Visual contrast sensitivity in adults with schizophrenia and relatives not affected

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Abstract

The aim of this study was to measure visual contrast sensitivity (CS) for vertical sine-wave gratings with spatial frequencies of 0,6; 5 and 10 in adults with medicated schizophrenic and no-affected relatives in the range of 20-30 years old. We measured the visual CS for ten volunteers without schizophrenia, nine schizophrenia patients and five no-affected relatives, all volunteers were free from identifiable ocular disease and had normal acuity, except the condition schizophrenia. We use a temporal two-alternative forced-choice psychophysical method with mean luminance of 40.1 cd/m^2. The results showed maximum contrast sensitivity occurred in the range of 5.0 cpd for both groups and that the visual CS for participants with schizophrenia was lower than those of adults without schizophrenia and the non-affected relatives. These results showed changes in the visual mechanisms that process vertical sine-wave gratings related the schizophrenia.

Keywords: visual perception; contrast limiar; schizophrenia; psychophysical.

Resumo

Medidas de sensibilidade ao contraste visual em adultos com esquizofrenia e parentes não acometidos. O objetivo do estudo foi medir a sensibilidade ao contraste (SC) visual de grades senoidais verticais com frequências espaciais de 0,6; 5 e 10 cpg em adultos com esquizofrenia medicados e parentes não acometidos na faixa de 20-30 anos. Foram estimadas a SC visual de 10 voluntários saudáveis, nove pacientes com esquizofrenia medicados e cinco parentes não acometidos. Todos com acuidade visual normal ou corrigida e estavam livres de doenças identificáveis, exceto a condição esquizofrenia. Foi utilizando o método psicofísico da escolha forçada temporal entre duas alternativas e luminância média de 40,1 cd/m^2. Os resultados mostraram que a SC visual máxima ocorreu na faixa de 5 cpg para os três grupos, que a SC visual dos participantes com esquizofrenia foi mais baixa do que a dos participantes saudáveis e do que os parentes não acometidos. Estes resultados sugerem alterações nos mecanismos visuais que processam grades senoidais verticais associadas à esquizofrenia.

Palavras-chave: percepção visual; limiar de contraste; esquizofrenia; psicofísica.

Schizophrenia is a highly incapacitating mental disorder that gathers serious neurophysiological, neurochemical and psychological disturbs (Laviolette, 2007). Its onset occurs by the end of adolescence / beginning of adult life, and it brings serious damages for the cognitive and social performance of the patient, as well as great suffering for its relatives. The disease reaches about 1% of the world population, with an increase to 6-17% of people with a first degree diagnosed relative, and to 50% in monozygotic twins (Gottesman, 1991).

Therefore, schizophrenia has been considered a syndrome with hereditary characteristics (hereditary coefficient of approximately 0.8 in a scale of 0 - no genetic participation of the disease or behavior trait, to 1- maximum participation) (Ross, Margolis, Reading, Pletnikov, & Joseph, 2006). However, the advances in the phenotypical analysis, neuroimaging, genetic and in molecular pathology studies (Harrison & Weinberg, 2005) render support for an etiological role based on mutations or polymorphism of several genes, as well as obstetric and premorbid developmental and cognitive abnormalities associated to schizophrenia (Chen, Chang, Liu, Hwang, & Hwu, 2004; Craddock & Forty, 2006; Riley & Kendler, 2006). Recent epidemiological and immunologic studies (Caspi & Moffitt, 2006) suggest that environmental etiologies related to the development of schizophrenia may include infectious diseases such as rubella, herpes (virus 1 and 2), cytomegalovirus, and toxoplasma gondii (Brown & Susser, 2002; Ross, Margolis, Reading, Pletnikov, & Joseph 2006), autoimmune diseases, toxins or traumatic events, obstetric or perinatal complications, as well as stress during pregnancy or childhood (Buka & Fan 1999; Fatemi & Folsom 2009; Keshavan & Roberts, 2006;

Lewis & Liberman 2000; Marcelis & van Os, 1998). Therefore, schizophrenia presents a complex and multifactorial etiology due to genetic and environmental aspects, and related to neural development through life (Lewis & Liberman 2000; Murray & Lappin, 2008; Reveley & Deakin 2000).

The symptomatic treatment is only partially successful, which makes it imperative the development of a therapeutic rationale based on the understanding of schizophrenia's etiology and on its pathogenesis. Nonetheless, until recently, the progress in schizophrenia has been slow and limited for a series of reasons, including the phenotype heterogeneity and the lack of clear pathological lesions as the ones that become references in Alzheimer and Parkinson study, and other neurodegenerative diseases (Ross & Margolis, 2005). Nowadays, one of the main focuses on mental health research, and a fundamental one, is the study investigating the schizophrenia development etiology.

The Visual Contrast Sensitivity is demonstrated to be an important instrument for its configuration changes according to the luminance conditions, the levels of development and pathological alterations, permitting strong inferences on the basic physiological mechanism, for instance, the functioning of parvo and magnocellular visual pathways (Akutsu & Legge, 1995; Benedek,G., Benedek, K., Kéri, & Janáky, 2003; Elliott & Situ, 1998; Slaghuis & Thompson, 2003; Suttle & Tumer, 2004). In this sense, the Contrast Sensitivity (CS) has been used to assess and diagnose alterations as consequence of optical factors (Owsley et al., 2000), and higher areas and visual pathways (Wesner & Tan, 2006), as well as disturbs not directly related to visual functions such as diabetes (Gualtieri et al., 2011), epilepsy (Bezerra, Alencar, Mousinho, & Santos, 2011), malnutrition (Santos & Alencar, 2010), and Alzheimer and Parkingson diseases (Elliott & Situ, 1998; Polat, Sagi, & Norcia, 1997; Silva et al., 2005; Vleugels, Van Nunen, Lafosse, Ketelaer, & Vandenbussche, 1998), among others.

Contrast sensitivity is a type of visual sensory threshold used to determine the lowest contrast intensity (i.e., the smallest difference between the crest and trough) necessary for the visual system to detect or discriminate a pattern on the wave form with different length or frequency distributed in space (De Valois & De Valois, 1988; Santos & Simas, 2001). That's why the sensory threshold measure is a very used tool to describe the visual system's behavior and diagnose changes due to abnormalities in the information processing and in locating damages in the nervous system pathways or areas.

Researches relating visual contrast sensitivity and schizophrenia, making use of vertical sine-wave gratings, are well established in the literature, although using psychophysical methods and different luminance conditions (Butler, Silverstein, & Dakine, 2008; Skottun & Skoyles, 2007; Skottun & Skoyles, 2008; Slaghuis, 1998; Slaghuis & Curran, 1999). On the other hand, it was found a single study relating visual CS to unaffected relatives that used different stimuli and had distinct purposes (Chen et al., 2003). Chen and colleagues measured the contrast threshold of patients with schizophrenia using typical and atypical medication, unaffected relatives, and control subjects, using a vertical sine-wave grating with spatial frequency of 0.5 cycles per degree of visual angle, and 5 Hz temporal modulation.

The results show that the visual contrast detection threshold for the healthy relatives group didn't differ from healthy subjects. However, this group presented impaired velocity discrimination in an evaluation of movement discrimination, compatible to the patients' velocity. In this study, patients who received atypical antipsychotic medication had a performance similar to the control group. Those who made use of typical antipsychotic medication demonstrated a higher contrast detection threshold; those who were not medicated demonstrated a lower contrast detection threshold than healthy volunteers.

Other studies that investigate changes associated to unaffected relatives of schizophrenia patients evaluate possible indicators of the responsibility for schizophrenia related to cognitive dysfunction, pertinent to this population (Bedwell, Esposito, & Miller, 2004; Karch et al., 2009; Skelley, Goldberg, Egan, Weinberger, & Gold, 2008;). Several authors suggest that the genetic risk for schizophrenia is accompanied by neural insufficiency associated to cognitive deficits, mainly in difficult tasks (Chen & Faraone, 2000; Karch et al., 2009; Nuechterlein et al., 2002; Skelley et al., 2008).

For example, Karch et al. (2009) examined the working memory and related cerebral functions in healthy volunteers, schizophrenic patients, and unaffected relatives, to determine the influence of the psychopathology in this process. The results showed the behavioral performance as well as neural response of unaffected relatives is in-between patients and control subjects, indicating light brain malfunction.

Skelley et al. (2008) evaluated changes in visual and verbal memory in patients with schizophrenia and healthy relatives. The results demonstrated a common impairment in verbal learning but not in memory for both patients and healthy relatives.

Lastly, Bedwell et al. (2004) evaluated the development of visual information processing of first-degree healthy relatives of schizophrenia patients. The aim of this study was to investigate whether the impairment in visual processing found in schizophrenia patients occurred due to chronic use of neuroleptic, or to the genetic load for this pathology. The results indicated sharp decline in relatives suggesting that these losses are genetically guided by the pathology.

The aim of the current study was to measure the achromatic visual CS of patients with schizophrenia and unaffected relatives, using concentric circular and static sine-wave gratings with 0.6; 5, and 10 cpd (Figure 1) with average luminance of 42.2 cd/m^2. The measures were accomplished with two-alternative forced-choice psychophysical method, a well established paradigm which minimizes the participant's response choice criteria effects.

The motivation for the present study was to use the Visual Contrast Sensitivity Function (CSF), a non-invasive classic technique, to measure the visual system response of unaffected relatives of schizophrenia patients, making use of psychophysical method, with vertical sine-wave grating and photopic luminance condition. The basic question is: do first-degree relatives of schizophrenia patients suffer cognitive impairment due to kinship, considering the genetic hypothesis of the disease? The idea is that visual CS may complement the clinical investigation and contribute to studies on visual and cognitive information

processing (Bedwell et al., 2004; Karch et al., 2009) relating schizophrenia and kinship. This study may, as well, help creating a susceptibility endophenotype profile for schizophrenia and speculate about the genetic contributions for the expression of this disturb.

The year incidence of schizophrenia is one of the most important public health problems, with severe socioeconomic repercussions, high costs of medical assistance, and reduction in the quality of life of its patients (McGrath, Saha, Chant, & Welham, 2008). According to the World Health Organization's ([WHO], 2009) report, an average of seven new cases become known for every 10,000 people in the world population. It is estimated that 30% of patients diagnosed with this disturb attempt suicide at least once (Lewis & Lieberman 2000), and approximately 10% of people with schizophrenia die from this act (Araripe, Bressan, & Busatto, 2007).

Briefly, systematic studies with CSF may contribute to a greater understanding of the sensorial mechanism connected to schizophrenia, pointing out to strategies for a better quality of life facing the symptoms, the knowledge, and the understanding of these disorders associated to social and cultural factors. It may also contribute to the development of more selective drugs that cause less collateral effect. The impact of these series of research has direct or indirect application in the neuroscience, psychology, medicine, pharmacology, biochemistry, public health, and many other fields.

Method

Participants

Took part in this study 24 adults, both sexes, with ages between 20-30 years, ten of whom without neuropsychiatric disorder (5 man, and 5 women, $M = 32.2$; $SD = 8.6$), 5 unaffected relatives (2 man, and 3 women, $M = 25.4$; $SD = 10.4$), and 9 diagnosed with schizophrenia (4 men, and 5 women, $M = 33.7$; $SD = 7.0$), in agreement with The Diagnostic and Statistical Manual of Mental Disorders (DSM IV, American Psychiatric Association, 1994). The schizophrenia patients were evaluated by psychiatrists from the Psychosocial Attending Center (CAPS - Brazilian acronym of *Centro de Atenção Psicosocial*) and led to the lab where the visual tests were performed. All the schizophrenia patients were using typical antipsychotic, three of them were using an association of Clopromazine and Haloperidol, six other used Haloperidol and Levomepromazine Maleate, concomitanty. All the volunteers presented normal or corrected visual acuity, tested with directional "E" Rasquin optotype cards, with no history of ocular or neurologic pathology.

The participation in the research was conditioned to the signing of the Consent Form, according to the Resolution No. 196/96 of the National Health Counsel (Health Ministry, Brazil), which handles the rules and norms of researches involving human beings. The research was approved by the Ethic Committee of Health Sciences Center.

Equipment and stimuli

The visual stimuli were displayed on a 21 inches,

monochromatic, CRT (Cathode Ray Tube) CLINTON MEDICAL digital video monitor, with 1024 x 768 pixels screen resolution, and 70 Hz frame rate, controlled by a microcomputer. A chair was fixed at a 150 cm distance from the video monitor, with a chin and forehead rest to control the distance. The LightScan software and the OptiCAL photometer (Cambridge Research Systems, Rochester, Kent) were used to measure the screen average luminance (42.2 cd/m^2). The laboratory environment was gray colored for better controlling the luminance. The experimental room dimensions were 2.5 x 2.0 m and it was illuminated by one 20 W Philips fluorescent lamp.

The visual stimuli used were formed by vertical and static sine-wave gratings with spatial frequency of 0.6, 5, and 10 cycles per degree of visual angle (Figure 1). They were circular with diameter of 7 degrees of visual angle, 150 cm distant. The neutral stimulus was gray, homogeneous, with medium luminance; all the stimuli were achromatic and presented in real time in the center of the screen. A software developed by the research group, written in C++ language was used to run the experiments, that means generating the stimuli, controlling their display, and registering the contrast threshold.
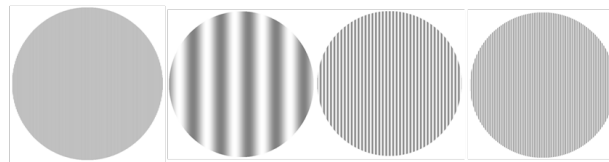

Figure 1
Examples of neutral stimulus and spatial frequency stimuli (e.g., 0.6, 5.0 and 10.0 cpd) which were originally calibrated to be seen at a distance of 150 cm.

Procedure

The visual CS measures were performed by a temporal two-alternative forced-choice psychophysical method (Wetherill & Levitt, 1965). This method is based on the probability of the participant's consecutive correct choices, in other words, in about 100 displays of 2-stimuli-choice (test and neutral stimuli) the spatial frequency (test stimulus) must be perceived in 79% of the times.

The procedure to measure the threshold for each frequency consisted on the simple successive pair stimuli presentation, one of them was the test stimuli that should be identified by the participant. The criterion used to vary the contrast of each spatial frequency tested was three consecutive right choices to decrease one unity, and one incorrect choice to increase by the same unity (0.08%).

During every experimental session a sequence of pair of stimuli was initiated with a sound, followed immediately by the presentation of the first stimulus per 2 seconds, after 1 second interval the second stimulus was also presented for 2 seconds, followed by the participant response. The stimuli presentation order was at random. The participants were instructed to press the left button on the mouse when the concentric sine-wave

grating (or spatial frequency) was presented first, and the right button when second, that means after the neutral stimulus. If the volunteer's response was correct it was followed by another sound and 3-second interval for the repetition of the sequence. Two different sounds were used, one to indicate the beginning of the stimuli pairs presentation and another to indicate the correct choice. The session duration varied between 5 and 10 minutes, depending on the participant's wrong and right answers until six reversions (or six contrast values) were performed, as required for the automatic concluding.

Each visual CS curve frequency was estimated at least two times (two experimental sessions) in different days, for each participant. In average, 12 curves were measured for each volunteer group; as each curve was formed by three spatial frequency, a total of 60 experimental sessions were performed by each group. All the estimates were measured at 150 cm distance with binocular vision and natural pupil.

All the participants received the following instruction: "a sequence of pairs of figures (or drawings) will be presented, one with light-dark circles and the other one completely gray. You must always choose the figure (or drawing) that contains the light-dark circles by pressing the left button (number 1) on the mouse when they are presented first, and the right (button number 2) when presented secondly (after the gray drawing).

It is important to mention that each session started with the test stimuli with supraliminal contrast level and when it was verified that the participants understood the instructions and answered accordingly the experiments began. For that matter, the instruction was repeated in a session for training and adjustment to the experimental setting, until the participants understood the instructions and could differentiate between the stimuli with light-dark circles and the homogenous one in gray tone.

After each session the software produced a sheet with the results with the experimental setting and the six contrast threshold values obtained through reversions. The contrast threshold values obtained for each frequency were grouped by conditions on spreadsheets (control group, relatives, and schizophrenia) and were transformed in CS (1/contrast threshold). In other words, the lower the contrast threshold, the higher the sensitivity of the human visual system, and vice-versa. Therefore, the lowest threshold values correspond to the highest CS values.

Statistical analyses

The data was organized by group (schizophrenic, relatives and control) and then treated with the STATISTICA software (Stat Soft). One-way Anova was performed to compare the contrast threshold for the three groups and Unequal N HSD post-hoc test to compare frequencies individually and between groups.

Results

The results demonstrate that photopic CSF of all participants presented similar general profiles with maximum sensitivity in the center of the curve (5 cpd), approximately, and with sensitivity reduction on the curve's edges (0.6 cpd, and 10 cpd). Nonetheless, it was noticed that relatives needed 1.6, 4.1, and 5.5 less contrast to process the 0.6, 5, and 10 cpd frequency,

respectively, when compared to schizophrenia patients. In comparison to the control group the schizophrenic needed 1.6, 4.1, and 5.1 more contrast to notice the 0.6, 5 and 10 cpd frequencies, respectively. The results also demonstrated that relatives presented a similar contrast sensitivity value when compared to control group.

Figure 2 shows the visual CS for the three groups: control, relatives and schizophrenia patients.
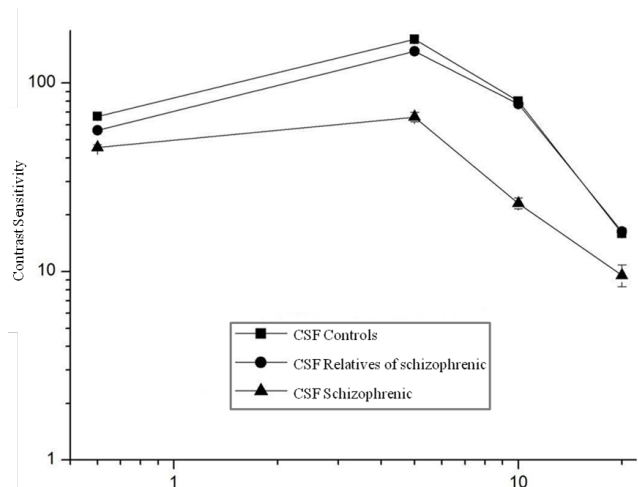

Figure 2

The estimated visual contrast threshold in control group (□■□), relatives of schizophrenic (□●□) and schizophrenic (□▲□) is shown as a spatial frequency function of 0.6, 5.0, and 10 cpd. The mean error bars were corrected to the sample's size to represent a 95% confidence interval.

The one-way Anova variance analyses demonstrated significant differences [$F(8, 952) = 43.100$, $p = 0.001$] in the comparison of the contrast threshold values for the three groups in the photopic condition. The Unequal N HSD post-hoc test showed significant difference only between the schizophrenic and the control group, and between the schizophrenic and relatives in all the frequencies ($p < 0.001$). The analysis didn't indicate significant differences between the control and the relatives group in any vertical sine-wave grating frequency tested: 0.6, 5, and 10 cpd ($p > 0.05$).

Discussion

The aim of the present study was to characterize the human visual system response of volunteers diagnosed with schizophrenia who were under medication, and unaffected relatives, using the visual contrast sensitivity curve for spatial frequency stimuli with vertical sine-wave grating. The research purpose was to investigate how schizophrenia interacts with the visual system response (CSF) or the basic sensorial mechanism involved in the visual patterns processing, considering as well the genetic susceptibility related to clinically healthy relatives.

The results of the photopic sine-wave gratings indicate that:

1) schizophrenia patients have a reduction in CSF in all spatial frequency tested (0.6, 5, and 10 cpd);

2) the sensitivity impairment of these patients was more prominent in 5 and 10 cpd frequencies;

3) non-psychotic relatives did not present a statistically different performance from the control group.

Changes in the CSF for vertical sine-wave gratings were somehow expected when considering studies which show movement perception distortion (Kéri, Antal, Szekeres, Benedek, & Janka, 2002; Slaghuis & Thompson, 2003), color (Alain, Bernstein, He, Cortese, & Zipursky, 2002; Bedwell et al., 2003), face recognition (Schwartz, Marvel, Drapalski, Rose, & Deutsch, 2002; Onitsuka et al., 2006), and Muller-Lyer illusion susceptibility (Pessoa, Monge-Fuentes, Simon, Suganuma, & Tavares, 2008), even those that report dynamic and static CSF alterations in medicated schizophrenia patients (Chen et al., 2003; O'Donnell et al., 2002; 2006; Slaghuis, 1998). The results also corroborate to the studies that describe changes in visual CS related to magno and parvocellular pathways in this disturb (Butler et al., 2005; Gutherie, McDowell, & Hammond, 2006; Kéri et al., 2002; Kiss, Janka, Benedek, & Kéri, 2006).

However, it is not prudent to associate damages in CS as the only consequence of alterations produced by schizophrenia. Probably other factors are related, for instance, the influence of antipsychotic medication on the visual contrast processing, since these medications modulate the functioning of the central nervous system. Moreover, there are studies reporting that the administration of antipsychotic medication along with dopamine antagonist leads to a global decrease in CS in schizophrenia patients (Chen et al., 2003; Tebartz, Greenlee, Foley, & Lücking, 1997).

When considering the results of unaffected relatives, studies comparing them to schizophrenia patients and healthy participants have emphasized neuropsychological (Rybakowski & Borkowska, 2002; Staal, Hijman, Hulshoff, & Kahn, 2000; Zanelli et al., 2009) and cognitive aspects (Bedwell et al., 2004). The literature indicates significant alterations in some cognitive and neuropsychiatric functions in unaffected relatives. For example, Staal et al. (2000) performed a study comparing human cognition attributes such as: abstraction, attention, executive functions, spatial memory, and motor functioning in three different groups (control group, psychotic patients and non-psychotic siblings of schizophrenia patients). The authors found changes only in executive functions and in the motor functioning. In a literature review Sitskoorn, Ebisch, Appels, Nuyen and Kahn (2004) showed that the cognitive impairments found in schizophrenia patients are present in unaffected relatives. According to the authors, this finding is consistent to the idea that certain cognitive deficiencies in relatives are caused by the genetic predisposition to schizophrenia. These deficiencies may be putative endophenotype for schizophrenia, even though they are not definite to the existence of co-heritage of these characteristics in the families (Sitskoorn et al., 2004).

Studies that investigated the schizophrenia genetic etiology defend that the risk to develop this disturb is directly associated to a biological kinship (Gottesman, 1991). In this sense, relatives of a patient have a greater chance to manifest this disease than the general population. This genetic load shared among relatives and the proband is associated to alterations found in healthy relatives (Toulopoulou, Rabe-Hesketh, King, Murray, & Morris, 2003).

Although the literature data leads to some cognitive and neuropsychological alterations in unaffected relatives of schizophrenia patients, in the current study it was found no impairment connected to stimulus contrast detection of vertical sine-wave gratings in spatial frequency tested in photopic luminance condition. These data may indicate that contrast sensitivity doesn't interact with this disease's endophenotype variability, or yet, that CSF is not sensible to alterations that reach this population. Moreover, it is necessary to consider that the relatives sample was heterogeneous, composed by nephews, nieces, and sisters, possibly masking alterations associated to genetic bonds. Nevertheless, this characteristic of the sample cannot be pointed out as the only excuse for the results. Other studies in which the sample was composed by first and second degree relatives of the proband found differences in cognitive tasks in this population (Karch et al., 2009).

However, the identification of vulnerability for schizophrenia is composed by a wide phenotype variability of this disease, and it has been postulated that cognitive and neuropsychological distinction can be used as endophenotype markers for genetic predisposition for schizophrenia (Rybakowski & Borkowska, 2002). In other words, studies describe some cognitive and neuropsychological changes in healthy relatives of schizophrenia patients that are usually associated to indicia of genetic factors in the etiology of schizophrenia. In this context, the results of the present study suggest that CS for vertical sine-wave gratings was demonstrated to be preserved in this population. This data may indicate that changes in CSF found in schizophrenia patients may be, partially, connected to the expression of the disease or to some factor associated to it.

References

Akutsu, H., & Legge, G. E. (1995). Discrimination of compound gratings: spatial-frequency channels or local features? *Vision Research*, *35*(19), 2685-95. doi:10.1016/0042-6989(95)00030-4

Alain, C., Bernstein, L. J., He, Y., Cortese, F., & Zipursky, R. B. (2002). Visual feature conjunction in patients with schizophrenia: an event-related brain potential study. *Schizophrenia Research,* 57, 69-79. doi: 10.1016/S0920-9964(01)00303-6.

Araripe, A. G. A., Bressan, R. A, & Busatto, G.(2007). Fisiopatologia da esquizofrenia: Aspectos atuais. *Revista de Psiquiatria Clínica, 34*(2), 198-203.

Bedwell, J. S., Brown, J. M., & Miller, L. S. (2003). The magnocellular visual system and schizophrenia: What can the color red tell us? *Schizophrenia Research, 63*, 273-284. doi: 10.1016/S0920-9964(02)00356-0

Bedwell, J. S, Esposito, S., & Miller, L. S. (2004). Accelerated age-related decline of visual information processing in first-degree relatives of persons with schizophrenia. *Psychiatry Research*, 125, 225–235. doi: 10.1016/j

Benedek, G., Benedek, K., Kéri, S., & Janáky, M. (2003). The scotopic low-frequency spatial contrast sensitivity develops in children between the ages of 5 and 14 years. *Neuroscience Letters*, *345*, 161-164.

Bezerra, P. C., Alencar, C. C. G., Mousinho, S. R., & Santos, N. A. (2011). Visual contrast sensitivity in tonic-clonic epileptic patients. *Psychology & Neuroscience, 4*, 31-36.

Brown, A. S., & Susser, E. S. (2002). In utero infection and adult schizophrenia. *Mental Retardation Developmental Disabilities Research Reviews, 8*(1), 51-7. doi: 10.1002/mrdd.10004

Buka, S. L., & Fan, A. P. (1999). Association of prenatal and perinatal complications with subsequent bipolar disorder and schizophrenia. *Schizophrenia Research*, *39*(2),113-9.

Butler, P. D., Silverstein, S. M., & Dakine, S. C. (2008). Visual Perception and Its Impairment in Schizophrenia. *Biological Psychiatry*, *64*, 40-47. doi: 10.1016/j.biopsych.2008.03.023

Butler, P. D., Zemon, V., Schechter, I., Saperstein, A. M., Hoptman, M.J., Lim, … Javitt, D. C. (2005). Early-stage visual processing and cortical amplification deficits in schizophrenia. *Archives of General Psychiatry*, *62*, 495–504. doi: 10.1001/archpsyc.62.5.495

Caspi, A., & Moffitt, T. E. (2006). Gene-environment interactions in psychiatry: Joining forces with neuroscience. *Nature Reviews Neuroscience, 7*(7), 583-90. doi: 10.1038/nrn1925

Chen, W. J., & Faraone, S. Y., (2000). Sustained attention deficits as markers of genetic susceptibility to schizophrenia. *American Journal of Medical Genetics. 97*(1), 52-7. doi: 10.1002/(SICI)1096-8628(200021)97:1<52::AID-AJMG7>3.0

Chen, W. J., Chang, C., Liu, S. K., Hwang, T. J., & Hwu, H. (2004). Sustained attention deficits in nonpsychotic relatives of schizophrenic patients: A recurrence risk ratio analysis. *Biological Psychiatry. 55*, 995–1000. doi: 10.1016/j.biopsych.2004.01.010. 0

Chen, Y., Levy, D. L., Sheremata, S., Nakayama, K., Matthysse, S., & Holzman, P. S. (2003). Effects of typical, atypical and no antipsychotic drugs on visual contrast detection in schizophrenia. *American Journal Psychiatry, 160*, 1795-1801.

Craddock, N., & Forty, L. (2006). Genetics of affective (mood) disorders. *European Journal Human Genetics. 14*(6), 660-668.

De Valois, R. L., & De Valois, K. K. (1988). *Spatial Vision.* New York: Oxford University Press.

Elliot, D. B., & Situ, P. (1998). Visual acuity versus letter contrast sensitivity in early cataract. *Vision Research*, *38*, 2047-2052.

Fatemi, S. H., & T. D. Folsom (2009). The neurodevelopmental hypothesis of course schizophrenia. *Current Psychiatry Report*, *8*(4), 329-334.

Gottesman, I. (1991). Schizophrenia genesis: The origins of madness. New York: W-H Freeman.

Gualtieri, M., Bandeira, M. L., Hamer, R. D., Damico, F. M., Moura, A. L. A., & Ventura, D. F. (2011). Contrast sensitivity mediated by inferred magno- and parvocellular pathways in type 2 diabetics with and without non-proliferative retinopathy. *Investigative Ophthalmology & Visual Science. 52*, 1151-1155.

Gutherie, A. H., McDowell, J. E., & Hammond, B. R. Jr. (2006). Scotopic sensitivity in schizophrenia. *Schizophrenia Research. 84*(2-3), 378-385.

Harrison, P. J., & Weinberger, D. R. (2005). Schizophrenia genes, gene expression, and neuropathology: on the matter of their convergence. *Molecular Psychiatry*, *10*, 40-68.

Marcelis, M., & van Os, J. (1998). Obstetric complications and familial morbid risk of psychiatric disorders. *American Journal of Medical Genetics, 81*(1), 29-36.

Karch, S., Leicht, G., Giegling, I., Lutz, J., Kunz, J., Buselmeier, M., & Mulert, C. (2009). Inefficient neural activity in patients with schizophrenia and nonpsychotic relatives of schizophrenic patients: evidence from a working memory task. *Journal of Psychiatric Research, 43*(15), 1185-94. doi: 10.1016/j.jpsychires.2009.04.004

Kéri, S., Antal, A., Szekeres, G., Benedek, G., & Janka, Z. (2002). Spatiotemporal visual processing in schizophrenia. *Journal of Neuropsychiatry and Clinical Neuroscience, 14*(2), 190-196. doi: 10.1176/appi.neuropsych.14.2.190

Keshavan, M. S., & Roberts M. (2006). Guidelines for clinical treatment of early course schizophrenia. *Current Psychiatry Report, 8*(4), 329-34. doi: 10.1007/s11920-006-0070-7

Kiss, I., Janka, Z., Benedek, G., & Kéri, S. (2006). Spatial Frequency Processing in Schizophrenia: Trait or State Marker? *Journal of Abnormal Psychology, 115*(3), 636–638. doi: 10.1037/0021-843X.115.3.636

Laviolette, S. R. (2007). Dopamine modulation of emotional processing in cortical and subcortical neural circuits: Evidence for a final common pathway in schizophrenia? *Schizophrenia Bulletin*, *33*(4), 971-81. doi: 10.1093/schbul/sbm048

Lewis, D. A., & J. A. Lieberman (2000). Catching up on schizophrenia: Natural history and neurobiology. *Neuron,* 28(2), 325-34.

McGrath, J., Saha, S., Chant, D., & Welham, J., (2008).Schizophrenia: A concise overview of incidence, prevalence, and mortality. *Epidemiology Review, 30*, 67-76. doi: 10.1093/epirev/mxn001

Murray, R. M., Lappin, J., & Di Forty, M. (2008). Schizophrenia: from developmental deviance to dopamine dysregulation. *European Neuropsychopharmacology*, *18* (Suppl. 3), S129-34. doi: 10.1016/j.euroneuro.2008.04.002

Nuechterlein, K. H., Asarnow, R F, Subotnik, K. L., Fogelson, D. L., Payne, D. L., Kendler, K. S., & Mintz, J. (2002). The structure of schizotypy: Relationships between neurocognitive and personality disorder features in relatives of schizophrenic patients in the UCLA Family Study. *Schizophrenia Research,* 54(1-2),121-30. doi: 10.1111/j.1469-8986.2012.01383

O`Donnell, V. F., Potts, G. F., Nestor, P. G., Stylianopoulos, K. C., Shenton, M. E., & McCarley, R. W. (2002). Spatial frequency discrimination in schizophrenia. *Journal of Abnormal Psychology*, *111*, 620-625.

O'Donnell, B. F., Bismark, A., Hetrick, W. P., Bodkins, M., Vohs, J. L., & Shekhar, A. (2006). Early stage vision in schizophrenia and schizotypal personality disorder. *Schizophrenia Research*, *86*, 89–98. doi: 10.1016/j.schres.2006.05.016

Onitsuka, T., Niznikiewicz, M. A., Spencer, K. M., Frumin, M., Kutoki, N., Lucia, L.C., … McCarley, R. W. (2006). Functional and structural deficits in brain regions subserving face perception in schizophrenia. *American Journal Psychiatry, 163*(3), 356-358. doi: 10.1176/appi.ajp.163.3.455

Owsley, C., Jackson, G. R., Cideciyan, A. V., Huang, Y., Fine, S. L., Ho, A. C., ... Jacobson, S. G. (2000). Psychophysical evidence for rod vulnerability in age-related macular degeneration. *Investigative Ophthalmology and Visual Science, 41*, 267-273.

Pessoa, V. F., Monge-Fuentes, V., Simon, C. Y., Suganuma, E., & Tavares, M. C. H. (2008). The Muller-Lyer illusion as a tool for schizophrenia screening. *Reviews in the Neurosciences*, *19*(2-3), 91-100. *doi*: 10.1515/rns.2011.011

Polat, U., Sagi, D., & Norcia, A. M. (1997) Abnormal long-range spatial interactions in amblyoplia. *Vision Research*, *37*, 737-744.

Reveley, M., & Deakin, J. (2000). The pharmacology of schizophrenia. New York,

Riley, B., & Kendler, K. S. (2006). Molecular genetic studies of schizophrenia. *European Journal of Human Genetics: EJH, 14*(6), 669-80. doi: 10.1038/sj.ejhg.5201571

Ross, D. E., & Margolis, R. L. (2005). Neurogenetics: Insights into degenerative diseases and approaches to schizophrenia. *Clinical Neuroscience Research, 5*, 3-14. doi: 10.1038/nature02998

Ross. C. A., Margolis, R. L., Reading, S. A. J., Pletnikov, M., & Joseph T. (2006) Neurobiology of Schizophrenia Review. *Neuron*, *52*, 139-153. doi: 10.1016/j.neuron.2006.09.015

Rybakowski, J. K., & Borkowska, A. (2002). Eye movement and neuropsychological studies in first-degree relatives of schizophrenic patients. *Schizophrenia Research, 54*(1-2), 105-10. doi: 10.1016/S0920-9964(01)00357-7

Santos, N. A., & Alencar, C. C. G. (2010). Early malnutrition diffusely affects children contrast sensitivity to sine-wave gratings of different spatial frequencies. *Nutritional Neuroscience, 3*, 1-6.

Santos, N. A., & Simas, M. L. B. (2001). Função de sensibilidade ao contraste: Indicador da percpção visual da forma e da resolução espacial. *Psicologia: Reflexão& Crítica, 14*(3), 589-597.

Schwartz, B. L., Marvel, C. L., Drapalski, A., Rose, R. B., & Deutsch, S. I. (2002). Configural processing in face recognition in schizophrenia. *Cognitive Neuropsychiatry, 7*(1), 15-39. doi: 10.1016/j.schres.2009.03.033

Silva, M. F., Faria, P., Regateiro, F. S., Forjaz, V., Januário, C., Freire, A., & Castelo-Branco, M. (2005). Independent patterns of damage within magno-, parvo- and koniocellular pathways in Parkinson's disease. *Brain, 128*, 2260–2271. doi: 10.1093/*brain*/awl292

Sitskoorn, M. M., Ebisch, S. J., Appels, M., Nuyen, J., & Kahn, R. S. (2004). Memory profiles in parents of patients with schizophrenia. *Psychiatry Research, 128*(1), 27-37. doi: 10.1016/j.psychres.2004.05.011

Skelley, S. L., Goldberg, T. E., Egan, M. F., Weinberger, D. R., & Gold, J. M. (2008). Verbal and visual memory: Characterizing the clinical and intermediate phenotype in schizophrenia. *Schizophrenia Research*, *105*(1-3), 78-85. doi: 10.1016/j.schres.2008.05.027

Skottun, B. C., & Skoyles, J. R. (2007). Contrast sensitivity and magnocellular functioning in schizophrenia. *Vision Research, 47*, 2923–2933.

Skottun, B. C., & Skoyles, J. R. (2008). Reply to Kéri, S. The magnocellular system and schizophrenia. *Vision Research, 48*,1183–1185. doi: 10.1016/j.visres.2007.07.016

Slaghuis, W. L. (1998) Contrast sensitive for stationary and drifting spatial frequency gratings in poditie and negative symptom schizophrenia. *Journal of Abnormal Psychology, 107*, 49-62.

Slaghuis, W. L., & Curran, C. E. (1999). Spatial frequency masking in positive- and negative-symptom schizophrenia. *Journal Abnormal Psychology, 108*(1), 42-50.

Slaghuis, W. L., & Thompson, A. K. (2003). The effect of peripheral visual motion on focal contrast sensitivity in positive- and negative-symptom schizophrenia. *Neurophsychologia, 4*, 968-980.

Staal, W. G., Hijman, R., Hulshoff Pol, H. E., & Kahn, R. S. (2000). Neuropsychological dysfunctions in siblings discordant for schizophrenia. *Psychiatry Research, 95*(3), 227-35.

Suttle, C. M., & Turner, A. M. (2004). Transient pattern visual evoked potentials in children with Down's syndrome. *Ophthalmic Physiological Optics, 24* (2), 91-9. doi: 10.1046/j.1475-1313.2003.00174.x

Tebartz van E. L, Greenlee, M. W., Foley, J. M., & Lücking, C. H. (1997). Contrast detection, discrimination and adaptation in patients with Parkinson's disease and multiple system atrophy. *Brain,120*(12), 2219-2228.

Toulopoulou, T., Rabe-Hesketh, S., King, H., Murray, R. M., & Morris, R. G. (2003). Episodic memory in schizophrenic patients and their relatives. *Schizophrenia Research, 63*, 261-271. doi: 10.1016/S0920-9964(02)00324-9

Vleugels, L., Van Nunen, A., Lafosse, C., Ketelaer, P., & Vandenbussche, E. (1998). Temporal and spatial resolution in foveal vision of multiple sclerosis patients. *Vision Research, 38*, 2987-2997.

Wesner, M. F., & Tan, J. (2006). Contrast sensitivity in seasonal and nonseasonal depression. *Journal of Affective Disorders, 95*, 19-28. doi: 10.1016/j.jad.2006.03.028

Wetherill, G. B., & Levitt, H. (1965). Sequential estimation of points on a psychometric function. *The British Journal of Mathematical and Statistical Psychology, 18*, 1-10.

Zanelli, J., Reichenberg, A., Morgan, K., Fearon, P., Kravariti, E., Dazzan, P., … Murray, R. M. (2009). Specific and generalized neuropsychological deficits: A comparison of patients with various first-episode psychosis presentations. *American Journal Psychiatry, 167*(1), 78-85. doi: 10.1176/appi.ajp.2009.09010118

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