatic stimuli only the M pathway can process the remaining LSF content (Tootell RB et al. 1988; Merigan WH and JH Maunsell 1993). These differences in the spatial frequency tuning of the two pathways has been used in several studies investigating the parallel processes in different visual tasks (Vuilleumier P et al. 2003; Bar M et al. 2006; Kveraga K, J Boshyan, et al. 2007; Butler PD et al. 2008; Laycock R et al. 2009; Denison RN et al. 2014).

The other possibility to selectively stimulate the M pathway is to reduce the luminance contrast of an achromatic stimulus under the threshold of the P system (Pokorny J and VC Smith 1997; Valberg A and I Rudvin 1997; Kachinsky ES et al. 2003). When using a simple stimulus as a disc the contrast can be calculated by the Michelson contrast formula using the luminance values of the stimulus and background. Since the M pathway is really sensitive for luminance contrast the P system can be selectively stimulated by stimuli which contain colour contrast, but no luminance contrast. These kinds of stimuli without luminance differences are called isoluminant (Gegenfurtner KR and DC Kiper 2003; Bushnell BN et al. 2011; Skottun B 2013). To create isoluminant stimuli for stimulating the P system heterochromatic flicker photometry (HFP) can be used. In this test different colours. e.g., red and green alternate as

brief flashes. For a very narrow range of luminance values, the two stimuli reach the isoluminant state, the two colours fuse and the perception of flashing caused by the luminance differences disappears. Using the measured luminance values the parvocellular system can be stimulated selectively (Kveraga K, J Boshyan, et al. 2007).

Fusion and fission in the visual pathways

Although the analysis of our surrounding seems to be an effortless and instantaneous process it requires tremendous amount of computation and the interplay of different cortical areas coding different visual features. As it was described earlier, colours, motion, depth and forms are processed by parallel pathways sending information to different cortical areas. This raises a question, namely, where the coherent conscious experience of the visual world comes from. The visual process is not completed with the coding of the different features of objects because without the fundamental cognitive functions as recognition and categorization we cannot spot the relevant information and cannot do efficient actions in the world. When viewing a scene containing different objects, the question is how the brain correctly pairs colour and shape, segregate different patterns and elements of the visual input to allocated objects. This is the main question of the so called binding problem. However, to build up a coherent perception of our surrounding it is not enough to understand the interactions in the visual domain, because the simultaneous presence of other modalities, auditory, chemical and haptic information can influence our perception as well. Previously the different sensory modalities were investigated separately and only the specific sensory areas were localized in the human brain, for example the visual cortex in the occipital lobe, auditory cortex in the temporal lobe, and the region specific for somatosensory information processing in the postcentral area. The interactions of these information enables us to operate efficiently in everyday life. The mechanism binding the different modalities together is the multisensory integration which allows to integrate or segregate the simultaneously incoming sensory signals based on the degree of their temporal, spatial and semantic congruence. Furthermore, the multisensory integration provides effective acquisition, decreasing sensory uncertainty and enables the generation of appropriate behavioural responses if one sense is inadequate. It can drive our attention, thus shortening reaction times. Multiple simultaneously presented sensory stimuli can lead to faster reaction times than responses to the same stimuli presented in isolation (Hershenson M 1962). The simultaneously presented stimuli can also enhance orientation discrimination (Stein BE et al. 1988; Stein BE et al. 1989) and improve target detection (Frassinetti F et al. 2002; Lovelace CT et al. 2003) . For example, the intensity of a light stimulus can be perceived greater when it is presented with a sound (Stein BE and MT Wallace 1996) and judgments of stimulus features as speed and orientation are often more accurate when information is available from multiply senses (Clark B and A Graybiel 1966; Manabe K and H Riquimaroux 2001; Soto-Faraco S et al. 2003). It has also an important role

in speech processing with the subtraction of inadequate spoken signals. e.g., in a noisy party the certainty can be greatly enhanced when the listener can see the speaker's face (Sumby WH and I Pollack 1954).

As it was mentioned multisensory integration improves our perception except in those situations when the incoming information is incongruent. This information can change our percept qualitatively (McGurk and ventriloquist effect) and quantitatively (double flash and flash fusion illusion). In the McGurk illusion the simultaneously presented conflicting lip movements can change speech segments that is heard, in the ventriloquist effect the perceived location of a sound shifts toward the visual source. In the double-flash illusion short sounds and brief flashes are simultaneously presented. Shams and her colleagues provided the first evidence that an auditory stimuli can quantitatively change our perceptual experience (Shams L et al. 2000). When one flash is presented with two tones, the second tone can evoke the perception of an illusory second flash (Shams L et al. 2000). Furthermore, when two flashes are presented with one tone the integration of the sensory events can induce the perception of two flashes fusing into one (Andersen TS et al. 2004; Watkins S et al. 2007).

Neurophysiological studies in nonhuman primates and -with the development of the non-invasive brain imaging techniques (fMRI, EEG, MEG)- more and more human studies provide the existence of a widespread system responsible for the integration of multisensory events. The integration of the simultaneously presented sensory inputs can occur in the heteromodal areas in the brain, regions, which receive more than one sensory input or in the multimodal areas as well where we can find multimodal neurons (Chavis DA and DN Pandya 1976; Benevento LA et al. 1977).

Since the discrimination of the summarized activity of the heteromodal (coactivating unimodal neurons) and multimodal areas (multimodal neurons) using non-invasive techniques is difficult, the animal models are necessary to understand this complex neuronal coding. The first multisensory neurons were described in the superior colliculus (SC) where the two-third or more of the neurons show multisensory profile. In adult cats, visual, auditory, and somatosensory inputs are integrated on the SC neurons. Multisensory SC neurons give rise to responses that are significantly different from those that are predicted on the basis of a simple summation of these inputs (Meredith MA and BE Stein 1986, 1986). Depending on the spatial and temporal relationships among the stimuli, dramatic response enhancements or depressions can be produced (Stein BE et al. 1994). Their modulated activity can show supraadittional responses where the firing rate of the neurons for the summed unimodal stimuli is lower than the activity for the multimodal inputs, or the opposite when one of their inputs causing

inhibition and the response of the neurons show subadditional characteristics (Stein BE and TR Stanford 2008). These neurons provide output pathways to the brainstem and spinal cord controlling the animal's behaviour (Meredith M et al. 1992; Wallace MT et al. 1993; Wilkinson LK et al. 1996). However, the development of the multisensory characteristic of the SC neurons depends on the inputs arriving from the cortical association areas: the anterior ectosylvian sulcus and rostrolateral suprasylvian sulcus (Jiang W et al. 2007; Jiang W et al. 2001). The fact that the cortical association areas have a crucial role in the multimodal integration further strengthened the necessity for the understanding of the cortical mechanisms.

In the cortex early tracing studies revealed connections between the unimodal areas and the higher order association cortical areas such as the ventral intraparietal areas, central premotor cortex, superior temporal polysensory region, and later single-unit registrations confirmed the presence of multimodal neurons in these areas (Jones E and T Powell 1970; Bruce C et al. 1981; Macaluso E and J Driver 2003; Graziano MS et al. 2004; Barraclough NE et al. 2005; Sadaghiani S et al. 2009). These studies agreed that the multisensory events of our environment are initially processed in segregated sensory-specific areas, but then they activate common, multisensory representations in associative cortices.

Neuroimaging studies provided evidence of this sensory convergence in humans. When stimulating selectively with one or another modality the specific sensory areas were activated, but during the multisensory stimulation the activation in the intraparietal sulcus (IPS), inferior parietal lobule, posterior part of the STS, and ventral premotor cortex was higher (Bruce C et al. 1981; Duhamel J-R et al. 1998; Bremmer F et al. 2001; Beauchamp MS, BD Argall, et al. 2004). The STS has an extensive connectivity network with the visual system, auditory cortex, posterior parietal region, and prefrontal areas. The multisensory neurons in the STS can be activated with the simultaneously presented visual, auditory and somatosensory information (Desimone R and CG Gross 1979). The integrative function of this region is important in the integration of different types of information within visual modality (visual form and motion information, (Oram M and D Perrett 1996; Beauchamp MS et al. 2003) object identification (Calvert GA 2001), learning associations between visual and auditory features (Messinger A et al. 2001; Naya Y et al. 2003; Tanabe HC et al. 2005); even if they are arbitrary like letters and the associated sounds (Beauchamp MS, KE Lee, et al. 2004). The intraparietal multisensory area gives output about the spatial information of the target to the prefrontal, premotor and visuomotor cortices thereby enabling the coordinated

eye, reaching and hand movements and the protection of the entire body (Duhamel J-R et al. 1998; Cappe C et al. 2012; Guipponi O et al. 2013; Cléry J et al. 2015).

The development of whole brain neuroimaging techniques in the entire brain quickly led to the discovery that regions traditionally considered as being sensory-specific areas also show multisensory activation. A haptic object recognition task can activate the occipital cortex and there is a functional overlap between the visual and tactile related brain activity during haptic object recognition. Not only the ventral parts, but the dorsal occipital regions are also involved in the visuo-haptic processing, this area is activated during tactile spatial discrimination task (Sathian K et al. 1997; Amedi A et al. 2001; Stoesz MR et al. 2003). Visual and tactile costimulation can activate the primary auditory cortex (Kayser C and NK Logothetis 2007; Lakatos P et al. 2007) and during synchronous audio-visual stimulation supra-additive responses in the primary visual cortex are in line with the change in our perception (Calvert GA 2001; Shams L et al. 2005).

Although we know more and more about the distributed networks enabling the integration of multisensory signals originating from the same event, how the different types of information is integrated in this multitude of integration sites remain unclear: spatial (where?), temporal (when?), object-related (what?), information may be integrated at different levels of the cortical hierarchy (for example: in the primary sensory cortices, higher order association regions or prefrontal cortex) (Werner S and U Noppeney 2010).

For investigating how the different stimulus aspects influence the audio-visual integration and the perceptual outcome we used the double flash illusion for specific stimulation of the dorsal and ventral pathway. The incongruency of briefly presented visual and auditory information can influence the visual perception causing illusions (Shams L et al. 2002). Several studies demonstrated cortical and subcortical activity differences behind the veridical and illusory perceptual outcome. Studies using fMRI revealed that there is an enhanced activity in the V1 during the audio-visual co-stimulation and this activity was increased during the perceptual outcome. In this study the authors demonstrated that the activity of the V1 follows more the subjective perception than the physical stimulation. However not only the V1 activity differed between the illusory and non-illusory percept, but the authors found evidence of the involvement of STS an SC in the integratory mechanisms (Watkins S et al. 2006). During this experiment the balanced stimulus presentation requires another incongruent combination in which two briefly presented flashes are accompanied by a single beep. The finding during the flash fusion condition was in line with the previous findings, when only single flash was used and reported that the activity was decreased in the

V1 (Watkins S et al. 2007). The disadvantage of these studies was the bad temporal resolution of the fMRI, thus we do not know whether the V1 is responsible for the integration or the STS which can modulate the V1 activity by feed-back connections. Investigations providing good temporal resolution, like magnetoencephalography (MEG) experiments have shown more extensive activity differences over occipital, parietal and anterior regions giving a potential explanation for the generation of illusion (Shams L et al., 2005). EEG studies examining the time-frequency domain have found that during the illusion oscillatory and induced gamma band responses were significantly higher, and audio-visual interactions were supra-additive (Bhattacharya J et al. 2002). The EEG experiments have shown that during the illusory flash perceptual activity was modulated strongly and with short latency values in trials where the illusory flash was perceived (Shams L et al. 2001; Watkins S et al. 2006; Mishra J et al. 2007; van Erp JB et al. 2014). Also, it has been found that the activation changes observed when the illusion was perceived were similar to those observed after real flashes, which finding proves that the integration of auditory stimuli can enhance the activity of those neurons which processed the visual information due to the very rapid interaction between auditory and visual areas, which enables the sensory system to process the presented stimuli as if they belonged to the same event (Mishra J et al. 2007; Mishra J et al. 2008; Roseboom W et al. 2013). These studies suggest that such processing of bimodal information could be based on communication between the primary visual cortex, superior temporal sulcus and primary auditory cortex (Mishra J et al., 2008; Watkins S et al., 2006; Watkins S et al., 2007).

Since the cortical regions belong to the two pathways processing different aspects of visual information it would be interesting to know how the two visual pathways contribute to the information exchange between the primary sensory cortices and the association areas. The physiological evidences for involvement of the ventral pathway in multisensory integration originated from the direct measurements of the neuronal activity of the IT using audio-visual stimulation in discrimination (Iwai E et al. 1987; Ringo JL and SG O'Neill 1993). In human studies the audio-visual integration mediated by the parvocellular pathway was proven in a tasks using metacontrast masking or short-wavelength visual stimuli, processed selectively by the P pathway: the co-stimulation with sound decreased the response latencies, increased the visibility of flashed targets and improved the orientation discrimination ability (Leo F et al. 2008; Jaekl PM and LR Harris 2009). The information of the ventral stream plays important role in object identification and in the formation of associations between complex objects and sounds (Calvert GA et al. 2001; Tanabe HC et al., 2005; Suied C et al. 2009), moreover the projections of the IT to multimodal areas like STS and ventrolateral prefrontal cortex plays an

important role in audio-visual speech perception (Bernstein LE and E Liebenthal 2014). There are several evidences for the effective involvement of the dorsal pathway in the crossmodal integration as well. Multisensory neurons and multisensory areas are more commonly assigned to the dorsal pathway; multisensory integration has been described in the posterior parietal cortex, temporal parietal association areas, right temporo-parietal junction and in the medial superior temporal area (Leinonen L et al. 1980; Andersen RA and CA Buneo 2002; Pasalar S et al. 2010; Huang R-S et al. 2012). Furthermore, damages in the different areas of the dorsal pathway can affect the integration of non-visual modalities with the visual events (Pisella L et al. 2009). This is in accordance with observations suggesting that enhanced visual detection can be attributed to the magnocellular system, as proposed by former and recent studies (Meredith MA 2002; Jaekl PM and S Soto-Faraco 2010). Although we can associate the results to the different pathways according to their known functions, the studies mentioned above used high contrast or complex stimuli, even in the double flash paradigm; high contrast discs or rings projected to the periphery were used as visual stimuli, so the contribution of the dorsal pathway or ventral stream to the multisensory integration is still unknown.

In this study, we investigated how the magno- and parvocellular pathways contribute to the development of the double flash and flash fusion illusions to understand how the different visual features processed by the parallel visual pathways and their different temporal characteristics can influence our perception when integrating with auditory information. Since the two visual pathways have different temporal resolutions they could be involved to a different extent in the two illusions in other words, different neuronal population of the occipital cortex and STS, or the areas could receive information through different pathways depending on the type of integration.

We used pathway-specific visual stimuli simultaneously with pure, meaningless tones for investigating the integration processes. We hypothesized that the parallel pathways in accordance to their different contribution in perception may play different role in multisensory integration which can be detected by the differences in the number of reported illusory percepts. Multimodal stimuli – especially in temporal context - are frequently used to gain better understanding of how different modalities can interact and influence our perception. The double flash and fusion illusions are appropriate phenomenons to investigate the temporal aspect of audio-visual integration. Still, it is not clear which mechanisms of the visual system contribute to these findings. The next logical step in understanding the neuronal background of the illusory flash phenomenon could be an approach where we make a functional distinction between the cortical pathways. We are aware of the fact that this distinction

(especially at higher levels than the primary visual cortex) is less and less valid, but this might serve as a good working frame for collecting more data about the double flash and flash fusion and the underlying mechanisms.

Methods

Subjects

Thirty-four healthy naive volunteers participated in the study. Seventeen (12 females; mean age: 22.6 years) of thirty-four subjects participated in the test with central visual stimulation, and the other seventeen subjects (13 females; mean age: 22.2 years) with peripheral visual stimulation. They had normal or corrected to normal vision and normal hearing, with no known neurological disorders. Their colour vision was tested by Ishihara colour perception test. Each participant signed an informed consent before the test. The experiment fulfilled the requirements of the Ethical Committee for Experimental Procedures of the University of Szeged.

Stimuli and procedure

Subjects were seated in a sound-attenuated dark room. Their heads were rested on a chin and forehead support to ensure a fixed viewing distance. The eyes of the subjects were 57cm away from the computer screen and the speakers; from this distance 1 cm on the monitor corresponds to 1° of visual angle. The stimuli were presented on a CRT monitor (ViewSonic PF815). The diameter and the resolution of the screen were 21’ and 800 x 600 at 60 Hz, respectively. The two computer speakers were positioned on both sides of the monitor, symmetrically, at 25° eccentricity from the fixation point. Subjects had to fix their gaze at the middle of the monitor, thus the size and position of the visual stimuli were held constant on the retina. A disc subtending a visual angle of 1.5˚ was displayed in a central or peripheral position as visual stimulus for the two groups of the subjects (central and peripheral stimulation, respectively). All stimuli were presented on a uniform green background (8.9 cd/ m^2). In the peripheral task a fixation point was placed in the middle of the screen and the stimulus was presented at 9.25˚ eccentricity (Watkins S et al., 2006). In the central task, the disc was presented in the middle of the screen without using fixation point.

We used four conditions with high contrast (HC) with white disc (63 cd/m^2, contrast 75%), low contrast (LC) with grey disc (9.7 cd/m^2, contrast 9%), subjective isoluminant (S-

iso) and (P-iso) physically isoluminant (8.9 cd/m2, without contrast difference) with red disc in both positions (Fig. 1).

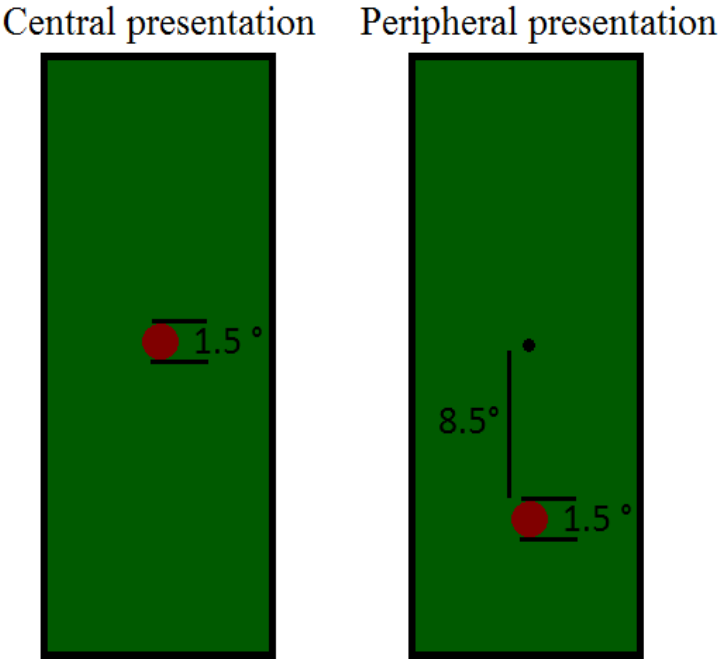

Figure 1. Illustration of stimulus presentation in central and peripheral isoluminant conditions. In both positions the visual angle of the presented disc was 1.5° on a green background. In the high contrast condition the contrast was 75 %. In the low contrast condition the contrast was 9 %. In the isoluminant condition a red disc was presented on the background. The little dark point in the centre of the panel represents the fixation point in the peripheral condition.

In the above mentioned experiments stimuli of the same size were used with high contrast. So we created a high contrast condition to make our results comparable with earlier findings. We chose a relatively high contrast value to exclude the big variability between subjects in the control condition. Low contrast stimulus was used to drive the M pathway. The contrast values were calculated using the Michelson equation:

$$\frac{I_{\max} - I_{\min}}{I_{\max} + I_{\min}},$$

where I_{max} and I_{min} represent the highest and lowest measured luminance values, respectively.

We used two types of isoluminant conditions. Both of them contained colour information, thus they drove the P pathway. The subjective isoluminant stimulus is known for driving most selectively the P pathway (Skottun, 2013), but because of the inter individual

differences regarding the point of isoluminant level the measured luminance differences between the background and stimuli showed different contrast values so we used a physical isoluminant condition as well containing only colour contour between the stimuli and the background.

To measure the subjective isoluminance level of the red disc compared to the green background we used the method of heterochromatic flicker photometry (HFP). Red and green discs were reversed at 14 Hz (Kveraga K et al., 2007) on a grey background. The size and position of the disc was the same as we used for the experiment. We created a range of red intensities and presented them one by one to the participants during the HFP test. Since isoluminance values change across the retina (Bilodeau L and J Faubert 1997), the test was performed both in the central and in the peripheral retina location as well. The luminance value of the green was the same as the background used in the experiment. The subjects viewed the display binocularly and were asked to choose the intensity value of red where the colours fused and no flicker was perceived. The isoluminant point was the average of at least three consecutive, independent measurements.

The central and peripheral tasks contained four blocks (four main conditions, HC, LC, S-iso, P-iso), and followed each other randomly to reduce the chance of fatigue or learning. One block contained 6 subconditions: 6 variations of flashes and tones (one flash, one flash with one tone, one flash with two tones, two flashes, two flashes with one tone, and two flashes with two tones). One subcondition consisted of 40 repetitions of trials, thus one block contained 240 semirandomly presented trials.

In the intertrial interval a gray background was presented for 1000 ms. The presentation of the trials started with the colour change of the background to green which was matched in luminance to the previous one. On this background, after 200 ms one or two discs were presented successively for 1 frame (17 ms) with one or two tones, according to the given condition. The stimulus onset asynchrony (SOA) between two flashes was 85 ms. The duration of the tones (3.5 kHz, 70 dB SPL) was 10 ms and the first one was presented at the same time as the first flash. The previously mentioned experiments used auditory and visual stimuli slightly shifted in time but as reported the two designs with simultaneously presented or shifted stimuli resulted only in slight differences (Watkins S et al., 2007).

After the presentation of flashes and tones the subject was asked to decide whether one or two discs were displayed independently of the tones and press the left (one flash) or right arrow (two flashes) button on the keyboard with the dominant hand as quickly and accurately as he or she can. After the subject pressed a button, the isoluminant grey background (8.9

cd/m^2) appeared as an intertrial interval for 1000 ms (Fig. 2). Feedback was not provided about the correctness of the response.

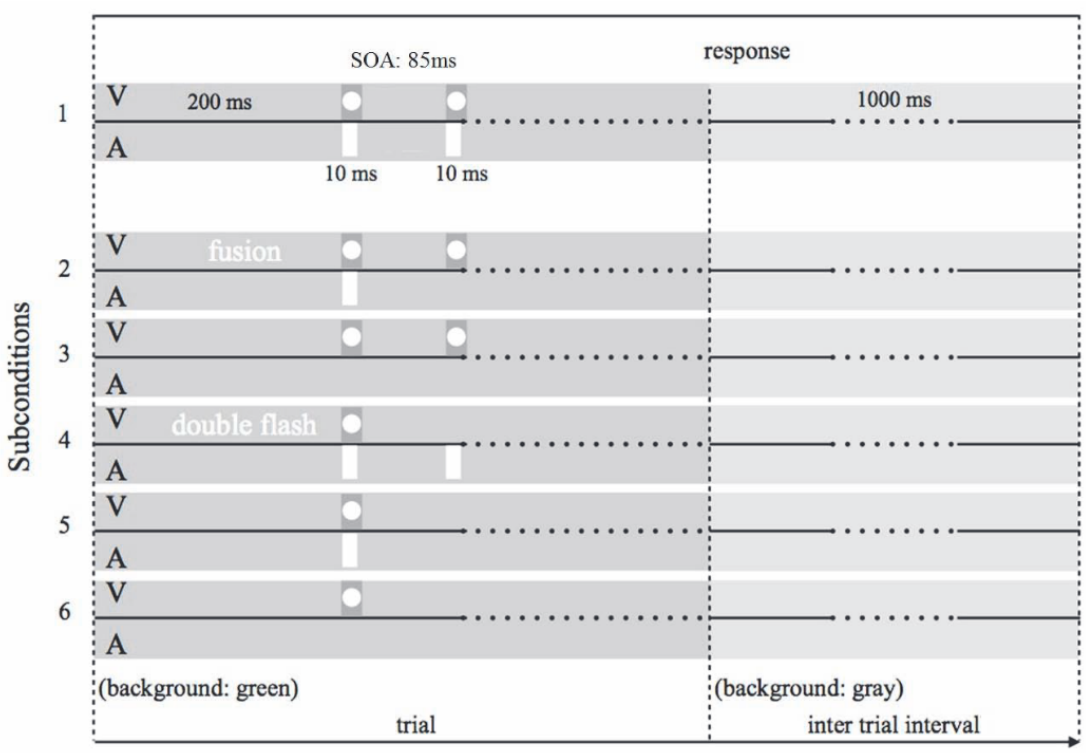

Figure 2.

Design of the task. Stimuli were presented on green background according to the subconditions. 1: two discs were presented with two tones; 2: two discs were presented with one tone; 3: two discs were presented without any tones; 4: one disc was presented with two tones; 5: one disc was presented with one tone; 6: one disc was presented without any tones. The duration of the tone was 10 ms and the SOA for the two tones was 85 ms. The duration of the visual stimuli was 17 ms and the SOA for the visual stimuli was 85 ms. After the response an isoluminant grey background was presented for 1000 ms.

Analysis

Signal detection theory was used to analyse the behavioural results. The rationale behind this is that this way we can verify that the illusions are caused by changes of perceptual sensitivity rather than by the general response bias. When a stimulus is presented, the observer must accurately perceive the stimulus as either a signal or non-signal; but the observer also sets a criterion by which he/she will make these decisions. The sensitivity of the observer refers to his perceptual ability to distinguish the signal from the background noise. In the

signal detection model the noise can be internal or external regarding the observer. This noise is a presumably normally distributed random variable. During the presentation of a signal, the signal plus noise distribution is shifted along the sensory dimensions (Fig. 3). Using this method one can describe the sensitivity of the subjects toward the visual stimuli during the process of decision. The sensitivity is expressed as d' = z(H) - z(F), where d' is sensitivity, and z is the inverse cumulative normal. Correct identification of the second flash was recorded as a 'hit' (H); when the subject reported one flash instead of two, it was recorded as a 'miss'. When one flash was reported as two, we accepted it as a 'false alarm' (F) and the correct identification of one flash was accepted as a 'correct rejection'. To calculate the d' value for control we used two sub-conditions without tones (one flash and two flashes). For fusion we used two sub-conditions with one tone (one flash with one tone and two flashes with one tone) and for double flashes we used two sub-conditions with two tones (one flash with two tones and two flashes with two tones).

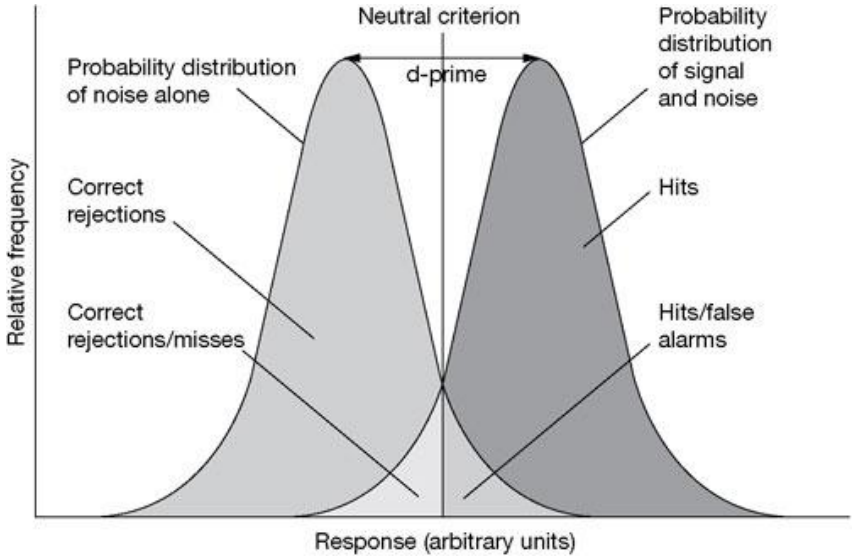

Figure 3.
(https://www.nature.com/article-assets/npg/nrneurol/journal/v4/n6/images/ncpneuro0794-f1.jpg)

To see the power of illusions we compared the control d' value to the d' for fusion or double flash using paired t-test (Watkins S et al., 2006) with Bonferroni correction in each condition. Thus, we accepted results as significant when the $p<0.025$. Since the strength of the illusions are characterised by this difference, we used these values to test the variance between the conditions with one-way repeated measures ANOVA in central and peripheral conditions. We used Bonferroni as a post-hoc test.

We calculated a criterion (C) to indicate response bias with the expression: C=-[z(pH)+z(pF)]/2 (Macmillan NA and CD Creelman 2004).

Results

The detailed data are collected in Table 1, 2, 3 and 4. Here we describe only the relevant statistical results. The criterion showed significant positive bias for fusion and negative bias for double flash compared to control criterion in all condition. This shows that one tone biased the participants to report one flash instead of two for fusion, and two tones biased them to report two instead of one for double flash illusions.

Central condition		C mean	SEM	d' mean	SEM
	sensitivity	-0.725	0.080	3.376	0.344
HC	fusion	-0.019	0.154	2.944	0.301
	double flash	-1.751	0.211	1.707	0.418
	sensitivity	-0.442	0.148	2.904	0.290
LC	fusion	0.318	0.114	2.496	0.295
	double flash	-1.556	0.162	1.616	0.375
	sensitivity	0.101	0.184	3.137	0.262
S-iso	fusion	0.889	0.127	2.078	0.323
	double flash	-0.947	0.226	2.139	0.326
	sensitivity	-0.324	0.134	3.325	0.346
P-iso	fusion	0.348	0.146	2.586	0.331
	double flash	-1.549	0.159	2.174	0.431

Table 1. This table shows means and standard errors of d’ values and Criterion in the condition with centrally presented stimuli. HC: high contrast, LC: low contrast, S-iso: subjectively isoluminant, P-iso: physically isoluminant.

Peripheral condition		C mean	SEM	d' mean	SEM
	sensitivity	-0.338	0.173	3.448	0.268
HC	fusion	0.613	0.213	2.602	0.353
	double flash	-1.918	0.152	1.563	0.248
	sensitivity	-0.560	0.156	2.910	0.262
LC	fusion	0.482	0.157	3.169	0.400
	double flash	-1.759	0.156	1.740	0.246
	sensitivity	-0.176	0.187	3.118	0.322
S-iso	fusion	0.428	0.169	2.564	0.355
	double flash	-1.609	0.171	1.682	0.254
	sensitivity	0.022	0.175	2.684	0.285
P-iso	fusion	0.776	0.163	1.994	0.275
	double flash	-1.885	0.168	1.214	0.271

Table 2. This table shows means and standard errors of d’ values and Criterion in the peripheral conditions. HC: high contrast, LC: low contrast, S-iso: subjectively isoluminant, P-iso: physically isoluminant.

Central condition		t(16)	p values
HC	fusion	4.715	<0.001
	double flash	4.989	<0.001
LC	fusion	5.178	<0.001
	double flash	6.673	<0.001
S-iso	fusion	5.492	<0.001
	double flash	5.311	<0.001
P-iso	fusion	4.206	<0.001
	double flash	6.729	<0.001

Table 3. This table shows the results of the statistical comparison concerning the criterion levels in the central condition. HC: high contrast, LC: low contrast, S-iso: subjectively isoluminant, P-iso: physically isoluminant.

Peripheral condition		t(16)	p values
HC	fusion	6.084	<0.001
	double flash	6.250	<0.001
LC	fusion	4.760	<0.001
	double flash	7.324	<0.001
S-iso	fusion	3.584	<0.01
	double flash	5.618	<0.001
P-iso	fusion	4.275	<0.001
	double flash	9.050	<0.001

Table 4. This figure shows the results of the statistical comparison concerning the criterion levels in the peripheral condition. HC: high contrast, LC: low contrast, S-iso: subjectively isoluminant, P-iso: physically isoluminant.

Central presentation: in the high contrast condition, no significant fusion effect was shown, $t(16)=1.71$, $p=0.10$), but there was a significant double flash effect after Bonferroni correction, $t(16)=5.06$, $p<0.001$ (Fig. 3). In the low contrast condition, no significant fusion effect was shown, $t(16)=2$, $p=0.05$, but there was a significant double flash effect, $t(16)=4.29$, $p<0.001$, with the same test (Fig. 3). In the subjective isoluminant condition, both significant fusion, $t(16)=5.167$, $p<0.001$, and significant double flash effect, $t(16)=3.72$; $p<0.01$, were shown (Fig. 3). In the physically isoluminant condition, both illusions, the fusion, $t(16)=2.771$, $p<0.05$, and also the double flash, $t(16)=2.74$, $p<0.05$, were significant (Fig. 3).

The repeated measures ANOVA of the difference scores for the central conditions did not reveal any significant differences between the different conditions (high-contrast, low contrast, subjectively or physically isoluminant), either for the fusion ($F(2.676, 42.81) = 1.748$, $p=0.17$) or for double flash ($F(2.472, 39.55) = 1.287$, $p=0.29$) illusions (Fig. 4).

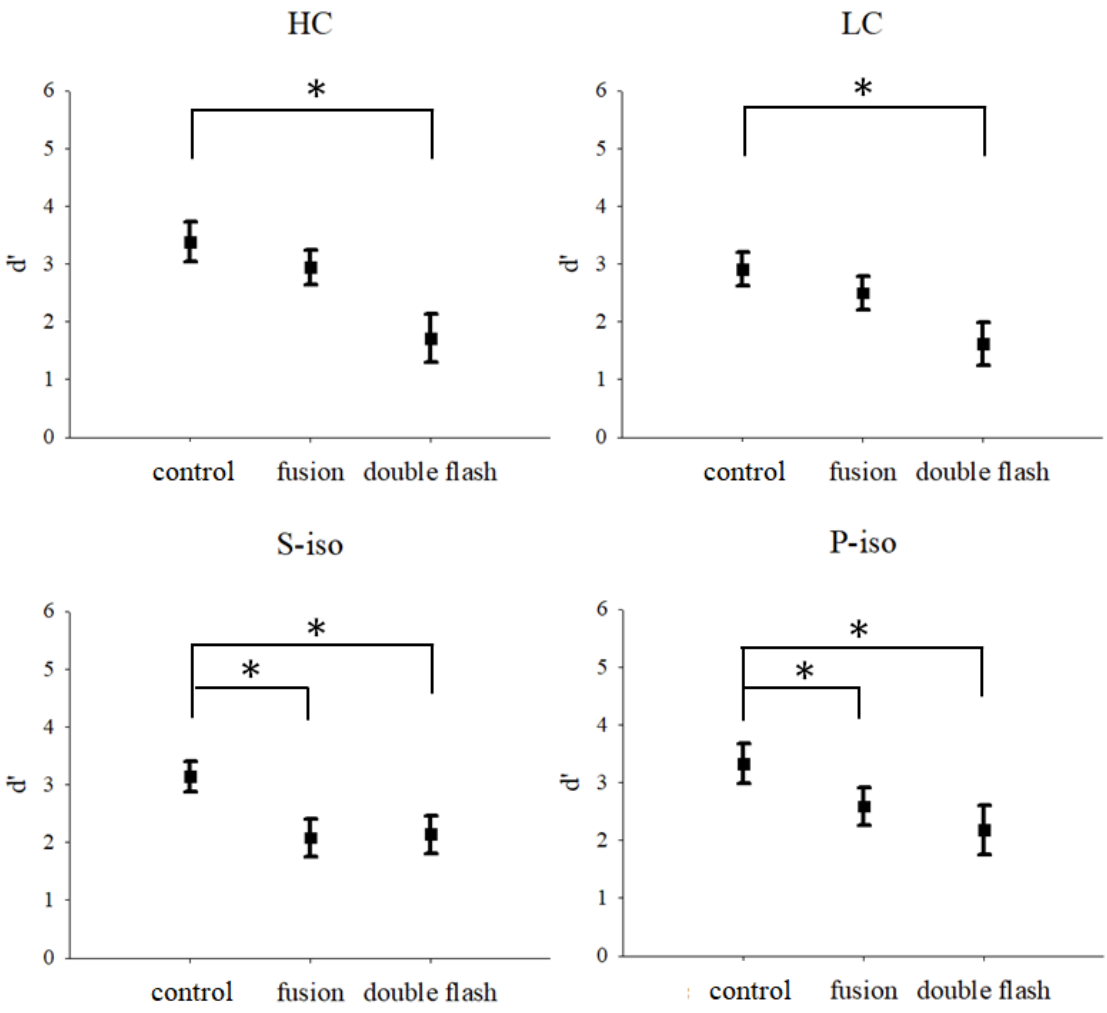

Figure 3.

Results of the psychophysical test in the central condition

The diagram shows the means and standard errors of d' values and the significant results of the paired t-test in the central conditions. Significant changes are indicated by asterisks, n=17. Panel HC: high contrast, panel LC: low contrast, panel S-iso: subjectively isoluminant, panel P-iso: physically isoluminant.

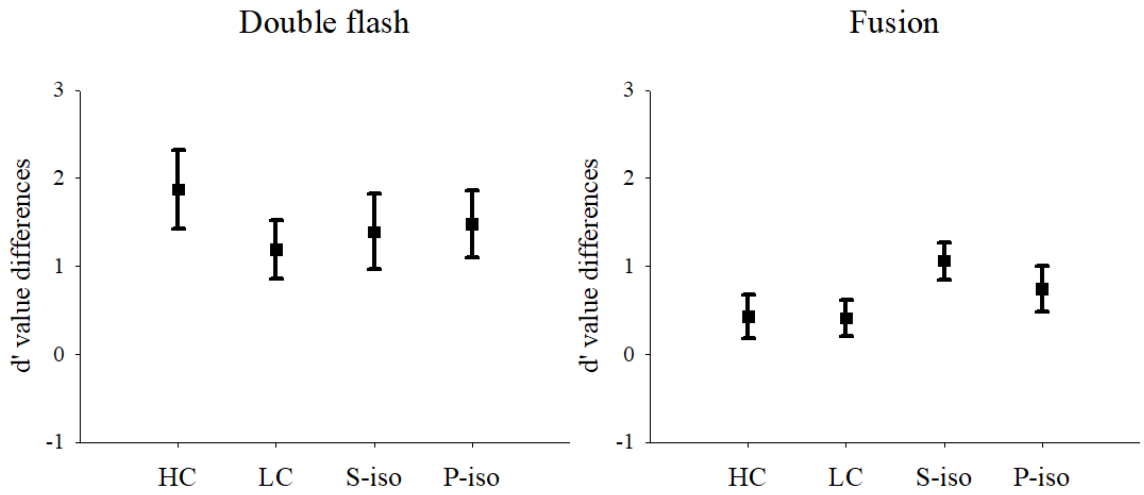

Figure 4.

Means and standard errors of differences between control and double flash d' values for double flash (ANOVA, F (2.472, 39.55) = 1.287; p=0.29; n=17) and between control and fusion d' values for fusion (ANOVA, F (2.676, 42.81) = 1.748; p=0.17; n=17). Abbreviations: HC: high contrast, LC: low contrast, S-iso: subjectively isoluminant, P-iso: physically isoluminant.

Peripheral presentation: in the high contrast condition, significant fusion effect $t(16)=3.47$, $p<0.01$, and double flash effects $t(16)=4.86$, $p<0.001$, were shown (Fig. 5). In the low contrast condition, no significant fusion effect was shown $t(16)=0.93$, $p=0.36$, but there was a significant double flash effect $t(16)=3.66$, $p<0.01$ (Fig. 5). In the subjective isoluminant condition, no significant fusion effect was shown, $t(16)=1.83$, $p=0.08$, but there was a significant double flash effect $t(16)=3.68$, $p<0.01$ (Fig. 5). In the physically isoluminant condition, significant fusion effect $t(16)=4.42$, $p<0.001$ and also double flash effect $t(16)=4.52$, $p<0.001$ were shown (Fig 5).

The repeated-measures ANOVA of the difference scores for the peripheral conditions showed significant differences between the different conditions (high-contrast, low contrast, subjectively or physically isoluminant) for the fusion effect (F (2.286, 36.58) = 3.898, $p<0.05$), but there were no significant differences between the different conditions for the double flash (F (2.684, 42.94) = 1.653, p=0.19) illusion (Fig. 6). In case of the fusion effect the Bonferroni multiple comparison test showed that in the LC condition the difference between the control d' and d' for fusion is bigger than these values in P-iso conditions.

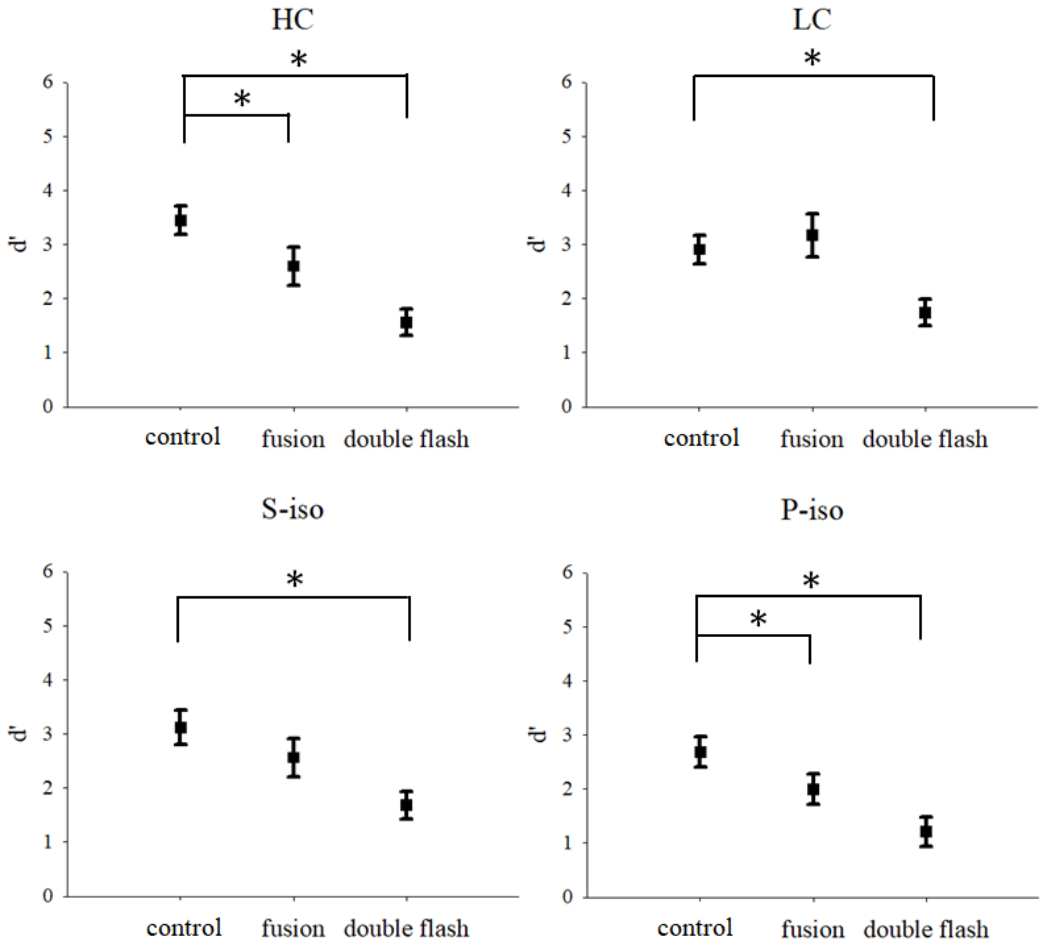

Figure 5.

Results of the psychophysical test in the peripheral condition

The diagram shows the means and standard errors of d' values and the significant results of the paired t-test in the peripheral conditions. Significance is indicated by asterisks, n=17. Abbreviations: HC: high contrast, LC: low contrast, S-iso: subjectively isoluminant, P-iso: physically isoluminant.

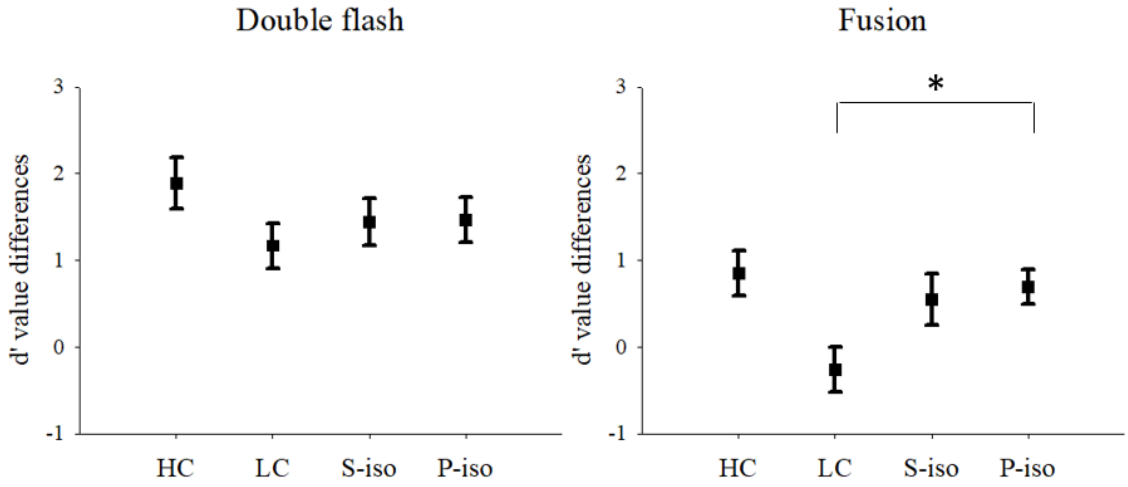

Figure 6.

Means and standard errors of differences between control and double flash d' values for double flash (ANOVA, F (2.684, 42.94) = 1.653; p=0.19; n=17) and between control and fusion d' values for fusion (ANOVA, F (2.286, 36.58) = 3.898 ; $p<0.05$; n=17). Bonferroni's multiple comparison test showed that the low contrast condition is different from physically isoluminant condition for fusion. Abbreviations: HC: high contrast, LC: low contrast, S-iso: subjectively isoluminant, P-iso: physically isoluminant.

Discussion

As it was demonstrated earlier the double flash illusion is a very robust phenomenon (Shams L et al., 2000). While the perception of the flash fusion illusion shows big differences among subjects it is fairly weak compared to double flash illusion (Mishra J et al., 2008). Generally, we found the same results as mentioned above with the stimulus set described. The variance of behavioural performance among participants shows a wide range; however, even so we got significant differences for the double flash in all conditions at both central and peripheral stimulus presentations. In some conditions the occurrence of the double flash illusion was more frequent at the peripheral than the central condition, which is in line with the early results (Bhattacharya J et al., 2002).

Previously reported studies suggested that widespread interconnections between the sensory and association cortices are involved in the multisensory processing, furthermore results using the double flash and flash fusion illusions suggest that the connection between the primary visual cortex and the STS can play a substantial role in the processing of these illusions (Watkins S et al. 2007; 2008). The aim of this study was to investigate how the different visual features processed by the parallel visual pathways and their different temporal characteristics can influence our perception when integrating with auditory information. For this we found driving selectively the dorsal and ventral visual pathways a useful approach. We designed eight stimuli type which were matched to the sensitivity of the different pathways. High contrast stimuli were used to test if our task is able to reproduce the previous studies. The high contrast visual stimulus drive both pathways. Low contrast stimuli can drive the M pathway separately, but this kind of stimulus is quite weak, so it cannot drive the whole pathway to its full extent. Both the subjective and the physical isoluminant stimuli contain colour information, thus they can drive the P pathway (Gegenfurtner KR and DC Kiper, 2003; Kveraga K et al., 2007). In addition, the subjective isoluminant stimuli are known to be selective for the P pathway (Skottun B 2013).

Beyond the optimization of colour and contrast content we used central and peripheral stimulation to favour the different pathways. The M pathway receives information mainly from the peripheral retina through the M ganglion cells. On the other hand, the P pathway receives information from the whole retina through the P ganglion cells, but the density of P ganglion cells decreases towards the periphery of the retina. Thus, the central stimulation facilitates the processing through P pathway, while peripheral stimulation drives both pathways. The physical isoluminant stimuli is containing only colour contrast without

luminance contrast which could drive the M system and the subjective isoluminant stimuli are regarded as selective stimuli for the P pathway. There is also a remarkable difference between the retinotopic areas in connecting to other areas, because anatomical connections were found between the primary auditory cortex, superior temporal polysensory area and the peripheral, retinotopically organized part of the V1 (Falchier A et al. 2002; Rockland KS and H Ojima 2003; Clavagnier S et al. 2004).

In spite of high variations of the behavioural performance and with the above mentioned restrictions, we found significant differences for the double flash illusion in high contrast conditions with central and peripheral stimulations, which is consistent with previous studies. We also found a strong double flash illusion in the pathway-specific conditions. This indicates that the incongruently added second tone can modulate the visual processing through M and P pathways and evokes the illusory perception of a second flash. In case of double flash, we did not find dependence on the two pathways, although this could be explained by the robustness of this illusion. The condition, which does not subserve the double flash illusion, might be more sensitive for the differences.

With central stimulation we found a strong significance for fusion illusion in the conditions with red-green colour information. An explanation behind these findings can be explained by the temporal resolution of the ventral pathway. The subjectively and physically isoluminant stimuli are mainly processed through the parvocellular system and ventral pathway having low temporal resolution. This system can be biased easily by the incongruent tone, thus it can fuse the flashes more easily and induce the flash fusion illusion. On the other hand, stimuli optimised for the M pathway are processed through a system having high temporal resolution, which can make distinctions between two flashes easily, thus it cannot sustain the fusion illusion.

With peripheral stimulation we found a strong significance for fusion in the physically isoluminant and in the high contrast conditions. In the high contrast condition the incidence of the flash fusion is not surprising, since it can vary as described earlier, depending on the particular group of participants (Mishra J et al., 2008). With stimuli optimised for the M pathway we could not induce the fusion illusion; it can be explained by the good temporal characteristics of this pathway. Furthermore, we found difference between the fusion which was found in physical isoluminant condition and the d' level in low contrast condition was supported also by the variance analysis.

In conclusion, we found that the robust double flash illusion can be induced on both M and P pathways. The fusion illusion can be induced in the P pathway, while the M pathway

does not support it. Because the fusion illusion appeared in the isoluminant conditions of the central presentation, and the pathway differences could be observed at the peripheral condition, the incidence of flash fusion seems to be pathway-specific depending on the temporal resolution of the given pathway.

As a continuation of this study we examined the anatomical connections underlying the double flash illusion. In the previously presented study we found that both the ventral and dorsal system is involved in the double flash illusion. Although several studies have revealed integration-related activity in the brain using different paradigms there has been no imaging study investigating the possible role of segregated visual streams in audio-visual integration. So in this study we investigated the anatomical correlations to understand how audio-visual integration can be supported through the dorsal and ventral visual pathways during the double flash illusion. Low-contrast achromatic stimuli projected to the peripheral part of the retina and chromatic isoluminant stimuli projected to the fovea were used to drive the dorsal and ventral pathways, respectively Fig. 7.

Figure 7.
Stimuli used during the experiment. The low-contrast achromatic stimuli were presented at the periphery, while the isoluminant green-red stimuli were presented in the centre of the monitor.

The psychophysical sensitivity results of our subjects (16 participants) were correlated with the white matter integrity as measured by diffusion tensor imaging to reveal small inter-individual variations in the white matter microstructure, which might explain the subject-to-subject differences in perceptual sensitivity. A correlation between the psychophysical results and local fractional anisotropy was found in the occipito-parietal white matter using the low-contrast condition, while when using chromatic, isoluminant stimuli correlation was found in the infero-temporal white matter.

The probabilistic tractography from the infero-temporal white matter region, which revealed a high correlation with the likelihood of perceiving a double-flash illusion in the isoluminant condition showed tracks running along the inferior border of the temporal lobe through the inferior fronto-occipital fascicle (an association track connecting the occipital lobe with the frontal lobe) and the inferior longitudinal fascicle (an association track connecting the occipital lobe to the temporal lobe). In the low contrast condition, the tractography initiated from the juxtacortical parieto-occipital cluster of the tract-based spatial statistical analysis showed fibres along the putative arcuate fascicle, running towards the frontal lobe (Kaposvári P et al. 2015) Fig. 8.

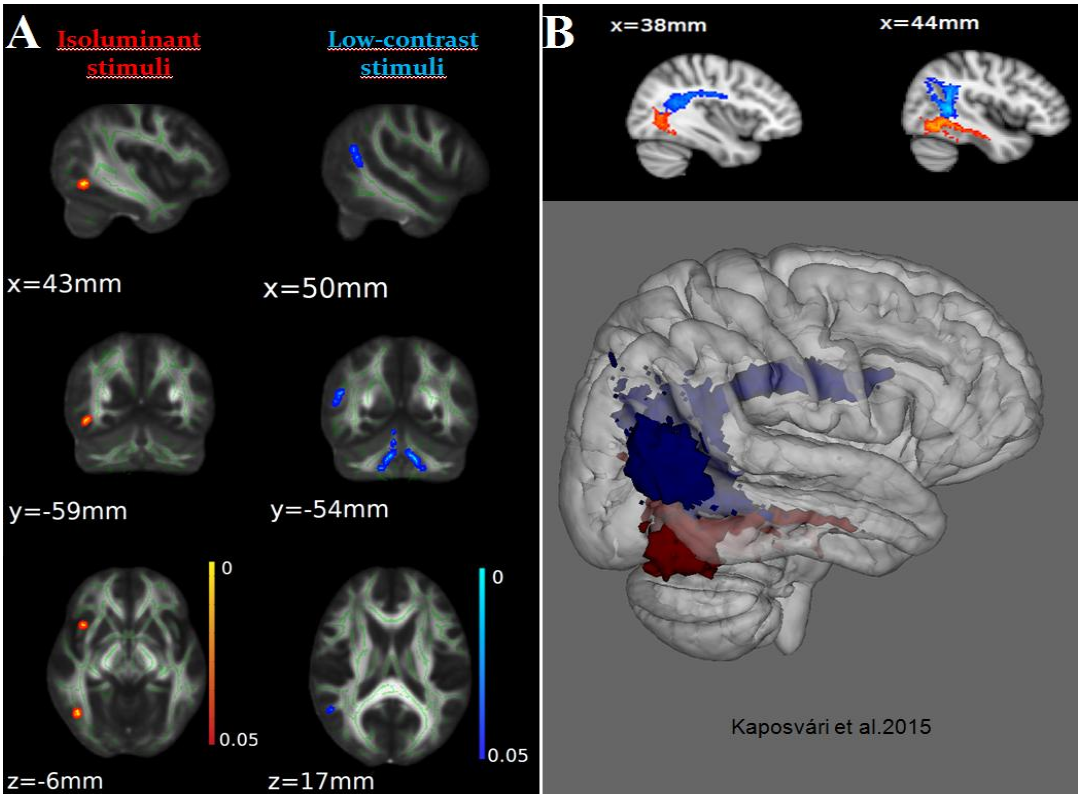

Figure 8.

Panel A: the correlation of local fractional anisotropy with a higher likelihood of perceiving a double-flash illusion. White matter microstructure as measured by local fractional anisotropy, showed correlation with the perceptual sensitivity to double flash illusion in the isoluminant (upper row) and low-contrast condition (lower row). The identified white matter regions overlap with the ventral and dorsal visual pathways, respectively. Panel B shows connectivity of clusters showing the correlation between local fractional anisotropy and behavioural data in the isoluminant (red) and low-contrast (blue) conditions. The white matter fibres identified by the tractography correspond to the ventral and dorsal visual pathways in the isoluminant and low-contrast conditions, respectively (Kaposvári P et al. 2015).

Investigations in the visual domain

Categorization, the grouping of stimuli into meaningful classes is a fundamental cognitive process which is essential in everyday life. It was defined as a fast, automatic and obligatory process requiring little attention. Several studies investigated the neuronal background of the fast and efficient information processing required, but identification of the underlying long distance interactions between the different stages of the visual system (parietal, prefrontal and inferotemporal cortex) requires further investigations (Bullier J et al. 2001; Freedman DJ et al. 2002; Kveraga K, J Boshyan, et al. 2007). Fast decisions about environmental information require categorization to distinguish between animate and non-animate things, plants and animals, vehicles and buildings, etc. (Fabre-Thorpe M 2011). Categorization serves not only distinction but also generalization when different objects are grouped on the basis of shared features (Keller F and W Schoenfeld 1950). As a fundamental process categorization is needed even if the visual environment does not favour perception of the fine details: fog, poor lighting, absence of colours, low contrast, short flashes of an image allow only decisions made on the basis of coarse global features or outlines of objects. Furthermore, sometimes only the periphery of the visual field is stimulated which is not ideal for the processing of the fine detailed visual information; still, we need to know whether this visual information has any relevance. However detailed analysis on the other hand, fine details, colours and edges are also important for the object identification.

For fast and efficient categorization relevant information and actual goals should be considered. This process might root in the two major visual processing streams: the M and P pathways. For the cortical areas the M pathway provides the first available information of our environment, reaching the visual cortex around 20 ms earlier then the information in the P pathway (Nowak L et al. 1995). When we have to react quickly to the environmental inputs (to distinguish between the dangerous and harmless situations) a rapid categorization is needed than can rely on the very coarse, colourless and robust information carried by the M pathway (Bar M 2003; Fabre-Thorpe M 2011).

Since a detailed description of the pathways was presented in the introduction here I focus only on those features of the M which are relevant to our study. The M pathway is very fast because of the axon size and the thick myelinisation. Differences in conduction speed between the two pathways can be demonstrated as early as the LGN where the M latencies precedes the P latencies by about 10 ms (Maunsell JH et al. 1999; Usrey WM and RC Reid 2000) than information arriving via the P has around 20 ms delay compared to the M in V1

(Nowak L et al. 1995; Schmolesky MT et al. 1998). After the V1 for the information carried by the M pathway it takes only 6-9 ms to reach V3, the MT, MST or the FEF (Schmolesky MT et al. 1998). For comparison, in the ventral stream the onset of the first neuronal responses in the inferotemporal cortex is around 70 ms (Perrett DI et al. 1982; Kiani R et al. 2005).

In the hierarchical, feed-forward processing model the complete processing of an object is built up by its detailed components. Nevertheless, previous studies indicate the importance of top-down influences on object representation by carrying information about perceptual task, behavioural context, expectations, modulating attention, thus, it can cause contextual facilitation of object processing (Chelazzi L et al. 1993; Motter BC 1993; Eger E et al. 2006; Fenske MJ et al. 2006; Kveraga K, AS Ghuman, et al. 2007; Zhou H and R Desimone 2011). On the basis of latency differences between the P and the M pathways, Nowak and his colleagues suggested that visual signals processed in the M might modulate activity in the P through feed-forward, lateral or feed-back connections (Nowak LG and J Bullier 1997). Information carried rapidly by the M pathway towards the frontal areas may exert a top-down effect. However, due to the fact that the M is sensitive only to LSFs and detects coarse features, the role of the M in object recognition was not investigated for long. Recently published papers, however, suggest that when time is an issue, the M carries sufficient data to extract relevant information, which – provided there is enough time– can be completed by colours and details carried by the P. Several experiments (see below) were carried out in order to investigate rapid categorization by using pathway-specific stimulation.

Research on decision making involving M information can benefit from the fact that images projected on the peripheral retina almost exclusively stimulate the rod system. In a study by Thorpe and colleagues (Thorpe M et al. 2001), participants had to decide about images and choose between animate/non-animate categories. Their results demonstrated that eccentricity did not have an influence on the accuracy of the decisions. This supports the idea that LSF information originating from the periphery of the retina is sufficient for categorization. It was also shown that rapid categorization is possible in the absence of colours (Delorme A et al. 2010). The M system is sensitive to the achromatic differences in luminance; the pathway can be stimulated by stimuli having low (<8%) contrast and LSF (Tootell RB et al. 1988). Experiments on monkey and human participants using contrast differences (Macé MJM et al. 2005; Macé MJ-M et al. 2010)were performed and showed that images with sufficiently low contrast are invisible for the P, so decisions concerning the stimuli must be based on information carried by the M pathway. If the P were the only pathway involved in visual categorization, low contrast stimuli should result in a dramatic

decrease in performance. However, at contrast values of 3% performance did not change significantly in either species, which suggests that it might be done on the basis of coarse information carried by the M (Bar M 2003; Bar M et al. 2006).

Different spatial frequencies carry different aspects of the visual stimuli. HSF carry information about edges and patterns, while LSF contain global information. The latter might be sufficient to make a first, global impression about the general shape of objects. LSF are involved in the contextual processing of visual information (Peyrin C et al. 2004) and psychophysical studies showed that LSF patterns (Sachs MB et al. 1971; De Valois KK et al. 1990; Sachs et al. 1971) and complex sceneries (Macé MJM et al. 2005; Macé MJM et al. 2010; Schyns and Oliva 1994) are perceived earlier than HSF. Electrophysiological results show that the first part of the activity of IT cells reflects global information (Sugase Y et al. 1999; Tamura H and K Tanaka 2001) and only the later part of the responses, after some ~50 ms, carries information about fine details (Sugase Y et al. 1999). This means that IT neurons respond first to LSF and global features and only after that to fine details.

According to the studies mentioned above and based on their EEG findings, Thorpe and Fabre-Thorpe suggested an M pathway based fast pathway which uses the same cortical areas as the ventral pathway. Thus, M information arrives at the IT faster and reaches the prefrontal cortex and the motor cortex earlier than information carried by the P pathway if a fast decision is needed (Fabre-Thorpe M et al,2001;(Thorpe S and M Fabre-Thorpe 2002). Reaction times in monkeys performing rapid visual categorization are as short as 180 ms, which leaves time only for a feed-forward processing through the IT to the motor cortex via the prefrontal and premotor cortices (Fabre-Thorpe et al., 1998). It was also suggested that M information supported P processing through fast, local feed-back circuits along the ventral visual stream (Fabre-Thorpe M 2011).

Bar and his colleagues, on the other hand, hypothesized a top-down process which, using the rapid processing in the M, the dorsal pathway, could provide the IT with coarse but fast information through the orbitofrontal cortex (OFC). This top-down mechanism by activating contextual associations and could limit the number of possible interpretations, decrease the amount of necessary computation and reduce the time needed for the object identification. This global information is essential for making fast decisions for survival (Bar M 2003). In these experiments, the two pathways were stimulated selectively and categorization was required (Bar M 2003; Kveraga K et al. 2007a; Kveraga K et al. 2007b). According to the findings the critical structure in top-down processes is the OFC, whose early activation can be attributed to processing visual information in the M pathway (Bar M 2003;

Kveraga K et al. 2007b). In addition, a study investigating the functional coupling of cortical areas found phase coupling between V1 and the OFC, and between the OFC and the IT(Lin F-H et al. 2004). Rokszin et al. (2016) investigated how the top-down effects are manifested in scalp ERPs when presenting LSF or HSF information. They found evidence of top-down, anterior effect for M pathway optimized images within the first 180 ms of visual processing. N1, the first negative component in the evoked potentials is known to be modulated by top-down influences such as prior expectations, attention factors (Melloni L et al. 2011; Pollux P et al. 2011). The modulation of this component was observable over the anterior scalp regions and the top-down effect was manifested in the shortening of this components on the posterior and parietal site in response to the LSF stimuli (Rokszin AA et al. 2016). In addition to the aforementioned evidences, there are anatomical studies investigating the connectivity between the frontal and temporal lobe. Connection is provided by the fibres of the uncinate fascicle and the external capsule connecting the OFC with the IT might play an essential role in the contextual information sharing (Cavada C and PS Goldman-Rakic 1989; Fang PC et al. 2005).

It is important to note that although the M is regarded as the main input for the dorsal or “Where?” pathway processing motion and serving spatial attention, nearly 50% of the M fibres feed information into the ventral stream (Ferrera VP et al. 1992; Nealey T and J Maunsell 1994). There is plenty of evidence supporting the role of the M pathway in fast categorization; however, it is unclear whether this information after leaving V1 reaches the IT via the dorsal (a top-down process through the OFC) or the ventral pathway (local feed-forward or feed-back circuits preceding P information) (Fig. 9).

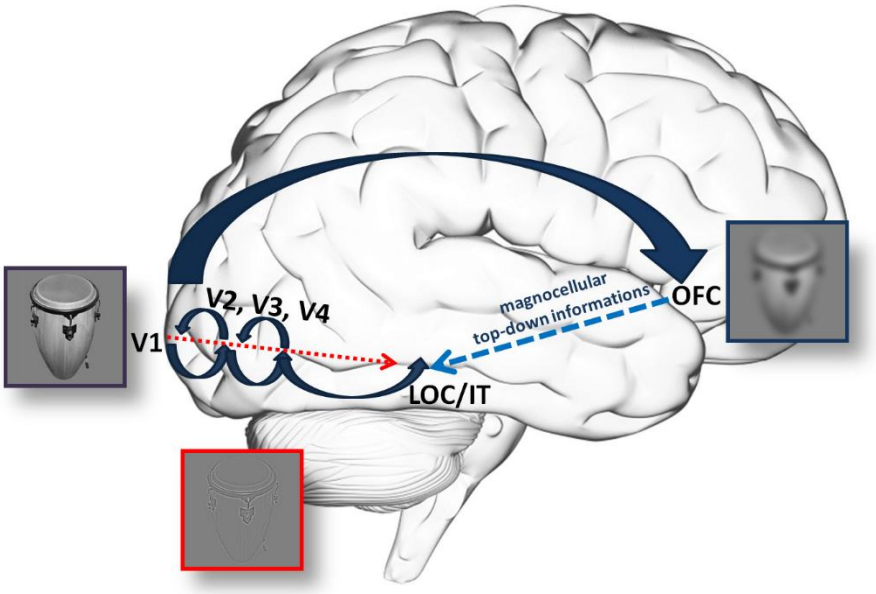

Figure 9.

An illustration of the hypothetical anatomical background for information processing through the (fast) magnocellular and parvocellular pathway. According to Thorpe M et al. 2011, M information supports P processing through fast, local feed-back circuits. On the other hand, Kveraga and his colleagues hypothesized a top-down process, which, using the rapid processing in the M, could provide the IT through the OFC with fast but coarse information. This can feed-back to the ventral stream to limit the number of possible interpretations, decrease the amount of necessary computation and the time needed.

The goal of our study was to determine which of the above scenarios is more likely: does M information responsible for fast visual decisions pass through the OFC or does it run together with the ventral pathway? One possible approach of the problem might be to interfere with the dorsal or ventral pathway to see whether the processing of those stimuli which are characteristic to the given pathway are affected or not. A logical choice is a non-invasive and reproducible electrical stimulation of the pathway(s).

Electrical stimulation manipulates the activity of cortical networks temporally and reversibly in a non-invasive and painless way and is today frequently used for investigating cognitive functions, functional neuronal networks, and it also provides promising treatments in psychiatric and neurological disorders (Polanía R et al. 2011; Kuo M-F and MA Nitsche 2012; Coffman BA et al. 2014; Kuo M-F et al. 2014). The method consists of a weak transcranial current (tDCS) flowing through the brain using two large surface electrodes (Nitsche MA and W Paulus 2000; Manuel AL et al. 2014), in order to influence cortical

functions. Previously animal studies demonstrated that the direct stimulation placed on the cortex has an influence on the resting membrane potential of the neurons under the stimulation electrode. The anodal stimulation causes depolarization, while the cathodal stimulation decreases the memrabe potential of the cells. i.e., has a hyperpolarizing effect (Bindman LJ et al. 1964; Purpura DP and JG McMurtry 1965). This effect is present during the stimulation and the effect of the stimulation could last up to one hour after the stimulation (Nitsche MA and W Paulus 2000, 2001). In human studies, for the better understanding of the effect, tDCS was tested in subjects using carbamazepine or flunarizin drugs, which are known sodium and calcium channel blockers. In these participants the stimulatory effect of the anodal stimulation was highly reduced or eliminated, while the cathodal stimulation remained effective, probably becouse of the cathodal stimulation induced hyperpolarisaton is related to the inhibition of sodium and calcium channels (Nitsche M et al. 2003; Stagg CJ 2014). Further investigations on the background mechanisms demonstrated that polarity specific changes are in line with the changed neurotransmission. Several studies reported that the anodal stimulation can inhibit the neurotransmission by gamma-aminobutiric acid, while the catodal stimulaion reduce the glutamergic neuronal activity (Nitsche MA et al. 2004; Stagg C et al. 2011). These results and many other unkonwn factors causing polarity specific effects could underly the folowing results. Stimulation of the primary motor cortex can change the cortical reactivity (the neuronal activity evoked by transcranial magnetic stimulation) in a polarity spacific manner, furthermore these polarity specific neuronal activity changes in the motor cortex were investigated using fMRI. The modulatory effects are reflected in the incerased blood oxigen level using anodal, and decreased blood oxigen level using cathodal stimulation (Baudewig J et al. 2001; Jang SH et al. 2009; Antal A et al. 2011; Kwon YH and SH Jang 2011). Not only the activity of neurons under the stimulated area can be modulated, but the tDCS can influence distant, but functionally connected regions (Polanía R et al. 2012; Saiote C et al. 2013). The stimulation can also act on the resting-state network activities: anodal stimulation can increase the functional connectivity between motor cortex, caudate nucleus and the parietal association areas, while the cathodal stimulation over the same region decreases the connectivity to the contralateral putamen. Other studies demonstrated widespreed changes in functional connectivity between the cortical regions like prefrontal cortex and premotor areas (Polanía R et al. 2012; Sehm B et al. 2012). According to these findings tDCS can be an effective tool to modulate the function of long distant cortical connections.

In the past few years several studies investigated visual processing in humans using non-invasive electrical stimulation to directly modulate visual cortices or modulating the

attentional effects in human subjects. The anodal stimulation over V1 increases the responsivity of the cortex, and its sensitivity for the TMS (transcranial magnetic stimulation) evoked phosphenes. It also increases contrast sensitivity, enhances the amplitude of N70 while the opposite effects were found using cathodal stimulation (Antal A et al. 2003, 2003; Antal A, TZ Kincses, et al. 2004; Kraft A et al. 2010). Furthermore, tDCS modulates human colour discrimination in a pathway-specific manner (Costa TL et al. 2012). The anodal stimulation over MT improves learning of visually guided tracking movements (Antal A, MA Nitsche, TZ Kincses, et al. 2004). After learning the anodal stimulation has no effect, but cathodal stimulation can increase the signal-to-noise ratio and improve the performance in the learned task (Antal A, MA Nitsche, W Kruse, et al. 2004). The tDCS over the posterior parietal cortex modulates visuospatial processing (Sparing R et al. 2009), bilateral stimulation over the anterior temporal lobe (right anodal, left cathodal) improves visual memory (Chi RP et al. 2010), cathodal stimulation of the temporo-parietal cortex reduces the magnitude of facial adaptation (Tímea VE et al. 2007). Also, anodal stimulation improves implicit learning when the left prefrontal cortex is stimulated (Kincses TZ et al. 2004) and enhances the recognition of facial expression when the right OFC is stimulated (Willis ML et al. 2015).

Since tDCS seems to be a powerful technique for investigation visual processing, we applied cathodal or anodal tDCS and sham stimulation as a control in a decision making test, over the OFC (Dayan E et al. 2013; Manuel AL et al. 2014; Willis ML et al. 2015). Our subjects were required to make a judgement on the real size of objects presented on the screen, i.e., whether the presented stimulus is bigger or smaller than an average shoebox? There were two sessions: the first one for registrating the reaction times and accuracies for the different stimulus types (the image set contained random selection of 50 HSF ans 50 LSF images). Between the two sessions tDCS stimulation was applied. Finally the same test was run using the rest of the stimulus set (the other random 50 HSF and 50 LSF images).

There are two possible scenarios concerning the outcome. If stimulation of the OFC does not have an effect on decisions concerning both M and P optimized stimuli, or if the effects are similar using both stimuli that would support the idea that fast M information is processed through the ventral pathway avoiding the OFC. Thus, only decision mechanisms were affected, but not the route of information flow. If, on the other hand, decisions about M stimuli were affected selectively, it would support the hypothesis that M information reaches the OFC, passes through it and is available for top-down modulation (Bar M et al., 2006).

Methods

Stimuli

The stimulus set contained 200 achromatic images of everyday objects, like a truck, ashtray, pen, piano, etc. One part of the images was collected from the Bank of Standardized Stimuli (Brodeur MB et al. 2010) others were selected and collected by one of the authors (A.B.). Stimuli were modified using Matlab and GIMP 2.8 programs. Stimuli were cut out from the original pictures, were standardized in the sense that all had the same size in their largest dimension (4,5° viewed from 57 cm) placed on the same background, transformed to grayscale images. Shine Toolbox was used to equalize the contrast and luminance values before filtering (Willenbockel V et al. 2010) . Images had resolutions of 72 pixels per inch and size of 500*500 pixel. The visual stimuli were modified to selectively stimulate the M or the P; they were filtered by Gaussian filter (12 pixel kerner, as lowpass filter) and highpass filter (0.5 radius) to attenuate the high and spatial frequencies, respectively. The M optimized stimuli contained LSF (<0.9 cycles per degree), while the P stimuli consisted of HSF (>4.7 cycles per degree, Fig. 10). This method is similar to the one used by Bar M et al. (2006). All stimuli had a mean luminance between 8-9 cd/m^2. No luminance matching was used after filtering. The images of the objects could be divided into two groups according to their real life size. One half of the objects were larger, while the others were smaller than an average shoe box. All stimuli were presented on a uniform grey background (8.9 cd/m^2). For stimulus presentation a 23-inch LCD (Tobii Pro TX300) monitor was used having screen resolution of 1920 x 1080 and vertical refresh rate of 60 Hz.

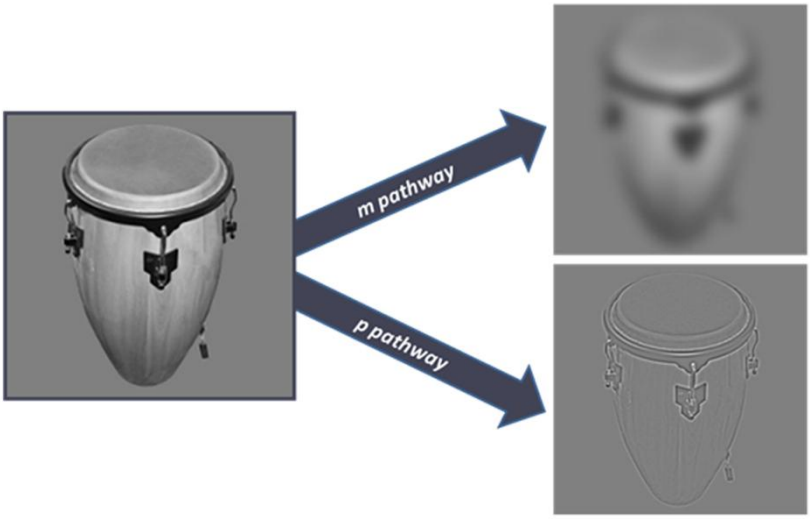

Figure 10.

The image on the left is the original unfiltered image of an object received by the retina. The right side of the figure shows the two kinds of stimuli used in the experiment. The upper image is filtered for the selective stimulation of the magnocellular, M pathway. The bottom image is optimized for the ventral stream, in accordance with the sensitivity of the parvocellular, P pathway.

Subjects

Forty-eight healthy subjects (university students, 19 females; mean age: 22.7 years) participated in the study. They were divided in three equal groups for cathodal, anodal and sham stimulation. Each subject had to perform the task before and after the stimulation (see below). All had normal or corrected-to-normal vision, including normal colour vision and none of them suffered from any neurological or psychiatric disorders. None of them had a history of excessive drug/alcohol/caffeine consumption. A questionnaire was provided regarding previous diseases, handedness (Oldfield RC 1971), sleep time, medication, mental and physical status. All study participants gave written informed consent in accordance with the Declaration of Helsinki; the study was approved by the ethical committee of the University of Szeged (Ref. no.: 165/2014).

Behavioural test

The subjects were seated in a sound-attenuated, dimly lit room, and viewed the computer screen from 57 cm. For stimulus presentation a custom made MATLAB code (MathWorks, Natick) and the Psychtoolbox Version 3 (Brainard DH and S Vision 1997) was used.

At the beginning of the experimental procedure all subjects received instructions on the computer screen to make sure that everyone was given identical instructions on how to solve the task. There were two sessions during the test, thus each subject was tested twice. In the first session, before the tDCS, half of the stimulus set (100 images) was presented, which contained an equal number of small, large, M and P optimized object images in a pseudorandom order. The second session started just after tDCS (or the sham stimulation) and the rest of the stimuli (other 100 images) were presented again in a pseudorandom order. During the psychophysical sessions the participants were required to make decisions about the object size and to answer the question whether the object displayed on the screen was larger or smaller than a shoebox (Kveraga K et al. 2007a). The left arrow key on the computer keyboard was associated with smaller, the right arrow key with larger objects. Size decisions were tested in a preliminary psychophysical experiment. The trials started with a centrally presented fixation-cross (250 ms) appearing before the stimulus in the centre of the screen, followed by the test stimulus. The trials were machine paced: if no response key was pressed for 3 s, the next image was presented. There was no feedback on the correctness of the responses (Fig. 11).

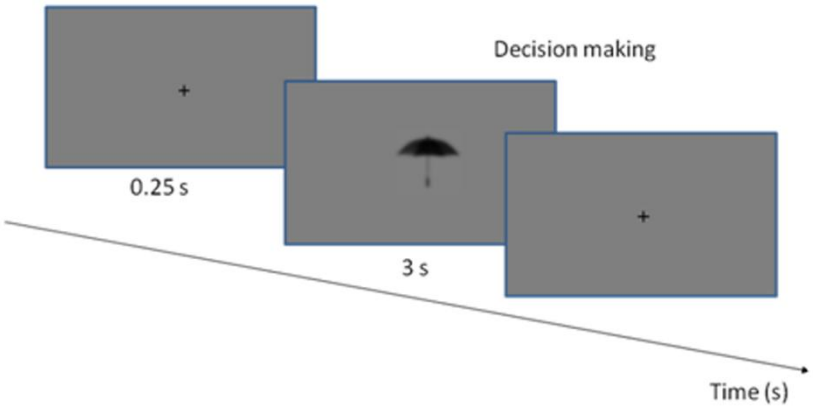

Figure 11.

The experimental procedure. The stimuli and the fixation point were presented in a grey background. Each trial started with the presentation of a fixation cross, which was visible for 0.25 s. The stimulus was presented until the decision was made, or up to 3 s.

Stimulation protocol

To modulate prefrontal cortical activity, transcranial direct current stimulation was applied (Kincses TZ et al. 2004; Nitsche MA et al. 2008, Manuel AL et al. 2014). Two rubber electrodes (surface: 5x7 cm) were used with a neuroConn DC-stimulator (neuroConn GmbH). The electrodes were arranged according to the study of Manuel AL et al. (2014). They reported a significant modulation of the OFC function (reality filtering) upon direct current stimulation. In their study, the electrical fields induced by tDCS were modelled to predict whether significant current reached the OFC. The model reached a significant current flow in the OFC when the electrodes were placed over the glabella and the vertex (Fpz and Cz of the 10–20 EEG system, respectively) and the electrical field values were calculated for 1 mA of inward current. In our study, the electrodes were placed on the midline; the centre of the relevant active tDCS electrode was over the putative OFC cortex (Fpz), while the reference electrode was over the vertex (identified by the standard 10-20 system). Stimulation was applied for 20 minutes with 1mA current intensity using 10 s fade in and fade out phase in cathodal and anodal stimulation protocol, respectively. Sham stimulation consisted of placing the electrodes on the skull, but no tDCS was applied with the exception of the 10 s fade in and 10 s fade out phases. This stimulation does not have any effect on cortical excitability, but causes the same itching sensation under the electrodes. The total duration of the sham phase was also 20 min. The study was a single-blind experiment: the experimenter was fully informed, but participants were not informed about the type of stimulation they received.

Statistics

To see the differences in processing time for the M and P optimized stimuli, SPSS Inc. software was used to compare response latencies and accuracies before stimulation (since the conditions were the same for each participant in this period); a paired t-test was applied, differences were considered as significant if the type I. error was <0.05. To evaluate the effects of transcranial stimulation we used repeated measures three-way ANOVA with between group factors being type of stimulation and within group factors being time of behavioural test, and pathway (M, P). We compared the response accuracy and the reaction times before and after the stimulation. Group averages and standard errors are shown in Table 5, comparisons in Fig. 12, Fig. 13 and Fig. 14.

stimulation type			means	±SD
sham n=16	I.	P optimized reaction time	0.97	0.448
		P optimized performance	89.25	5.698
		M optimized reaction time	0.85	0.318
		M optimized performance	91.00	4.258
	II.	P optimized reaction time	0.89	0.387
		P optimized performance	87.73	4.926
		M optimized reaction time	0.83	0.329
		M optimized performance	91.75	2.910
cathodal n=16	I.	P optimized reaction time	0.93	0.356
		P optimized performance	89.81	3.016
		M optimized reaction time	0.88	0.356
		M optimized performance	92.25	4.187
	II.	P optimized reaction time	0.89	0.332
		P optimized performance	90.24	3.710
		M optimized reaction time	0.83	0.300
		M optimized performance	89.87	4.023
anodal n=16	I.	P optimized reaction time	1.05	0.411
		P optimized performance	91.12	5.058
		M optimized reaction time	0.98	0.358
		M optimized performance	91.25	3.856
	II.	P optimized reaction time	0.97	0.367
		P optimized performance	91.24	2.993
		M optimized reaction time	0.89	0.339
		M optimized performance	97.00	2.633

Table 5.

Means of accuracies and reaction times with their standard deviations in each condition. Rows marked with I indicate values before, with II indicate values after stimulation.

Results

Before the stimulation, the three groups of volunteers performed the task under identical conditions (n=48). Paired t-test was used for the statistical evaluation. The percentage of correct answers was 91.50 ±SD=4.05 using M stimuli, comparing with accuracy of P stimuli (mean 90.06, ±SD=4.69) the difference was not significant p=0.12 (df=47, t=1.58, Fig. 12). Decisions about stimuli optimized for the M yielded shorter response latencies than those for P stimuli (mean M latency = 0.90 s, ±SD=0.20 s, mean P= 0.98 s, ±SD=0.23 s, p<0.01, df=47, t=-3.95, Fig. 12). These results suggest that the reaction time differences originate from the different processing times needed for M and P optimized stimuli, not from the differences in the recognisability of the M and P stimuli sets. This test verified that M optimized stimuli are associated with shorter response latencies (Bar M et al., 2006).

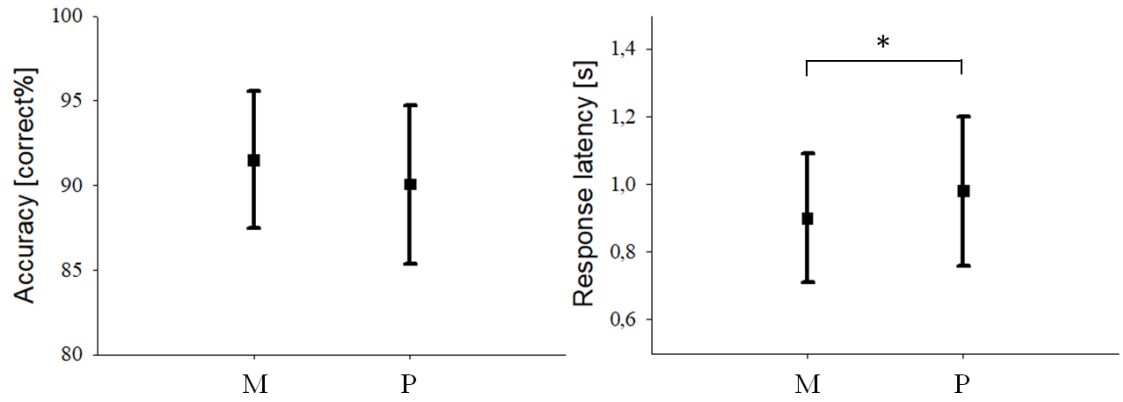

Figure 12.

The accuracies and response latencies during the decision task before tDCS

Central data points: means, bars: mean ± SD. There was no significant difference between correct decisions about stimuli optimized for the M and the P. For M stimuli, the response latencies are shorter than for P stimuli (n=48, p<0.01).

A repeated measures three-way ANOVA was used to test main effects and possible interactions between changes in response latencies according to the types of stimulation. The within factors were the pathway (M, P), time of the behavioural test (before and after the stimulation) and group factor was type of stimulation (anodal, cathodal, and sham). All possible interaction terms were taken into account. Concerning the response latency times we did not find significant effects in the cases of stimulation type [$F_{(2, 45)}$ = 1.336, p = 0.273, partial eta-squared = 0,06]. The reaction times showed differences according to the pathway

factor [$F_{(1, 45)}$ = 28.46, p < 0.01, partial eta squared = 0.39] and the time factor [$F_{(1, 45)}$ = 8.69, p < 0.01, partial eta-squared = 0.16]. The after stimulation reaction times became faster in the case of all stimulus type, and the response latencies for M stimuli were faster throughout the test. While analysing the interactions, we did not find interaction between the pathway and stimulation type factor [$F_{(2, 45)}$ = 0.59, p = 0.56, partial eta-squared = 0.03], time and stimulation type factor [$F_{(2, 45)}$ = 0.36, p = 0.69, partial eta-squared = 0.016] and pathway and time factors [$F_{(1, 45)}$ = 0.65, p = 0.42, partial eta-squared = 0.014]. Furthermore, there was no significant interaction between the three factors examined [$F_{(2, 45)}$ = 1.99, p = 0.15, partial eta-squared = 0.81] (Fig. 13).

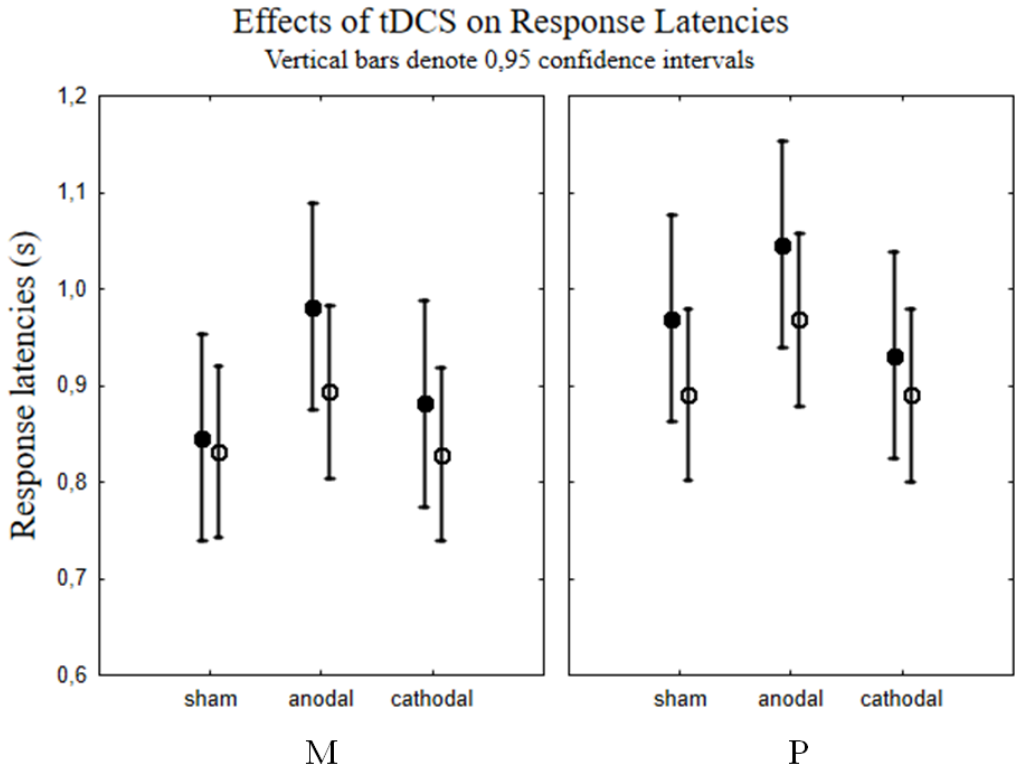

Figure 13.

Effects of tDCS on response latencies

On the left panel the repeated measures three-way ANOVA results of the response latencies in the psychophysical tests are presented (full circles show the measured latencies before stimulation, full squares show the response latencies after stimulation) M optimized stimuli (n=48). Data points denote means, vertical bars 0.95 confidence intervals. None of the stimulation types affected the response latencies. On the right the repeated measures three-way ANOVA results of the response latencies in the psychophysical test for P optimized stimuli are shown (n=48). The response latencies were not changed by stimulations.

To see how transcranial stimulation of the OFC affected accuracy levels three-way ANOVA with repeated measures was used to test main effects and possible interactions between the changes in accuracy and types of stimulation. The factors again were the pathway (M-P), type of stimulation and time (before or after the stimulation). All possible interaction terms were taken into account. The interaction of all factors was significant [$F_{(2, 45)} = 5.81$, $p < 0.01$, partial eta-squared = 0.21]. Using stimulation type factor we found significant difference between the groups [$F_{(2, 45)} = 4.77$, $p < 0.01$, partial eta-squared = 0.18]. In the case of pathway factor we also found significant difference [$F_{(1, 45)} = 13.74$, $p < 0.01$, partial eta-squared = 0.23], but the interaction of the aforementioned factors was not significant [$F_{(2, 45)} = 1.03$, $p = 0.36$, partial eta-squared = 0.04]. Examining the effect of time factor we did not find significant differences [$F_{(1, 45)} = 1.79$, $p = 0.19$, partial eta squared = 0.04]. The interaction of time and stimulation type factor was significant [$F_{(2, 45)} = 9.64$, $p < 0.01$, partial eta-squared = 0.30] but there were no significant interactions between the time and pathway factors [$F_{(1, 45)} = 2.78$, $p = 0.10$, partial eta-squared = 0.06]. The existence of the three-factor interaction suggests that the interaction between time and stimulation depends on the level of pathway factor (P and M stimuli, representing two levels), with other words, the dependence between change in time and the stimulation (representing three levels) differs in the P and M stimuli, therefore the relationship between change in time and stimulation was evaluated at the levels of stimulus presented in the figure below. Estimated marginal means and confidence intervals in the figure are based on the results of the omnibus ANOVA (Fig. 14.)

We used Bonferroni post-hoc test to examine between which groups and conditions the significant effect can be found. The most important differences were found between accuracies measured before and after stimulation when presenting M stimuli and using anodal ($p < 0.01$) and cathodal stimulation ($p = 0.015$). The accuracy increased when anodal stimulation was used, while the cathodal stimulation decreased the percentage of correct answers. Comparing on the level of pathway factor we found significant differences between the sham group after stimulation values ($p < 0.01$) and anodal group after stimulation values ($p < 0.01$). Furthermore, there were differences between the different groups, the accuracy for the M stimuli after the stimulation differed between the sham and anodal groups ($p < 0.01$) and anodal and cathodal groups ($p < 0.01$). The accuracies measured after the stimulation using PC stimuli differed between the sham and anodal groups ($p < 0.05$).

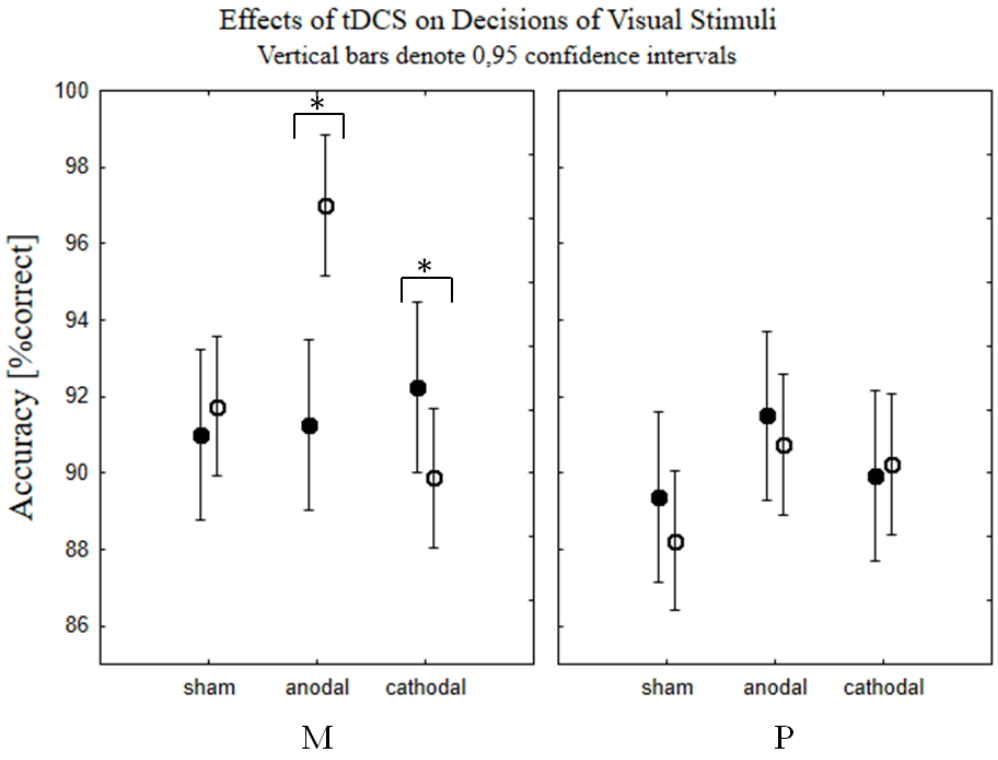

Figure 14.

Effects of tDCS on decisions of visual stimuli

Repeated measures three-way ANOVA results of the accuracies in the psychophysical tests are presented on the figures (n = 48), full circles: before stimulation, full squares: after stimulation. The left panel presents the accuracy changes using M optimized stimuli. Anodal tDCS resulted in a better accuracy for these images, while the cathodal stimulation impaired the performance. Sham stimulation did not have any effect on the accuracy. On the right panel accuracies in the psychophysical tests for P optimized stimuli are shown. None of the stimulation types affected the performance. Data points denote means, vertical bars show 0.95 confidence intervals. Asterisk indicates significant differences ($p < 0.05$).

Discussion

In this study we investigated whether we could selectively modulate the processing of M optimized stimuli by using tDCS for modulating the activity of the OFC. We hypothesized that if the stimulation causes no changes or it changes the response latencies or accuracies for both pathways optimized stimuli, that support the idea of the fast information processing trough the ventral pathway, however if the stimulation has a selective effect on the M stimulus processing, then the result can confirm the hypothesis that M information passes the OFC, and therefore might be used for a top-down modulation of visual processing.

Several points have to be addressed when discussing the results.

The first question is whether our stimuli are fit for the magno- and parvocellular pathways? It has been reported earlier that decisions concerning M optimized stimuli are faster than those optimized for P stimuli (Kveraga K et al, 2007). Our results confirmed that the stimuli used in this study are indeed suitable for driving the dorsal or ventral pathway specifically, since the stimuli had identical size and the only difference being the different spatial frequency content, we see no other explanation for the measured differences in response latency time. The significant difference in response latency times before the stimulation favoured M optimized stimuli but did not favour P optimized stimuli, indicating that pathway optimization was successful.

TDCS had a clear and significant effect on response accuracies. How can this be interpreted? The rationale behind our study was that transcranial stimulation may have a direct impact on baseline cortical excitability (Stagg CJ and MA Nitsche 2011) and the observation that predictions might accelerate the perception of our environment by pre-stretching or priming bottom-up processing. Most studies agree that the phenomenon is based on the information carried by the magnocellular pathway. The M and the dorsal pathway, however, also feed information into the ventral pathway through different stages of the cortical visual system (Felleman DJ and DE Van 1991; Chen C-M et al. 2006) but it is not clear what the exact source of this information is. Is M information processed simultaneously, together with P information in the ventral pathway (Macé MJM et al. 2005, Fabre-Thorpe M 2011) or does M information arrive through top-down connections to the IT via the OFC (Bar M et al., 2006; Kveraga K et al. 2007). The question is further complicated by the observation that connections between areas V5, V4 and the IT, furthermore between the prefrontal cortex and the IT can facilitate object recognition (Tomita H et al. 1999; Chen C-M et al. 2006; Eger E et

al. 2006; Kveraga K, AS Ghuman, et al. 2007). Cathodal stimulation of the OFC exerts an inhibitory effect, since neurons under the stimulation electrode become less excitable and presumably decrease the level of the secreted neurotransmitter glutamate (Filmer HL et al. 2014). Anodal stimulation in our experiments supported OFC functions: accuracy improved considerably for LSF stimuli (HSF stimuli were not affected), while the cathodal stimulation slightly decreased it. This is line with the meta-analysis data reported by Jacobson L et al. (2012), namely, in cognitive tasks anodal stimulation often improves performance (Jacobson L et al. 2012). The OFC consists of two large regions: medial and lateral parts. The former plays a role in higher cognitive functions, associative, reward linked learning, processing emotions, integrating sensory modalities and, most importantly, making decisions (Kringelbach ML and ET Rolls 2004; Wallis JD 2012). The fact that stimulation affected only decisions about LSF images supports the idea that magnocellular information passes through the OFC. According to Bar M et al., (2006) this information might be used for top-down facilitation of decision making. The role of the OFC in decision making especially when previous knowledge or predictions are concerned was studied in fMRI experiments (Summerfield C et al. 2006; Miall R et al. 2014; Erez Y and J Duncan 2015).

The last question is how tDCS influences the motor cortex and thus behavioural response latencies? Response latency in psychophysical studies includes sensory processing, decision making and motor response. When interpreting our results, one must also consider that the arrangement of electrodes for modulating the OFC (Manuel AL et al. 2014)also stimulates the motor cortex when cathodal stimulation is used, but inhibits it when anodal stimulation is applied. Results regarding the effects of tDCS on motor reactions are far from clear. The main effect of tDCS is biasing cortical excitability. The underlying mechanism is still debated but current work suggests that it shares similarities with the activity-dependent synaptic plasticity (Dayan E et al., 2013). Most studies agree that there is a large variability among subjects when evaluating the effects of stimulation (e.g., (Pope PA and RC Miall 2012; Wiethoff S et al. 2014; Davidson TW et al. 2016). The situation is further complicated by the fact that the same stimulating pair of electrodes will have obviously opposing effects on the motor cortex and on the OFC; factors influencing the motor component of the decision and responding process thus might mask the effects on the sensory part. In a meta-analytical review Jacobson L et al. (2012) concluded, that it is quite common to see the AeCi effect (anodal stimulation, cathodal inhibition) on latency times in motor experiments where evoked potentials are studied; in this respect our study might be an exception, since no significant

differences in response latencies could be shown. We have to note however, that only behavioural response latencies and no evoked potentials were analysed in this study.

In summary, our behavioural results show that using tDCS we could modulate the cortical activity of the OFC, which has an effect on the top-down mechanism during the fast categorization of M optimized stimuli (Bar M et al., 2006). Our results do not exclude the possibility that magnocellular input fed into the ventral pathway may accelerate visual processing, but they give further evidence for the essential role of top-down processes originating from the OFC in visually based decisions. To understand the exact neuronal background and tracking the flow of information along the cortical pathways require electrophysiological methods (extracellular unit recording at several locations simultaneously) with a good temporal resolution.

Summary

We experience our sensory surrounding coherent and stable in space and time despite the dynamical environmental changes in intensity, modality and salience of the stimuli. Still, those widespread connections that underlie multimodal perception and vision are not obvious. Visual information about motion, form and colour is carried not by a single hierarchical pathway, but by at least two parallel pathways in the brain. Traditionally, the magnocellular pathway has been associated with extraction of motion and spatial information of objects using the cortical regions of the dorsal visual stream while the parvocellular pathway is responsible for the analysis of fine details of static images. These pathways interact with each other and with other modalities to make our perception as accurate as possible. In our studies we investigated how the interaction of the mentioned pathways and other modalities form our perception.

First, we investigated how the temporal resolution of the visual system plays a fundamental role in the establishment of coherent multimodal perception. Inconsistent information from different modalities can be misleading for perception. This phenomenon can be observed with simultaneously presented inconsistent numbers of brief flashes and short tones. The conflict of bimodal information is reflected in double flash or fission, and flash fusion illusions, respectively.

As the parallel visual pathways have different temporal resolution we presume that these pathways play different roles in the integration of conflicting information from different modalities. To test this hypothesis, we used the double flash illusion. This illusion can be evoked by conflicting visual and auditory inputs. The multimodal integration of inconsistent numbers of simultaneously presented brief flashes and short tones can cause two type of illusory perception flash fission and flash fusion.

Since the visual stimulus is a briefly flashing circle, earlier studies suggested that the illusion can be mediated mostly by the magnocellular pathway. However, the potential changes recorded during this illusory percept could be observed over the primary visual cortex and the well known multimodal area, superior temporal sulcus. It has not been investigated whether the separated visual information effected the perception on multimodal level.

We used pathway-optimised stimuli to induce the illusions on separately driven visual streams. Our results show that both pathways support the double flash illusion, while the presence of the fusion illusion depends on the activated pathway. The magnocellular pathway,

which has better temporal resolution, does not support fusion, while the ventral pathway which has worse temporal resolution shows the fusion illusion strongly.

In our second study we investigated the role of the two pathways in a categorization task. Fast categorization is essential in everyday life, but the neuronal background of the fast and efficient information processing required has not been established yet. There are two main hypotheses known; both agree that primary, global impressions are based on the information supplied through the magnocellular pathway. In this study a categorization task was performed by 48subjects. They had to make decisions about size of the presented objects. Pathway specific stimuli was used for driving the magno- and parvocellular pathways on the basis of their spatial frequency preference. Although the ventral pathway is known for the categorization of objects, our psychophysical results were in line with the previous studies suggesting that the fast decisions require magnocellular information. However, it is unclear whether this information is available through the magnocellular pathway that provides information directly for the ventral pathway or through top-down mechanisms by connections between the dorsal pathway and the ventral pathway via the frontal cortex.

Transcranial direct-current stimulation was used to assess the role of frontal areas, a target of the magnocellular pathway. Stimulation did not bias the accuracy of decisions when stimuli optimised for the parvocellular pathway were used. In the case of stimuli optimised for the magnocellular pathway, anodal stimulation improved and the cathodal stimulation worsened the subjects' accuracy in the behavioural test. Our results support the hypothesis that fast visual categorization processes rely on top-down mechanisms that promote fast predictions through coarse information carried by magnocellular pathway via the orbitofrontal cortex.

In these studies we demonstrated how the magnocellular and parvocellular pathways play different roles in the formation of a stable representation of our sensory surrounding.

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Fusion and Fission in the Visual Pathways

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Summary

Inconsistent information from different modalities can be delusive for perception. This phenomenon can be observed with simultaneously presented inconsistent numbers of brief flashes and short tones. The conflict of bimodal information is reflected in double flash or fission, and flash fusion illusions, respectively. The temporal resolution of the vision system plays a fundamental role in the development of these illusions. As the parallel, dorsal and ventral pathways have different temporal resolution we presume that these pathways play different roles in the illusions. We used pathway-optimized stimuli to induce the illusions on separately driven visual streams. Our results show that both pathways support the double flash illusion, while the presence of the fusion illusion depends on the activated pathway. The dorsal pathway, which has better temporal resolution, does not support fusion, while the ventral pathway which has worse temporal resolution shows fusion strongly.

Key words

Audio-visual integration • Double flash • Fusion • Illusion

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Introduction

Visual stimuli, presented simultaneously, can interfere with each other even if they are positioned far away from the attended stimulus. Effects on the perception of the attended stimulus can also be demonstrated if the two stimuli belong to different modalities, e.g., visual and auditory (Wilson 1987), or even visual and haptic (Ernst *et al.* 2000, Wozny *et al.* 2008). The combination of one or two brief flashes simultaneously presented with one or two short tones results in two inconsistent conditions. The first is where one flash is presented with two tones; in this case, the second tone added induces an illusion of a second flash (Shams *et al.* 2000). The second is where two flashes are presented with one tone; in this case, the tone can induce the perception of two flashes fusing into one (Andersen *et al.* 2004, Watkins *et al.* 2007). Several studies demonstrated cortical and subcortical activities behind the behavioral observation. Electrophysiological evidence shows that the illusion induced extra activity can be detected over the primary visual cortex (Watkins *et al.* 2006, 2007). Magnetoencephalography (MEG) experiments, for example, have shown that the activity of cortical visual areas can be modulated with sound stimuli at occipital, parietal and anterior regions (Shams *et al.* 2005). Electroencephalography (EEG) studies have found that, during the illusion, oscillatory and induced gamma band responses were significantly higher, and audio-visual interactions were supra-additive (Bhattacharya *et al.* 2002). EEG and evoked potential experiments have shown that, during the illusory flash, perceptual activity was modulated strongly and with short latency in trials where the illusory flash was perceived (Shams *et al.* 2001). Also, it has been found that the potentials observed after the illusory flash were similar to those observed after real flashes. This indicates that the underlying neuronal mechanism is similar in both cases and is a result of a very rapid interaction between auditory and visual areas initiated by the second sound (Mishra *et al.* 2007, 2008). FMRI data have shown illusory flash related brain activity in superior colliculus,

the primary visual cortex, and in the right superior temporal sulcus (STS, Watkins *et al.* 2006, 2007). Also, another group found fusion illusion related activity in superior temporal cortex (Mishra *et al.* 2008). These studies suggest that such processing of bimodal information could be based on communication between the primary visual cortex, superior temporal sulcus (STS) and primary auditory cortex (Mishra *et al.* 2008, Watkins *et al.* 2006, 2007). Since these areas serve as a target for the cortical visual streams as well, it would be interesting to know how the two visual pathways contribute to the information exchange between the primary visual cortex and, for instance, the STS.

The interaction-related activity of the superior colliculus (Watkins *et al.* 2006) shows the M-pathway is involved in audio-visual interaction. This is in accordance with observations suggesting that the enhanced visual detection can be attributed to the magnocellular system, as proposed by former and recent studies (Jaekl and Soto-Faraco 2010, Meredith 2002). Whether the P pathway or ventral stream contributes to the double flash and fusion illusions is unknown.

We do not know to what extent the different pathways are involved in the two illusions or how the interaction spreads between the two pathways during these illusions.

The M pathway is known for processing achromatic, low contrast stimuli very fast (Bullier and Nowak 1995, Maunsell *et al.* 1990, Merigan and Maunsell 1993, Shapley 1990).

The M-pathway can be selectively stimulated with stimuli having low spatial frequency and low contrast; however, these weak stimuli cannot drive this pathway at full extent (Derrington and Lennie 1984, Kaplan and Shapley 1986, Lee *et al.* 1995, Leonards and Singer 1997). According to a recent theory the M pathway can send information into the inferotemporal cortex through the orbitofrontal areas, thus preparing it for the incoming, slower activation through the P pathway (Kveraga *et al.* 2007).

In contrast, the P pathway conducts information about colors and high spatial frequencies with a much slower speed and needs much higher contrast (about 8 % at least) when detecting achromatic stimuli (Hicks *et al.* 1983, Tootell *et al.* 1988). The parvocellular pathway has worse temporal resolution (Derrington and Lennie 1984) as compared to the M pathway. (The magnocellular units in the macaque lateral geniculate body have the highest sensitivity for stimuli modulated at temporal frequencies close to 20 Hz, while the optimum for parvocellular units is close to 10 Hz.) Stimuli containing high spatial frequencies can drive this system selectively. Since the P pathway is responsible for coding color information, it can also be selectively stimulated with isoluminant color stimuli (Tobimatsu *et al.* 1996).

In this study, we investigated how the magno- and parvocellular pathways contribute to the development of the double flash and flash fusion illusions. Making a distinction between two consecutively presented flashes depends on the temporal resolution capacities of the observer. Indeed, Metha and Mullen (1996) showed higher performance of the flicker detection in achromatic condition compared to the condition with red-green stimuli. The auditory information can be more effective on a slower, less sensitive system. Therefore, the two visual pathways with different temporal resolutions could be involved with different degrees in the two illusions; in other words, STS could receive information through different pathways depending on the type of integration.

We used pathway-specific visual stimuli simultaneously with pure, meaningless tones as input for the integration processes. We hypothesized that the parallel pathways in accordance to their temporal resolution play different roles in the illusions. Multimodal stimuli – especially in temporal context – are frequently used to get better understanding of how different modalities can combine and influence the processing of each other. The double flash and fusion illusions are appropriate phenomenons to investigate the temporal aspect of audio-visual integration. Still, it is not clear which mechanisms of the visual machinery contribute to these findings. The next logical step in understanding the neuronal background of the illusory flash phenomenon could be an approach where we make a functional distinction between the cortical pathways. We are aware of the fact that this distinction (especially at higher levels than the primary visual cortex) is less and less valid, but this might serve as a good working frame for collecting more data about the double flash and flash fusion and the underlying mechanisms.

Methods

Participants

Thirty-four healthy naive volunteers participated in the study. They had normal or corrected vision and normal hearing, with no known neurological disorders. Their color vision was found to be good by the Ishihara

color perception test. Each one signed an informed consent before the test. The experiment fulfilled the requirements of the Ethical Committee for Experimental Procedures of the University of Szeged.

Seventeen (12 females; mean age: 22.6 years) of thirty-four subjects participated in the test with central visual stimulation, and the other seventeen subjects (13 females; mean age: 22.2 years) with peripheral visual stimulation.

Stimuli and procedure

Subjects were seated in a sound-attenuated dark room. Their heads were rested on a chin and forehead support. The eyes of the subjects were 57 cm away from the computer screen and the speakers.

The stimuli were presented on a CRT monitor (ViewSonic PF815). The diameter and the resolution of the screen were 21 inches and 800 x 600 at 60 Hz, respectively.

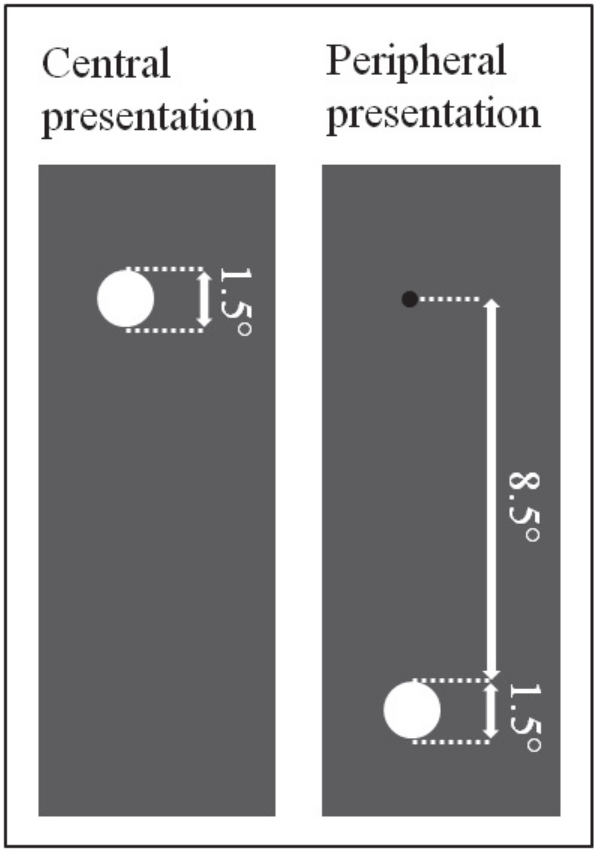

Fig. 1. Location and luminance of the stimuli. Grey scaled versions of the presented stimuli in central and peripheral conditions. In both positions the visual angle of the presented disc was 1.5° on a green background. In the high contrast conditions the contrast was 75 %. In the low contrast conditions the contrast was 9 %. In the isoluminant conditions a red disc was presented on the background. The little dark point on the upper part of the panel represents the fixation point in the peripheral condition.

The two computer speakers were positioned on both sides of the monitor, symmetrically, at 25° from the fixation point. Subjects had to fix their gaze at the middle of the monitor, thus the size and position of the visual stimuli were held constant on the retina. A disc subtending a visual angle of 1.5° was displayed in a central or peripheral position as visual stimulus for the two groups of the subjects (central and peripheral stimulation, respectively).

All stimuli were presented on a uniform green background (8.9 cd/m^2). We used four conditions with high contrast (HC) with white disc (63 cd/m^2, contrast 75 %), low contrast (LC) with grey disc (9.7 cd/m^2, contrast 9 %), subjective isoluminant (S-iso) and physically isoluminant (P-iso) with red disc in both positions (Fig. 1). In the above mentioned experiments the same size of stimuli were used with high contrast. So we created a high contrast condition to make our results comparable with earlier findings. With low contrast stimuli we can drive the M pathway. We chose a relatively high contrast value to exclude the big variability between subjects in the control condition. The contrast values were calculated using the Michelson equation.

We used two types of isoluminant conditions. Both of them had color information, thus they drove the P pathway. The physically isoluminant stimuli have only color information, but the different colors drive the visual system with different strength. The subjective isoluminant stimulus is known as it can drive most selectively the P pathway (Skottun 2013). In the peripheral task a fixation point was placed in the middle of the screen and the stimulus disc was presented it at 9.25° eccentricity (Watkins *et al.* 2006). In the central task, the disc was presented in the middle of the screen without fixation point.

To measure the subjective isoluminance level of the red disc compared to the green background we used the method of heterochromatic flicker photometry (HFP). Red and green discs were reversed at 14 Hz (Kveraga *et al.* 2007) on a gray background. The size and position of the disc was the same as we used for the main experiment. We created a range of red intensities and presented them one by one to the participants during the HFP test. Since isoluminance changes across the retina (Bilodeau and Faubert 1997), the test was performed both in the central and the peripheral retina location as well. The luminance value of the green was the same as the background we used in the main experiment. The subjects

viewed the display binocularly and were asked to choose the intensity value of red where minimal or no flicker was perceived. The isoluminant point was the average of at least three consecutive, independent and consequent measurements.

The central and peripheral tasks contained four blocks (four main conditions, HC, LC, S-iso, P-iso), and followed each other randomly to reduce the chance of fatigue or learning. One block contained 6 subconditions: 6 variations of flashes and tones (one flash, one flash with one tone, one flash with two tones, two flashes, two flashes with one tone, and two flashes with two tones). One subcondition consisted of 40 repetitions of trials, thus one block contained 240 semirandom-presented trials.

The presentation of the trial started with the green background. On this background, after 200 ms one or two discs were presented for 1 frame (17 ms) with one or two tones, according to the given condition. The stimulus onset asynchrony (SOA) between two flashes was 85 ms. The duration of the tones (3.5 kHz, 70 dB SPL) was 10 ms, and the first one was presented at the same time as the first flash. The SOA between the two tones was 85 ms. The previously mentioned experiments used auditory and visual stimuli slightly shifted in time but as reported the two designs with simultaneously presented or shifted stimuli resulted only in slight differences (Watkins *et al.* 2007).

After the presentation of flashes and tones the subject was asked to decide whether one or two discs were displayed independently of the tones and press the left (one flash) or right arrow (two flashes) button on the keyboard with the dominant hand. After the subject pressed a button, an isoluminant grey background (8.9 cd/m^2) appeared as intertrial interval for 1000 ms (Fig. 2). Feedback was not provided about the correctness of the response.

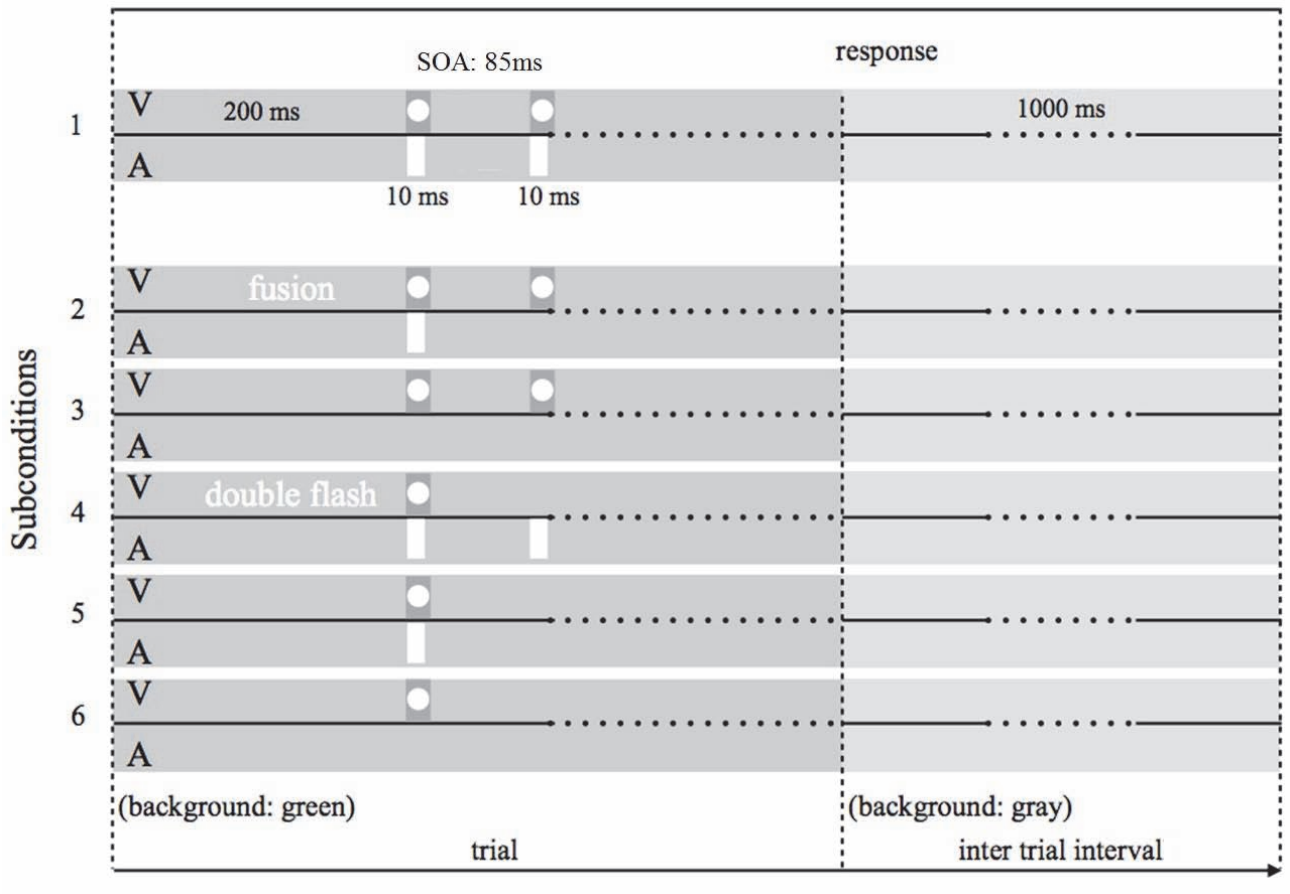

Fig. 2. Design of the task. Stimuli were presented were on green background according to the given subconditions. 1: two discs were presented with two tones; 2: two discs were presented with one tone; 3: two discs were presented without any tones; 4: one disc was presented with two tones; 5: one disc was presented with one tone; 6: one disc was presented without any tones. The duration of the tone was 10 ms and the SOA for the two tones was 85 ms. The duration of the visual stimuli was 17 ms and the SOA for the visual stimuli was 85 ms. After the response an isoluminant gray background was presented for 1000 ms.

Analysis

Signal detection theory was used to analyze the behavioral results. The rationale behind this is that this way we can verify that the illusions are caused by changes of perceptual sensitivity rather than by the general response bias. This method can describe the sensitivity of the subjects toward the visual stimuli during the process of decision. The sensitivity is expressed as $d' = z(H) - z(F)$, where d' is sensitivity, and z is the inverse cumulative normal. Correct identification of the second flash was recorded as a 'hit' (H); when the subject reported one flash instead of two, it was recorded as a 'miss'. When one flash was reported as two, we accepted it as a 'false alarm' (F) and the correct identification of one flash was accepted as a 'correct rejection'. To calculate the d' value for control we used two sub-conditions without tones (one flash and two flashes). For fusion we used two sub-conditions with one tone (one flash with one tone and two flashes with one tone) and for double flashes we used two sub-conditions with two tones (one flash with two tones and two flashes with two tones).

To see the power of illusions we compared the control d' value to the d' for fusion or double flash using paired t-test (Watkins *et al.* 2006) with Bonferroni correction in each condition. Thus we accepted results as significant when the $p<0.025$. Since the strength of the illusions are characterized by this difference, we used these values to test the variance between the conditions with one-way repeated measures ANOVA with Greenhause-Geisser correction in central and peripheral conditions. We used Bonferroni as a post-hoc test.

We calculated a criterion (C) to indicate response bias with the expression

$C = -[z(pH) + z(pF)]/2$ (Macmillan and Creelman 2004)

Thus the positive value of the C shows the bias when the subjects report rather one, and negative value when two flashes.

Table 1. Criterion and d' values in the condition where stimuli were presented centrally.

Central condition		Criterion mean	SEM	d' mean	SEM
HC	*sensitivity*	−0.725	0.080	3.376	0.344
	fusion	−0.019	0.154	2.944	0.301
	double flash	−1.751	0.211	1.707	0.418
LC	*sensitivity*	−0.442	0.148	2.904	0.290
	fusion	0.318	0.114	2.496	0.295
	double flash	−1.556	0.162	1.616	0.375
S-iso	*sensitivity*	0.101	0.184	3.137	0.262
	fusion	0.889	0.127	2.078	0.323
	double flash	−0.947	0.226	2.139	0.326
P-iso	*sensitivity*	−0.324	0.134	3.325	0.346
	fusion	0.348	0.146	2.586	0.331
	double flash	−1.549	0.159	2.174	0.431

Data are means and standard errors. HC: high contrast, LC: low contrast, S-iso: subjectively isoluminant, P-iso: physically isoluminant

Results

The detailed data are collected in Table 1, 2, 3 and 4. Here we describe only the relevant statistical results. The criterion showed significant positive bias for fusion and negative bias for double flash compared to control criterion in all condition. This shows that one tone biased the participants to report one flash instead of two for fusion, and two tones biased them to report two instead of one for double flash illusions.

Central presentation: In the high contrast condition, no significant fusion effect was shown, $t(16)=1.71$, $p=0.10$), but there was a significant double flash effect after Bonferroni correction, $t(16)=5.06$, $p<0.001$ (Fig. 3A).

In the low contrast condition, no significant fusion effect was shown, $t(16)=2$, $p=0.05$, but there was a significant double flash effect, $t(16)=4.29$, $p<0.001$, with the same test (Fig. 3B). In the subjective isoluminant condition, both significant fusion, $t(16)=5.167$, $p<0.001$, and significant double flash effect, $t(16)=3.72$; $p<0.01$, were shown (Fig. 3C).

Table 2. Criterion and d' values in the condition where stimuli were presented peripherally.

Peripheral condition		Criterion mean	SEM	d' mean	SEM
HC	*sensitivity*	−0.338	0.173	3.448	0.268
	fusion	0.613	0.213	2.602	0.353
	double flash	−1.918	0.152	1.563	0.248
LC	*sensitivity*	−0.560	0.156	2.910	0.262
	fusion	0.482	0.157	3.169	0.400
	double flash	−1.759	0.156	1.740	0.246
S-iso	*sensitivity*	−0.176	0.187	3.118	0.322
	fusion	0.428	0.169	2.564	0.355
	double flash	−1.609	0.171	1.682	0.254
P-iso	*sensitivity*	0.022	0.175	2.684	0.285
	fusion	0.776	0.163	1.994	0.275
	double flash	−1.885	0.168	1.214	0.271

Data are means and standard errors. HC: high contrast, LC: low contrast, S-iso: subjectively isoluminant, P-iso: physically isoluminant

Table 3. The results of the statistical comparison concerning the criterion levels under the central condition.

Central condition		t(16)	p values
HC	*fusion*	4.715	<0.001
	double flash	4.989	<0.001
LC	*fusion*	5.178	<0.001
	double flash	6.673	<0.001
S-iso	*fusion*	5.492	<0.001
	double flash	5.311	<0.001
P-iso	*fusion*	4.206	<0.001
	double flash	6.729	<0.001

HC: high contrast, LC: low contrast, S-iso: subjectively isoluminant, P-iso: physically isoluminant

Table 4. The results of the statistical comparison concerning the criterion levels under the pheripheral condition.

Peripheral condition		t(16)	p values
HC	*fusion*	6.084	<0.001
	double flash	6.250	<0.001
LC	*fusion*	4.760	<0.001
	double flash	7.324	<0.001
S-iso	*fusion*	3.584	<0.01
	double flash	5.618	<0.001
P-iso	*fusion*	4.275	<0.001
	double flash	9.050	<0.001

HC: high contrast, LC: low contrast, S-iso: subjectively isoluminant, P-iso: physically isoluminant

In the physically isoluminant condition, both illusions, the fusion, $t(16)=2.771$, $p<0.05$, and also the double flash, $t(16)=2.74$, $p<0.05$, were significant (Fig. 3D).

The repeated measures ANOVA of the difference scores for the central conditions did not reveal any significant differences between the different conditions (high-contrast, low contrast, subjectively or physically isoluminant), either for the fusion ($F(2.676, 42.81)=1.748$, $p=0.17$) or for double flash ($F(2.472, 39.55)=1.287$, $p=0.29$) illusions (Fig. 3E-F).

Peripheral presentation: In the high contrast condition, significant fusion effect, $t(16)=3.47$, $p<0.01$, and double flash effects, $t(16)=4.86$, $p<0.001$, were shown (Fig. 4A).

In the low contrast condition, no significant fusion effect was shown, $t(16)=0.93$, $p=0.36$, but there was a significant double flash effect, $t(16)=3.66$, $p<0.01$ (Fig. 4B).

In the subjective isoluminant condition, no significant fusion effect was shown, $t(16)=1.83$, $p=0.08$, but there was a significant double flash effect, $t(16)=3.68$, $p<0.01$ (Fig. 4C).

In the physically isoluminant condition, significant fusion effect, $t(16)=4.42$, $p<0.001$, and also double flash effect, $t(16)=4.52$, $p<0.001$, were shown (Fig. 4D).

The repeated-measures ANOVA of the difference scores for the peripheral conditions showed significant differences between the different conditions (high-contrast, low contrast, subjectively or physically isoluminant) for the fusion effect ($F(2.286, 36.58)=$

3.898, p<0.05), but there were no significant differences between the different conditions for the double flash (F (2.684, 42.94)=1.653, p=0.19) illusion (Fig. 4E-F). In case of the fusion effect the Bonferroni multiple comparison test showed that in the LC condition the difference between the control d' and d' for fusion is bigger than these values in P-iso conditions.

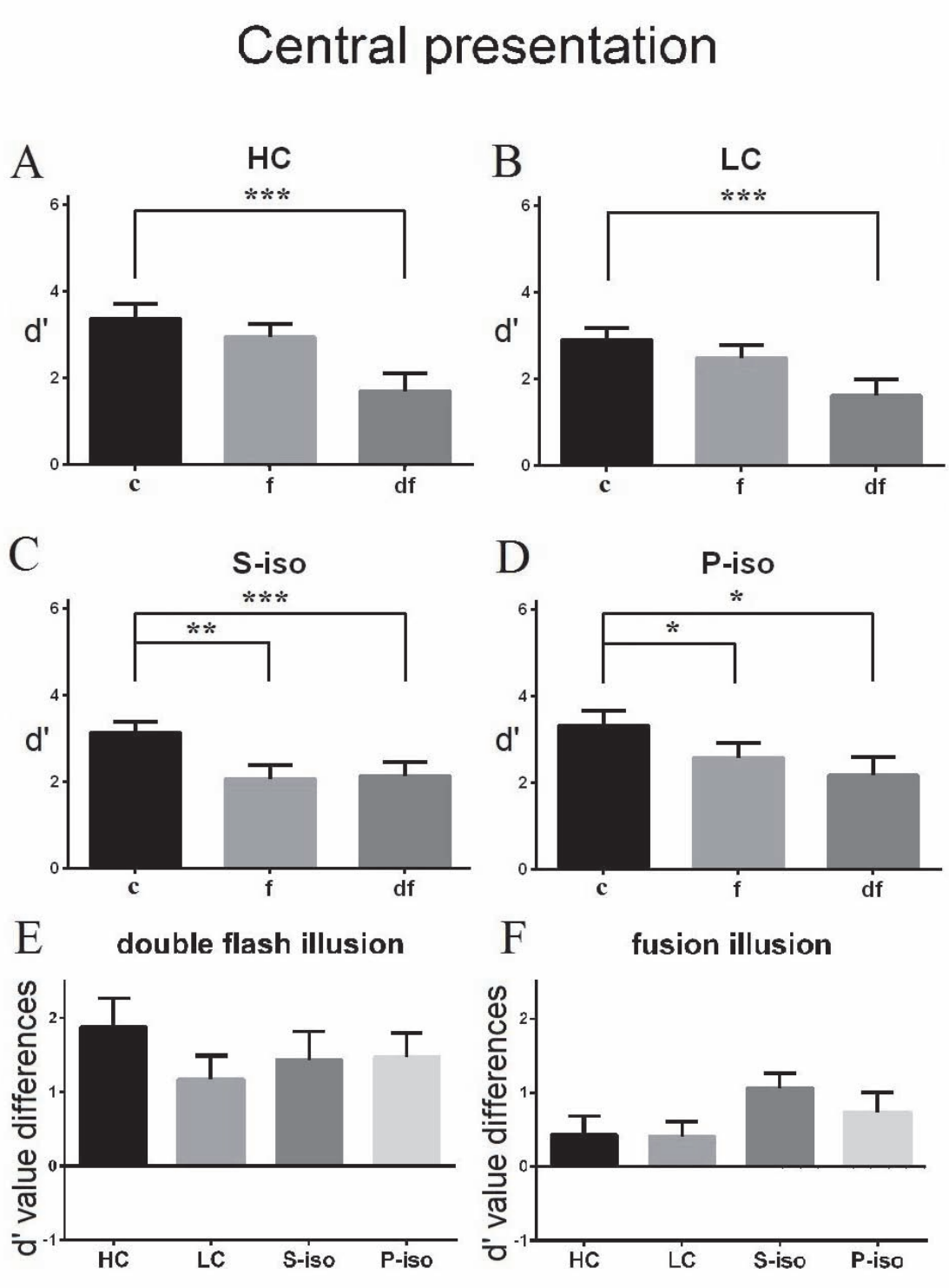

Fig. 3. Results of the psychophysical test in the central condition. The diagram shows the means and standard errors of d' values and the significant results of the paired t-test in the central conditions. Significant changes p<0.05 (*), p<0.01 (**) and p<0.001 (***) are indicated by asterisks, n=17. **Panel A**: HC: high contrast, **panel B**: LC: low contrast, **panel C**: S-iso: subjectively isoluminant, **panel D**: P-iso: physically isoluminant. **Panel E** and **F** show the means and standard errors of differences between control and double flash d' values for double flash (ANOVA, F (2.472, 39.55)=1.287; p=0.29; n=17) and between control and fusion d' values for fusion (ANOVA, F (2.676, 42.81)=1.748; p=0.17; n=17). c: control, f: fusion, df: double flash

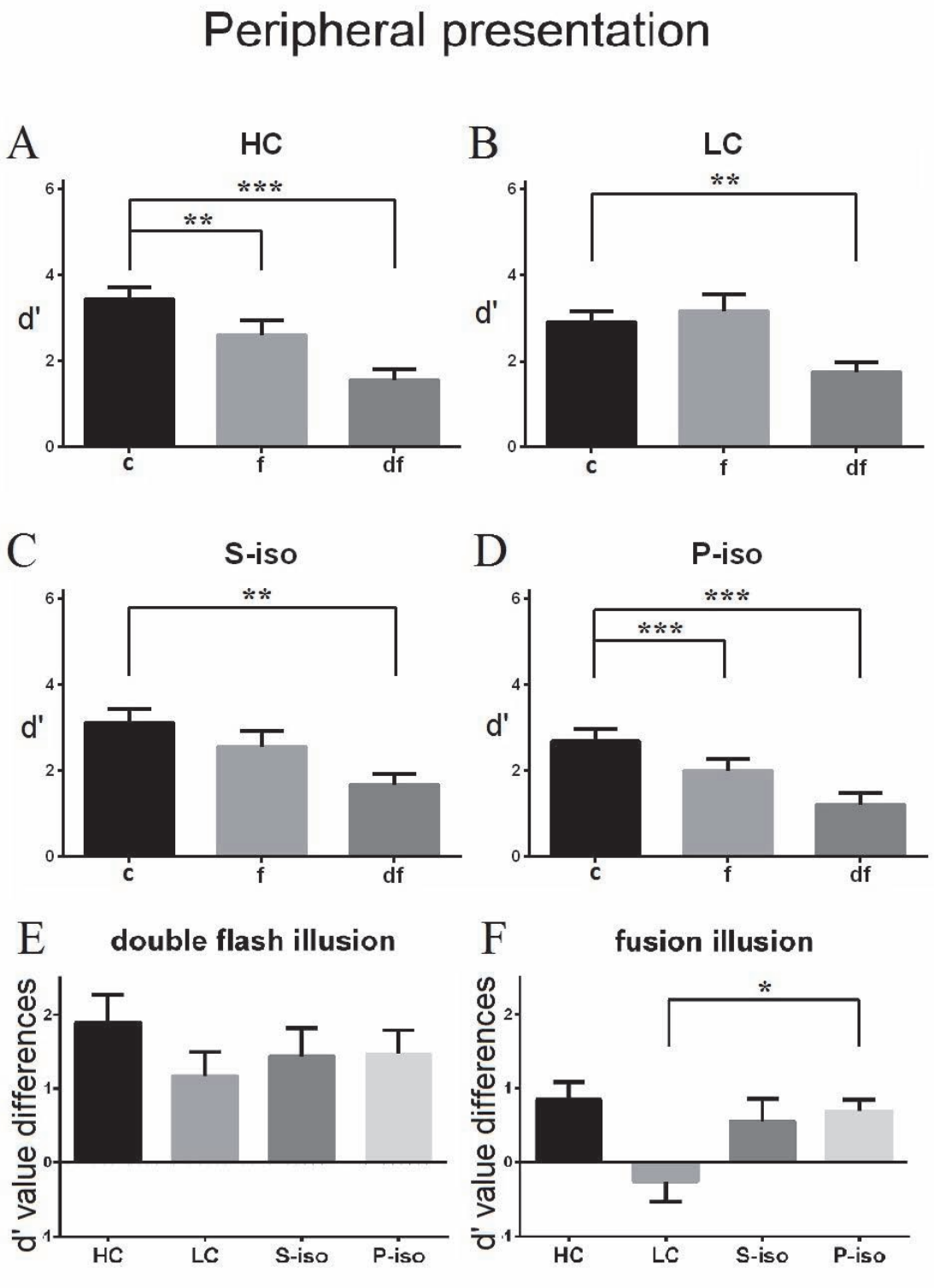

Fig. 4. Results of the psychophysical test in the peripheral condition. The diagram shows the means and standard errors of d' values and the significant results of the paired t-test in the peripheral conditions. Significant changes $p<0.05$ (*), $p<0.01$ (**) and $p<0.001$ (***) are indicated by asterisks, n=17. **Panel A**: HC: high contrast, **panel B**: LC: low contrast, **panel C**: S-iso: subjectively isoluminant, **panel D**: P-iso: physically isoluminant. **Panel E** and **F** show the means and standard errors of differences between control and double flash d' values for double flash (ANOVA, F (2.684, 42.94)=1.653; p=0.19; n=17) and between control and fusion d' values for fusion (ANOVA, F (2.286, 36.58)=3.898; $p<0.05$; n=17). Bonferroni's multiple comparison test showed that the LC condition is different from P-iso condition for fusion. c: control, f: fusion, df: double flash

Discussion

As described earlier the double flash illusion is a very robust phenomenon (Shams *et al.* 2000). The demonstration of the flash fusion is more difficult because this illusion is fairly weak compared to double flash illusion, the variations in the behavioral performances among participants are quite large; a group of participants did not even report this illusion (Mishra *et al.* 2008). Thus unless the visibility (modulated by eccentricity and size) of the originally used high contrast disc is extremely poor, the incidence of the flash fusion would be stochastic, depending on the given group of participants (Mishra *et al.* 2008). Generally, we found the same results as mentioned above with the stimulus set described. The variety of behavioral performance among participants shows a wide range; however, even so we got significant differences for the double flash in all conditions at both central and peripheral stimulus presentations. In some conditions the occurrence of the double flash illusion was more frequent at the peripheral than the central condition, which is consistent with the early results (Bhattacharya *et al.* 2002).

Previously reported theory suggests that the connection between the primary visual cortex and the STS can play a substantial role in the processing of these illusions. Our aim was to investigate this processing from a different aspect. For this we found driving the different visual pathways a useful approach. We designed stimuli which are matched to the sensitivity of the different pathways. However, we have to note that entirely selective stimulation of the M or P pathway is not possible. High contrast stimuli can drive both pathways strongly. Low contrast stimuli can drive the M pathway separately, but this kind of stimulus is quite weak, so it cannot drive the whole pathway to its full extent. Both the subjective and the physical isoluminant stimuli contain color information, thus they can drive the P pathway. In addition the subjective isoluminant stimuli are known to be selective for the P pathway.

To separate the pathways better we used central and peripheral stimulation. The M pathway receives information mainly from the non-central retina through the M ganglion cells. On the other hand, the P pathway receives information from the whole retina through the P ganglion cells, but the density of P ganglion cells decreases towards the periphery of the retina. Thus, the central stimulation facilitates the processing through P pathway, while peripheral stimulation drives both pathways. However, our central stimulation cannot stimulate only the P pathway, because the stimuli, used in other studies and our own as well, are relatively big. There is also a remarkable difference between the retinotopic areas in connecting to other areas, because anatomical connections were found between the primary auditory cortex, superior temporal polysensory area (STP) and the peripheral, retinotopically organized part of the V1 (Clavagnier *et al.* 2004, Falchier *et al.* 2002, Rockland and Ojima 2003).

In spite of high variations of the behavioral performance and with the above mentioned restrictions, we found significant differences for the double flash illusion in high contrast conditions with central and peripheral stimulations, which is consistent with previous studies. We also found a strong double flash illusion in the pathway-specific conditions. This indicates that the incongruently added second tone can modulate the visual processing through M and P pathways and evokes the illusory perception of a second flash. In case of double flash we did not find dependence on the two pathways, although this could be explained by the robustness of this illusion. The condition, which does not subserve the double flash illusion, might be more sensitive for the differences.

With central stimulation we found a strong significance for fusion in the conditions with red-green color information. These P pathway optimized (subjectively and physically isoluminant) stimuli are mainly processed through a system having low temporal resolution. This system can be biased easily by the incongruent tone, thus it can fuse the flashes more easily and induce the flash fusion illusion. On the other hand, stimuli optimized for the M pathway are processed through a system having high temporal resolution, which can make distinctions between two flashes easily, thus it cannot sustain the fusion illusion.

With peripheral stimulation we found a strong significance for fusion in the physically isoluminant and in the high contrast conditions. In the high contrast condition the incidence of the flash fusion is not surprising, since it can vary as described earlier, depending on the given group of participants (Mishra *et al.* 2008). With stimuli optimized for the M pathway we could not induce the fusion illusion. Although we did not find a significant fusion illusion in the subjectively isoluminant condition peripherally, however the difference between the fusion which was found in physical isoluminant condition and the d' level in low

contrast condition was supported also by the variance analysis.

In conclusion, we found that the robust double flash illusion can be induced on both M and P pathways. The fusion illusion can be induced in the P pathway, while the M pathway does not support it. Although the difference could be observed only at the peripheral condition, the incidence of flash fusion seems to be pathway-specific depending on the temporal resolution of the given pathway. Thus the origins of the fusion and double flash illusion related activity in STS seem to not identical and it presumes different mechanisms of integration.

Conflict of Interest

There is no conflict of interest.

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List of Abbreviations

Low contrast condition: LC
High contrast condition: HC
Subjectively isoluminant condition: S-iso
Physically isoluminant condition: P-iso
f: fusion
df: double flash
c: control

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Transcranial Stimulation of the Orbitofrontal Cortex Affects Decisions about Magnocellular Optimized Stimuli

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Visual categorization plays an important role in fast and efficient information processing; still the neuronal basis of fast categorization has not been established yet. There are two main hypotheses known; both agree that primary, global impressions are based on the information acquired through the magnocellular pathway (MC). It is unclear whether this information is available through the MC that provides information (also) for the ventral pathway or through top-down mechanisms by connections between the dorsal pathway and the ventral pathway via the frontal cortex. To clarify this, a categorization task was performed by 48 subjects; they had to make decisions about objects' sizes. We created stimuli specific to the magno- and parvocellular pathway (PC) on the basis of their spatial frequency content. Transcranial direct-current stimulation was used to assess the role of frontal areas, a target of the MC. Stimulation did not bias the accuracy of decisions when stimuli optimized for the PC were used. In the case of stimuli optimized for the MC, anodal stimulation improved the subjects' accuracy in the behavioral test, while cathodal stimulation impaired accuracy. Our results support the hypothesis that fast visual categorization processes rely on top-down mechanisms that promote fast predictions through coarse information carried by MC via the orbitofrontal cortex.

Keywords: tDCS, OFC, categorization, magnocellular pathway, top-down

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INTRODUCTION

Fast decisions about environmental information require categorization to distinguish between animate and non-animate things, plants and animals, vehicles and buildings, etc. (Fabre-Thorpe, 2011). Categorization serves not only distinction but also generalization when different objects are grouped on the basis of shared features (Keller and Soenfeld, 1950). The visual environment does not always favor perception: fog, poor lighting, absence of colors, low contrast, short flashes of an image allow only decisions made on the basis of coarse, global features or outlines of objects. In addition, sometimes only the periphery of the visual field is stimulated; still, we need to know whether this visual information has any relevance. For a detailed analysis on the other hand, fine details, colors and edges are important.

For fast and efficient categorization relevant information and actual goals should be considered. This process might root in the two major visual processing streams: the magnocellular pathway

(MC) and the parvocellular pathway (PC). The majority of axons leaving the retina belong to either the MC or the PC. The MC runs (partly) to the frontal lobe, while the end of the PC stream is in the inferotemporal cortex (IT), a region essential for visual recognition. Instead of a detailed description (but see e.g., Mishkin and Ungerleider, 1982; Goodale and Milner, 1992) of the fundamental differences in the properties of the MC and the PC, here we focus only on those features of the MC which are relevant to our study. The MC pathway is very fast. Differences in conduction speed between the two pathways can be demonstrated as early as the lateral geniculate body (LGB): information arriving via the PC has some 20 ms delay as compared to the MC, and this difference is also present in V1 (Maunsell and Newsome, 1987; Nowak et al., 1995; Schmolesky et al., 1998). After V1 it takes only 6–9 ms to reach V3, the middle temporal area (MT), the middle superior temporal area (MST) or the frontal eye field (FEF) (Schmolesky et al., 1998).

On the basis of latency differences between the PC and the MC, Nowak and his colleagues suggested that visual signals processed in the MC might modulate activity in the PC through feed-forward, lateral or feed-back connections (Nowak and Bullier, 1997). Information carried rapidly by the MC toward the frontal areas may exert a top-down effect. In contrast with the hierarchical views of visual processing, this top-down effect is supposed to be able to modulate lower regions from higher cortical areas which have been activated earlier (Knierim and van Essen, 1992; Zipser et al., 1996). However, due to the fact that the MC is sensitive only to coarse features, the role of the MC in object recognition was not investigated for long. Recently published papers, however, suggest that when time is an issue, the MC carries sufficient data to extract relevant information, which—provided there is enough time—can be completed by colors and details carried by the PC. Several experiments (see below) were carried out in order to investigate rapid categorization by using pathway-specific stimulation.

Research on decisions concerning MC information can benefit from the fact that images projected on the peripheral retina almost exclusively stimulate the rod system. In a study by Thorpe and colleagues (Thorpe et al., 2001), participants had to decide about images and choose between animate/non-animate categories. Their results showed that eccentricity did not have an influence on the accuracy of the decisions and that low spatial frequency (LSF) information originating from the periphery of the retina was sufficient for categorization. It was also shown that rapid categorization is possible in the absence of colors (Delorme et al., 2010). The MC is sensitive to the achromatic differences in luminance; the pathway can be stimulated by stimuli having low (<8%) contrast and LSF (Tootell et al., 1988). Experiments on monkey and human participants using contrast differences (Mace et al., 2005, 2010) were performed and showed that images with sufficiently low contrast are invisible for the PC, so decisions concerning the stimuli *must* be based on information carried by the MC. If the PC were the only pathway involved in visual categorization, low contrast stimuli should cause a dramatic decrease in performance. However, at contrast values of 3% performance did not change significantly in either species, which suggests that it might be done on the basis of coarse information carried by the MC (Bar et al., 2001; Bar, 2003).

Different spatial frequencies carry different aspects of the visual stimuli. High spatial frequencies (HSFs) carry information about edges and patterns, while LSFs contain global information. The latter might be sufficient to make a first, global impression about the general shape of objects. Psychophysical studies show that LSF patterns (Sachs et al., 1971; De Valois et al., 1990) and complex sceneries (Schyns and Oliva, 1994; Mace et al., 2005, 2010) are perceived earlier than high SF. Electrophysiological results show that the first part of the activity of IT cells reflects global information (Sugase et al., 1999; Tamura and Tanaka, 2001) and only the later part of the responses, after some 51 ms, carries information about fine details (Sugase et al., 1999). This means that IT neurons respond first to low LSF and global features and only after that to fine details.

According to the studies mentioned above and based on their EEG findings, Thorpe and Fabre-Thorpe suggested an MC based, fast pathway which uses the same cortical areas as the ventral pathway. Thus, MC information arrives at the IT faster and reaches the prefrontal cortex and the motor cortex earlier than information carried by the PC if a fast decision is needed (Fabre-Thorpe et al., 2001; Thorpe and Fabre-Thorpe, 2003). Reaction times in monkeys performing rapid visual categorization are as short as 180 ms, which leaves time only for a feed-forward processing through the IT to the motor cortex via the prefrontal and premotor cortices (Fabre-Thorpe et al., 1998). It was also suggested that MC information supported PC processing through fast, local feed-back circuits along the ventral visual stream (Fabre-Thorpe, 2011).

Bar and his colleagues, on the other hand, hypothesized a top-down process which, using the rapid processing in the MC through the dorsal pathway could provide the IT with coarse but fast information through the orbitofrontal cortex (OFC). This top-down mechanism can limit the number of possible interpretations, decrease the amount of necessary computation and reduce the time needed. This global information is essential for making fast decisions for survival (Bar, 2003). In these experiments, the two pathways were stimulated selectively and categorization was required (Bar, 2003; Kveraga et al., 2007a,b). According to the findings, the critical structure in top-down processes is the OFC, whose early activation can be attributed to processing visual information in the MC (Bar, 2003; Kveraga et al., 2007b). In addition, a study investigating the functional coupling of cortical areas found phase coupling between V1 and the OFC, and the OFC and the IT (see Lin et al., 2004). Rokszin et al. (2016) investigated how the top-down effects are manifested in scalp ERPs when presenting low or high SF information. They found evidence of top-down, anterior effect for MC optimized images within the first 200 ms of visual processing (shorter N1 latencies and amplitude changes spreading to anterior scalp regions). The connection is provided by the fibers of the uncinate fascicle and the external capsule connecting the OFC with the IT (Cavada and Goldman-Rakic, 1989; Cavada et al., 2000; Fang et al., 2005).

It is important to note that although the MC is regarded as the main input for the dorsal or "Where?" pathway processing

motion and serving spatial attention, nearly 50% of the MC fibers feed information into the ventral stream (Ferrera et al., 1992; Nealey and Maunsell, 1994). There is plenty of evidence supporting the role of the MC pathway in fast categorization; however, it is unclear whether this information after leaving V1 reaches the IT via the dorsal (a top-down process through the OFC) or the ventral pathway (local feed-forward or feed-back circuits preceding PC information) (**Figure 1**).

The goal of our study was to determine which of the above scenarios is more likely: does MC information responsible for fast visual decisions pass through the OFC or does it run together with the ventral pathway? One possible approach of the problem might be to interfere with the dorsal or ventral pathway to see whether the processing of those stimuli which are characteristic to the given pathway is affected or not. A logical choice is a non-invasive and reproducible electrical stimulation of the pathway(s).

Electrical stimulation manipulates the activity of cortical networks transitionally and reversibly in a non-invasive and painless way. The method consists of a weak transcranial current (tDCS) flowing through the brain using two large surface electrodes (Nitsche and Paulus, 2000; Manuel et al., 2014), which can influence cortical functions. In the past few years several studies investigated visual processing in humans using non-invasive electrical stimulation to directly modulate visual cortices in human subjects (Antal et al., 2001). The anodal stimulation over V1 increases the sensitivity of phosphenes (Antal et al., 2003a), contrast sensitivity, enhances the amplitude of N70 while the opposite effects were found using cathodal stimulation (Antal et al., 2003b,c, 2004a; Kraft et al., 2010). Futhermore, tDCS modulates human color discrimination in a pathway-specific manner (Costa et al., 2012). The anodal stimulation over MT improves learning of visually guided tracking movements (Antal et al., 2004c). After learning the anodal stimulation has no effect, but cathodal stimulation can increase the signal-to-noise ratio and improve the performance in the learned task (Antal et al., 2004b). The tDCS over the posterior parietal cortex modulates visuospatial processing (Sparing et al., 2009), bilateral stimulation over the anterior temporal lobe (right anodal, left cathodal) improves visual memory (Chi et al., 2010), cathodal stimulation of the temporo-parietal cortex reduces the magnitude of facial adaptation (Varga et al., 2007). Also, anodal stimulation improves implicit learning when the left prefrontal cortex is stimulated (Kincses et al., 2004) and enhances the recognition of facial expression when right OFC is stimulated (Willis et al., 2015). For a review see Antal et al. (2011) and Costa et al. (2015).

Effects of tDCS might be explained by the modulation of the resting membrane potentials of the stimulated area. Single cell recording studies have shown that cathodal stimulation can decrease firing activity, while the anodal stimulation have the opposite effect (Bindman et al., 1964; Purpura and McMurtry, 1965). In humans the tDCS has similar polarity dependent effects (Nitsche and Paulus, 2000, 2001). It seems that tDCS effects appear to be site specific but not site limited; the latter effects might be based on plasticity mechanisms.

Since tDCS seems to be a powerful technique for investigation visual processing, we applied cathodal or anodal tDCS and sham stimulation as a control in a decision making test, over the OFC

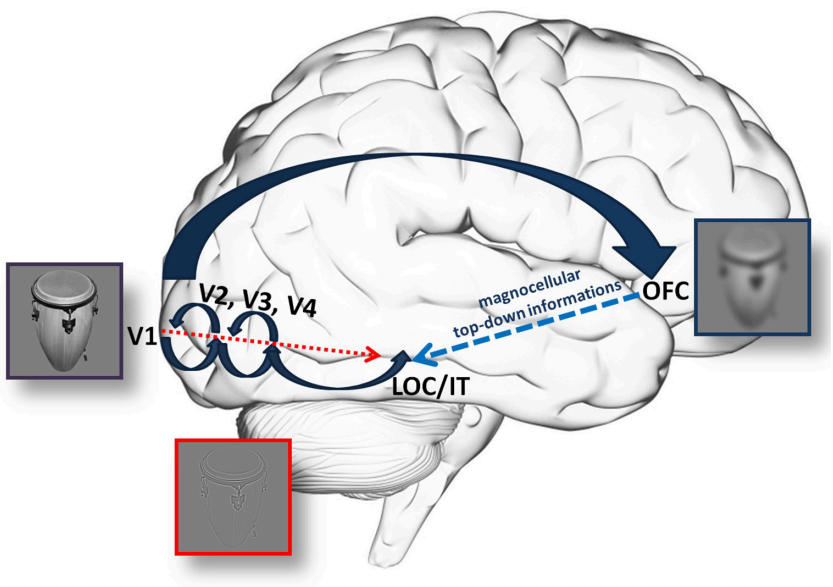

FIGURE 1 | An illustration of the hypothetical anatomical background for information processing through the (fast) magnocellular and parvocellular pathway. According to Fabre-Thorpe (2011), MC information supports PC processing through fast, local feed-back circuits. On the other hand, Kveraga and his colleagues hypothesized a top-down process, which, using the rapid processing in the MC, could provide the IT through the OFC with fast but coarse information. This can feed-back to the ventral stream to limit the number of possible interpretations, decrease the amount of necessary computation and the time needed. Please note, that arrows merely indicate a supposed, general flow of information and not necesseraly anatomical stages. This is especially true for large arrow indicating the dorsal pathway, where the route of information is not yet clear.

(Nitsche et al., 2008; Dayan et al., 2013; Manuel et al., 2014; Willis et al., 2015). Our subjects were required to make a judgment on the real size of objects seen on the screen, i.e., whether they fit in a shoebox or not? There were two sessions; between the two sessions tDCS stimulation was applied.

There are two possible scenarios concerning the outcome. If stimulation of the OFC does not have an effect on decisions concerning *both* MC *and* PC optimized stimuli, or if the effects are similar using *both* stimuli that would support the idea that fast MC information is processed through the ventral pathway avoiding the OFC. Thus, only *decision mechanisms* were affected, but not the *route of information flow*. If, on the other hand, decisions about MC stimuli were affected selectively, it would support the hypothesis that MC information reaches the OFC, passes through it and is available for top-down modulation (Bar et al., 2006).

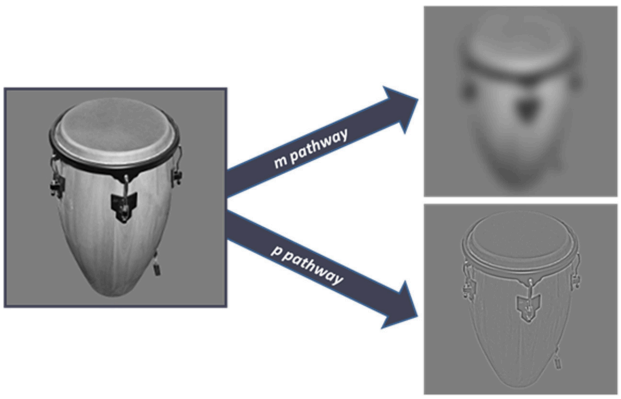

FIGURE 2 | The image on the left is the original unfiltered image of an object received by the retina. The right side of the figure shows the two kinds of stimuli used in the experiment. The upper image is filtered for the selective stimulation of the magnocellular pathway. The bottom image is optimized for the ventral stream, in accordance with the sensitivity of the parvocellular pathway.

MATERIALS AND METHODS

Stimuli

The stimulus set contained 200 achromatic images of everyday objects, like a truck, ashtray, pen, piano, etc. One part of the images was collected from the Bank of Standardized Stimuli (Brodeur et al., 2010) others were selected and collected by one of the authors (A.B.). Stimuli were modified using Matlab and GIMP 2.8 programs. Stimuli were cut out from the original pictures, were standardized in the sense that all had the same size in their largest dimension (4,5° viewed from 57 cm) placed on the same background, transformed to grayscale images. Shine Toolbox was used to equalize the contrast and luminance values before filtering (Willenbockel et al., 2010). Images had resolutions of 72 pixels per inch and size of 500*500 pixel. The visual stimuli were modified to selectively stimulate the MC or the PC; they were filtered by Gaussian filter (12 pixel kerner, as lowpass filter) and highpass filter (0.5 radius) to attenuate the high and spatial frequencies, respectively. The MC optimized stimuli contained LSF (<0.9 cycles per degree), while the PC stimuli consisted of HSF (>4.7 cycles per degree, **Figure 2**). This method is similar to the one used by Bar et al. (2006). All stimuli had a mean luminance between 8 and 9 cd/m^2. No luminance matching was used after filtering. The images of the objects could be divided into two groups according to their real life size. One half of the objects were larger, while the others were smaller than an average shoe box. All stimuli were presented on a uniform gray background (8.9 cd/m^2). For stimulus presentation a 23-inch LCD (Tobii Pro TX300) monitor was used having screen resolution of 1,920 × 1,080 and vertical refresh rate of 60 Hz.

Subjects

Forty-eight healthy subjects (university students, 19 females; mean age: 22.7 years) participated in the study. They were divided in three equal groups for cathodal, anodal and sham stimulation. Each subject had to perform the task before and after the stimulation (see below). All had normal or corrected-to-normal vision, including normal color vision and none of them suffered from any neurological or psychiatric disorders. None of them had a history of excessive drug/alcohol/caffeine consumption. A questionnaire was provided regarding previous diseases, handedness (Oldfield, 1971), sleep time, medication, mental and physical status. All study participants gave written informed consent in accordance with the Declaration of Helsinki; the study was approved by the ethical committee of the University of Szeged (Ref. no.: 165/2014).

Behavioral Test

The subjects were seated in a sound-attenuated, dimly lit room, and viewed the computer screen from 57 cm. For stimulus presentation a custom made MATLAB code (MathWorks, Natick) and the Psychtoolbox Version 3 (Brainard, 1997) was used.

At the beginning of the experimental procedure all subjects received instructions on the computer screen to make sure that everyone was given identical instructions on how to solve the task. There were two sessions during the test, thus each subject was tested twice. In the first session, before the tDCS, half of the stimulus set (100 images) was presented, which contained an equal number of small, large, MC and PC optimized object images in a pseudorandom order. The second session started just after tDCS (or the sham stimulation) and the rest of the stimuli (other 100 images) were presented again in a pseudorandom order. During the psychophysical sessions, the participants were required to make decisions about the object size and to answer the question whether the object displayed on the screen was larger or smaller than a shoebox (Kveraga et al., 2007a). The left arrow key on the computer keyboard was associated with smaller, the right arrow key with larger objects. Size decisions were tested in a preliminary psychophysical experiment. The trials started with a centrally presented fixation-cross (250 ms) appearing before the stimulus in the center of the screen followed by the test stimulus. The trials were machine paced: if no response key was pressed for

3 s, the next image was presented. There was no feedback on the correctness of the responses (**Figure 3**).

Stimulation Protocol

To modulate prefrontal cortical activity, transcranial direct current stimulation was applied (Kincses et al., 2004; Nitsche et al., 2008; Manuel et al., 2014). Two rubber electrodes (surface: 5 × 7 cm) were used with a neuroConn DC-stimulator (neuroConn GmbH). The electrodes were arranged according to the study of Manuel et al. (2014). They reported a significant modulation of the OFC function (reality filtering) upon direct current stimulation. In their study, the electrical fields induced by tDCS were modeled to predict whether significant current reached the OFC. The model reached a significant current flow in the OFC when the electrodes were placed over the glabella and the vertex (Fpz and Cz of the 10–20 EEG system, respectively) and the electrical field values were calculated for 1 mA of inward current. In our study, the electrodes were placed on the midline; the center of the relevant active tDCS electrode was over the putative OFC cortex (Fpz), while the reference electrode was over the vertex (identified by the standard 10–20 system). Modulation was applied for 20 min with 1 mA current intensity using 10 s fade in and fade out phase in cathodal and anodal stimulation protocol, respectively. Sham stimulation consisted of placing the electrodes on the skull, but no tDCS was applied with the exception of the 10 s fade in and 10 s fade out phases. This stimulation does not have any effect on cortical excitability, but causes the same itching sensation under the electrodes. The total duration of the sham phase was also 20 min. The study was a single-blind experiment: the experimenter was fully informed, but participants were not informed about the type of stimulation they received.

Statistics

To see the differences in processing time for the MC and PC optimized stimuli, SPSS Inc. software was used to compare response latencies and accuracies before stimulation (since the conditions were the same for each participant in this period); a paired *t*-test was applied, differences were considered as significant if the type I. error was <0.05. To evaluate the effects of transcranial stimulation we used repeated measures three-way ANOVA with between group factors being type of stimulation and within group factors being time of behavioral test, and pathway (MC, PC). We compared the response accuracy and the reaction times before and after the stimulation. Group averages and standard errors are shown in **Table 1**, comparisons in **Figures 4–6**.

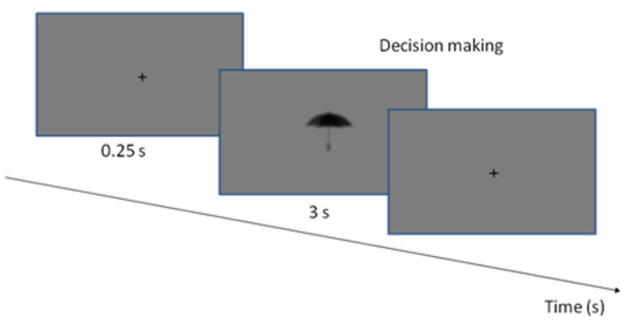

FIGURE 3 | The experimental procedure. The stimuli and the fixation point were presented in a gray background. Each trial started with the presentation of a fixation cross, which was visible for 0.25 s. The stimulus was presented until the decision was made, or up to 3 s.

RESULTS

Before the stimulation, the three groups of volunteers performed the task under identical conditions ($n = 48$). Paired *t*-test was used for the statistical evaluation. The percentage of correct answers was 91.50 ± $SD = 4.05$ using MC stimuli, comparing with accuracy of PC stimuli (mean 90.06, ± $SD = 4.69$) the difference was not significant $p = 0.12$ ($df = 47$, $t = 1.58$, **Figure 4A**). Decisions about stimuli optimized for the MC yielded shorter response latencies than those for PC stimuli (mean MC latency = 0.90 s, ±$SD = 0.20$ s, mean $PC = 0.98$ s, ±

TABLE 1 | Means of accuracies and reaction times with their confidence intervals in each condition.

Stimulation type			Means	Confidence intervals
Sham $n = 16$	I.	PC optimized reaction time	0.97	0.86–1.08
		PC optimized performance	89.25	87.05–91.45
		MC optimized reaction time	0.85	0.74–0.95
		MC optimized performance	91.00	88.80–93.19
	II.	PC optimized reaction time	0.89	0.80–0.98
		PC optimized performance	87.73	85.94–89.53
		MC optimized reaction time	0.83	0.74–0.92
		MC optimized performance	91.75	89.95–93.54
Cathodal $n = 16$	I.	PC optimized reaction time	0.93	0.82–1.04
		PC optimized performance	89.81	87.61–92.01
		MC optimized reaction time	0.88	0.77–0.99
		MC optimized performance	92.25	90.05–94.45
	II.	PC optimized reaction time	0.89	0.80–0.98
		PC optimized performance	90.24	88.44–92.03
		MC optimized reaction time	0.83	0.74–0.92
		MC optimized performance	89.87	88.07–91.66
Anodal $n = 16$	I.	PC optimized reaction time	1.05	0.94–1.15
		PC optimized performance	91.12	88.93–93.32
		MC optimized reaction time	0.98	0.87–1.09
		MC optimized performance	91.25	89.05–93.45
	II.	PC optimized reaction time	0.97	0.88–1.06
		PC optimized performance	91.24	89.44–93.04
		MC optimized reaction time	0.89	0.80–0.98
		MC optimized performance	97.00	95.20–93.55

Rows marked with I indicate values before, with II indicate values after stimulation.

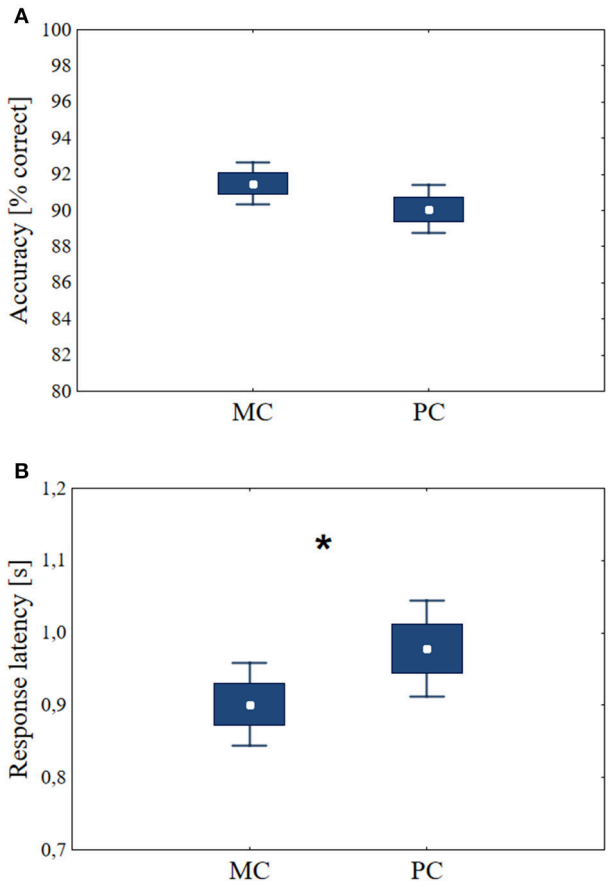

FIGURE 4 | The accuracies and response latencies during the decision task before tDCS. Central data points: means, boxes: mean ± SE, bars: mean ± 1.96 SE. **(A)** There was no significant difference between decisions about stimuli optimized for the MC and the PC. **(B)** For MC stimuli, the response latencies are shorter than for PC stimuli ($n = 48$, $p < 0.01$). Asterisk indicates significant differences ($p < 0.05$).

$SD = 0.23$ s, $p < 0.01$, $df = 47$, $t = -3.95$, **Figure 4B**). These results suggest that the reaction time differences originate from the different processing times needed for MC and PC optimized stimuli, not from the differences in the recognizability of the MC and PC stimuli sets. This test verified that MC optimized stimuli are associated with shorter response latencies (Bar et al., 2006).

Response Latencies

A repeated measures three-way ANOVA was used to test main effects and possible interactions between changes in response latencies according to the types of stimulation. The within factors were the pathway (MC, PC), time of the behavioral test (before and after the stimulation) and group factor was type of stimulation (anodal, cathodal, and sham). All possible interaction terms were taken into account. Concerning the response latency times we did not find significant effects in the cases of stimulation type [$F_{(2, 45)} = 1.336$, $p = 0.273$, partial eta-squared = 0,06]. The reaction times showed differences according to the pathway factor [$F_{(1, 45)} = 28.46$, $p < 0.01$, partial eta squared = 0.39] and the time factor [$F_{(1, 45)} = 8.69$, $p < 0.01$, partial eta-squared = 0.16]. The after stimulation reaction times became faster in the case of all stimulus type, and the response latencies for MC stimuli were faster throughout the test. While analyzing the interactions, we did not find interaction between the pathway and stimulation type factor [$F_{(2, 45)} = 0.59$, $p = 0.56$, partial eta-squared = 0.03], time and stimulation type factor [$F_{(2, 45)} = 0.36$, $p = 0.69$, partial eta-squared = 0.016] and pathway and time factors [$F_{(1, 45)} = 0.65$, $p = 0.42$, partial eta-squared = 0.014]. Furthermore, there was no significant interaction between the three factors examined [$F_{(2, 45)} = 1.99$, $p = 0.15$, partial eta-squared = 0.81] (**Figure 5**).

Accuracy Changes

To test how transcranial stimulation of the OFC affected accuracy levels three-way ANOVA with repeated measures was used to test main effects and possible interactions between the changes in accuracy and types of stimulation. The factors again were the pathway (MC-PC), type of stimulation and time (before or after the stimulation). All possible interaction terms were taken into account. The interaction of all factors was significant [$F_{(2, 45)} = 5.81$, $p < 0.01$, partial eta-squared = 0.21]. Using stimulation type factor we found significant difference between the groups [$F_{(2, 45)} = 4.77$, $p < 0.01$, partial eta-squared = 0.18]. In the case of pathway factor we also found significant difference [$F_{(1, 45)} = 13.74$, $p < 0.01$, partial eta-squared = 0.23], but the interaction of the aforementioned factors was not significant [$F_{(2, 45)} = 1.03$, $p = 0.36$, partial eta-squared = 0.04]. Examining the effect of time factor we did not find significant differences [$F_{(1, 45)} = 1.79$, $p = 0.19$, partial eta squared = 0.04]. The interaction of time and stimulation type factor was significant [$F_{(2, 45)} = 9.64$, $p < 0.01$, partial eta-squared = 0.30] but there were no significant interactions between the time and pathway factors [$F_{(1, 45)} = 2.78$, $p = 0.10$, partial eta-squared = 0.06]. The existence of the three-factor interaction suggests that the interaction between time and stimulation depends on the level of pathway factor (PC and MC stimuli, representing two levels), with other words, the dependence between change in time and the stimulation (representing three levels) differs in the PC and MC stimuli, therefore the relationship between change in time and stimulation was evaluated at the levels of stimulus presented in the figure below. Estimated marginal means and confidence intervals in the figure are based on the results of the omnibus ANOVA (**Figure 6**).

We used Bonferroni *post-hoc* test to examine between which groups and conditions the significant effect can be found. The most important differences were found between accuracies measured before and after stimulation when presenting MC stimuli and using anodal ($p < 0.01$) and cathodal stimulation ($p = 0.015$). The accuracy increased when anodal stimulation was used, while the cathodal stimulation decreased the percentage of correct answers. Comparing on the level of pathway factor we found significant differences between the sham group after stimulation values ($p < 0.01$) and anodal group after stimulation values ($p < 0.01$). Furthermore, there were differences between the different groups, the accuracy for the MC stimuli after the stimulation differed between the sham and anodal groups

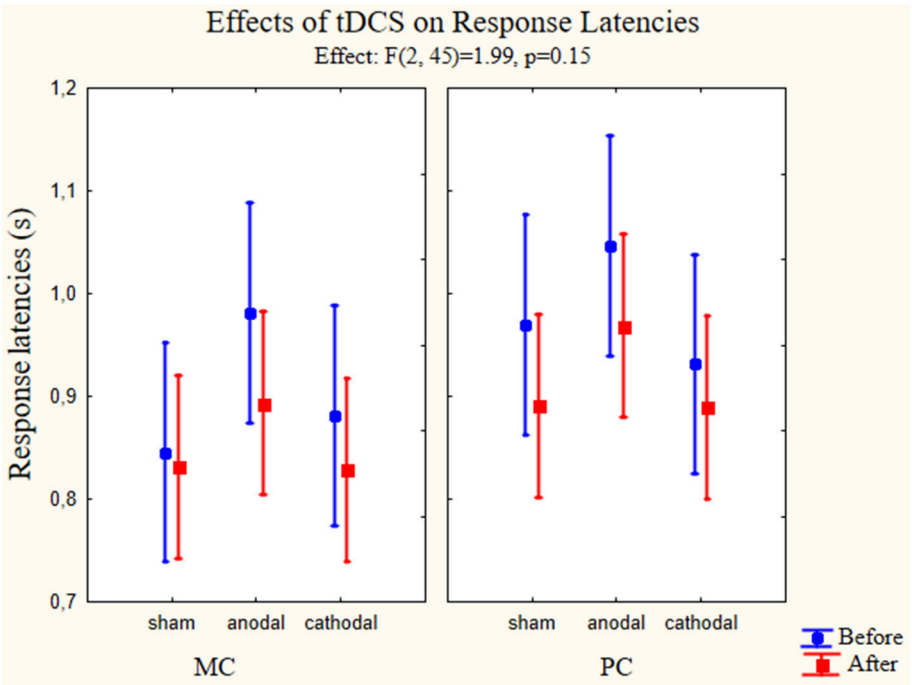

FIGURE 5 | Effects of tDCS on response latencies. Repeated measures three-way ANOVA results of the response latencies in the psychophysical tests ($n = 48$). On the left panel the response latencies for MC optimized stimuli are presented. On the right panel we presented the values measured using PC optimized stimuli. Full circles show the measured latencies before stimulation, full squares show the response latencies after stimulation. Data points denote means, vertical bars show 0.95 confidence intervals. None of the stimulation types affected the response latencies.

($p < 0.01$) and anodal and cathodal groups ($p < 0.01$). Also the accuracies measured after the stimulation using PC stimuli differed between the sham and anodal groups ($p < 0.05$).

DISCUSSION

Here we report that we could selectively modulate the processing of magnocellular optimized stimuli by influencing the activity of the prefrontal cortex using tDCS. This result confirms the hypothesis that magnocellular information passes the orbitofrontal cortex, and therefore might be used for a top-down modulation of visual processing.

Several points have to be addressed when discussing the results.

The first question is whether our stimuli fit for the magno- and parvocellular pathways? It has been reported earlier that decisions concerning MC optimized stimuli are faster than those optimized for PC stimuli (Kveraga et al., 2007a,b). Our results confirmed that the stimuli used in this study are indeed suitable for driving the dorsal or ventral pathway specifically. The significant difference in response latency times *before the stimulation* favored MC optimized stimuli but did not favor PC optimized stimuli, indicating that pathway optimization was successful.

TDCS had a clear and significant effect on response accuracies. How can this be interpreted? The rationale behind our study was that transcranial stimulation may have a direct impact on baseline cortical excitability (Stagg and Nitsche, 2011) and the observation that predictions might accelerate the perception of our environment by pre-stretching or priming bottom-up processing. Most studies agree that the phenomenon is based on the information carried by the MC. The MC and the dorsal pathway, however, also feed information into the ventral, PC through different stages of the cortical visual system (Merigan et al., 1993; Chen et al., 2007) but it is not clear what the exact source of this information is. Is MC information processed simultaneously, together with PC information in the ventral pathway (Mace et al., 2005; Fabre-Thorpe, 2011) or does MC information arrive through top-down connections at the IT via the OFC (Bar et al., 2006; Kveraga et al., 2007a,b)? The question is further complicated by the observation that connections between areas V5, V4 and the IT, furthermore between the prefrontal cortex and the IT can facilitate object recognition (Tomita et al., 1999; Chen et al., 2007; Eger et al., 2007). Cathodal stimulation of the OFC exerts an inhibitory effect, since neurons under the stimulation electrode become less excitable and presumably decrease the level of neurotransmitter glutamate (Filmer et al., 2014). Anodal stimulation in our experiments supported OFC functions: accuracy improved considerably for LSF stimuli (HSF stimuli were not affected), while cathodal stimulation decreased accuracy. This is in line with the meta-analysis data reported by Jacobson et al. (2012), namely, in cognitive tasks anodal stimulation often improves performance. Also, several studies report a decrease in performance when applying cathodal

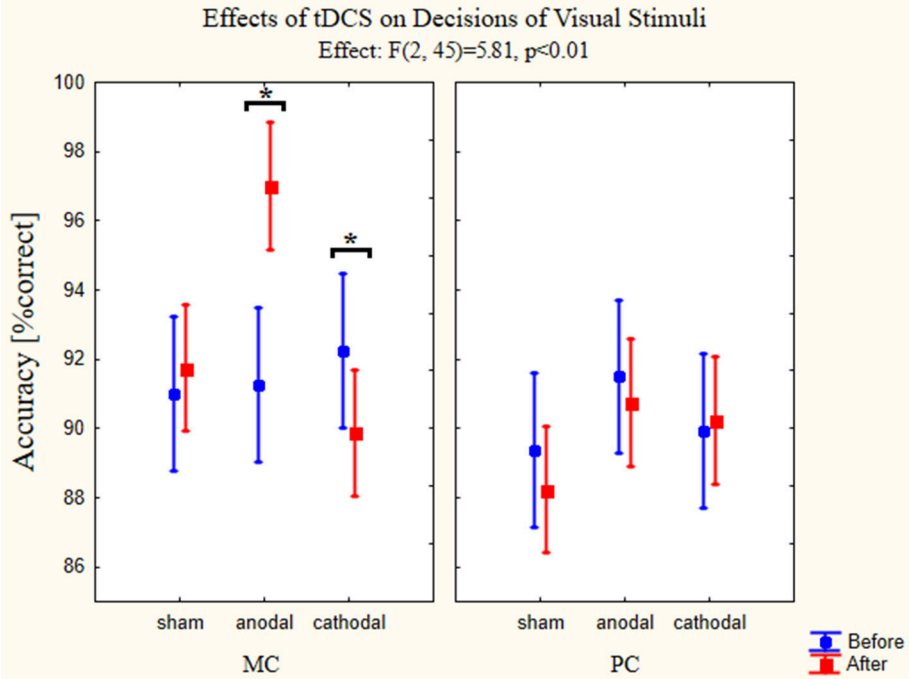

FIGURE 6 | Effects of tDCS on decisions of visual stimuli. Repeated measures three-way ANOVA results of the accuracies in the psychophysical tests are presented on the figures ($n = 48$). (full circles: before stimulation, full squares: after stimulation). The left panel presents the accuracy changes using MC optimized stimuli. Anodal tDCS resulted in a better accuracy for these images, while the cathodal stimulation impaired the performance. Sham stimulation did not have any effect on the accuracy. On the right panel accuracies in the psychophysical tests for PC optimized stimuli are shown. None of the stimulation types affected the performance. Data points denote means, vertical bars show 0.95 confidence intervals. Asterisk indicates significant differences ($p < 0.05$).

stimulation (e.g., Stone and Tesche, 2009; Sparing et al., 2009; Kraft et al., 2010). While this might not be the case in general, i.e., that anodal stimulation improves, cathodal stimulation impairs cognitive function, in some cognitive fields like perception and attention studies the likelihood to get opposite effects after anodal and cathodal stimulation, respectively, is exceptionally high (Jacobson et al., 2012).

The OFC consists of two large regions: medial and lateral parts. The former plays a role in higher cognitive functions, associative, reward linked learning, processing emotions, integrating sensory modalities and, most importantly, making decisions (Kringelbach and Rolls, 2004; Wallis, 2012). The fact that stimulation affected only decisions about LSF images supports the idea that magnocellular information passes the OFC. According to Bar et al. (2006) this information might be used for top-down facilitation of decision making. The role of the OFC in decision making especially when previous knowledge or predictions are concerned was studied in fMRI experiments (Summerfield et al., 2006; Miall et al., 2014; Erez and Duncan, 2015).

The last question is how tDCS influences the motor cortex and thus behavioral response latencies? Response latency in psychophysical studies includes sensory processing, decision making and motor response. When interpreting our results, one must also consider that the arrangement of electrodes for modulating the OFC (Manuel et al., 2014) stimulates the motor cortex when cathodal stimulation is used, but inhibits it when anodal stimulation is applied. Results regarding the effects of tDCS on motor reactions are far from clear. The main effect of tDCS is biasing cortical excitability. The underlying mechanism is still debated but current work suggests that it shares similarities with the activity-dependent synaptic plasticity (Dayan et al., 2013). Most studies agree that there is a large variability among subjects when evaluating the effects of stimulation (e.g., Wiethoff et al., 2014; Pope et al., 2015; Davidson et al., 2016). The situation is further complicated by the fact that the same stimulating pair of electrodes will have obviously opposing effects on the motor cortex and on the OFC; factors influencing the motor component of the decision and responding process thus might mask the effects on the sensory part. In a meta-analytical review Jacobson et al. (2012) concluded, that it is quite common to see the AeCi effect (anodal stimulation, cathodal inhibition) on latency times in motor experiments where evoked potentials are studied; in this respect our study might be an exception, since no significant differences in response latencies could be shown. We have to note however, that only behavioral response latencies and no evoked potentials were analyzed in this study.

In summary, our behavioral results show that using these electrode positions we could modulate the cortical activity of the OFC, which has an effect on the top-down mechanism during the fast categorization of MC optimized stimuli (Bar et al., 2006). Our results do not exclude the possibility

that magnocellular input fed into the ventral pathway may accelerate visual processing, but they give further evidence for the essential role of top-down processes originating from the OFC in visually based decisions. The goal of our study was to investigate the effects of bilateral stimulation of the orbitofrontal cortex, but for the correct interpretation of the reaction time changes another electrode arrangement is needed. Using electrodes on the two sides of the supraorbital region (Kincses et al., 2004; Fecteau et al., 2007; Ferrari et al., 2015) could enable the examination of dynamic changes of magnocellular processing and the differences between the function of the left and right OFC. However, the exact neuronal background and tracking the flow of information along the cortical pathways require electrophysiological methods (extracellular unit recording at several locations simultaneously) with a good temporal resolution.

AUTHOR CONTRIBUTIONS

AB: design of the work, critical revision, final approval, accountable for all aspects. GCs: data acquisition, first draft, final approval, accountable for all aspects. MN: data acquisition, critical revision, approval, accountable for all aspects. PC: intrepretation of data, draft, approval, accountable for all aspects TK: intrepretation of data, draft, approval, accountable for all aspects GyS: statistical analysis, draft, approval, accountable for all aspects

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