A Fresh Look on Schizophrenia

(Herzog and Brand, 2015)

Schizophrenia research on the phenotype level is usually concerned with the obvious cognitive and personality abnormalities of the patients. However, as we argued in a current review article (Herzog et al., 2013), cognitive tests are usually not the most sensitive measures to investigate the disease because of their poor signal to noise ratio, poor test re-test reliability, and complex neurobiological functions making. It is hard to identify the underlying causes of schizophrenia. Contrary to widespread claims, cognitive paradigms are usually not endophenotypes of schizophrenia (e.g., Chkonia et al. 2010a). We propose that visual tests, particularly when optimized for schizophrenia research, are much more sensitive and specific tools. For example, congenitally blind people are protected against the disease (Silverstein et al., 2012). Amongst the variety of techniques, visual masking has been shown to be one of the most sensitive visual tests (Figure 1, Chkonia et al. 2010b; Heinrichs 2001). As we review, unaffected relatives show clear performance deficits (Chkonia et al., 2010b), performance deficits are stable over the time course of 18 months (Chkonia et al., 2010b), and depressive patients and abstinent alcoholics show no masking deficits compared to healthy controls (specificity; Chkonia et al. 2012). Masking is an endophenotype and indeed genetic correlates, related to the nicotinic system, were shown by our group (Bakanidze et al., 2013).

For decades, visual masking deficits were attributed to a deficient visual magno-cellular system. However, this claim surprises because, as we show in the review, all empirical evidence actually speaks against any involvement of the magno-cellular system (Figure 2). Even more surprisingly, the original hypothesis was based on a trivial mis-understanding about the mechanisms of visual masking (confusion of A-type with B-type masking). This is a pity because, as we propose, masking deficits in schizophrenia patients are much more general than being restricted to visual dysfunctions. Visual dysfunctions are emanations of general and deep dysfunctions dedicated to deficient neuromodulation and thus offer insights into the causes of the disease in general (Figure 3).

In conclusion, we propose that visual tests, and particularly visual masking, are very sensitive and specific tools to investigate the underlying genetic,
Figure 1: In backward masking, a target is followed by a mask. Here the target is called a Vernier and the task is to indicate whether the lower bar of the Vernier is offset to the left or to the right (as shown).

neural, and behavioral abnormalities of schizophrenia. Visual tests, if optimized for the disease, outperform most other phenotype measures. However, the mechanisms, which were proposed for decades, cannot explain masking deficits.
Figure 2: Dual channel approach. Any stimulus is processed in both the fast M-system, sensitive to location and motion information, and in the slower P-system, sensitive to detailed form and color information. The target is presented (upper part of figure). First, a fast M-system response is elicited (narrow triangle), followed by the sustained P-system response (broad triangle). If the mask is presented at an intermediate SOA (lower part of figure), e.g., at 50 ms, the M-system response to the mask inhibits the P-system response to the target (dashed arrow). As a consequence, B-type masking occurs. If the M-system is hyper-active in schizophrenia patients, the P-system response is even stronger inhibited. B-type is more pronounced. However, there is neither empirical nor conceptual support for this hypothesis. From Herzog and Brand 2015.
Figure 3: Hypothetical mechanisms of target enhancement. (A) A vernier is presented and processed along the visual hierarchy including the retina, the LGN, the primary visual cortex V1, and higher visual areas. Because of the very short presentations times (2040 ms), only a weak neural response is elicited (small ticks next to the neurons indicated by the blue diamonds). (B) If there is target enhancement by recurrent processing, attention, ACh neuromodulation, or other factors, the weak response of the vernier is amplified. Even if the vernier has disappeared on the screen, neural responses may be present because of recurrent amplification. If a masking grating follows the vernier (not shown), recurrent amplification is interrupted and other forms of target enhancement are needed to reach good performance. If target enhancement is dysfunctional, a weaker enhancement leads to poorer performance (as in A). These considerations are highly simplified and the underlying mechanisms are largely unknown. Attention is likely to play an important role because without attention to the vernier, performance is strongly deteriorated in healthy observers. Our main proposal is that weak target stimuli need task-dependent enhancements and that these may be dysfunctional in schizophrenic patients. From Herzog et al. 2013.
References


