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Perception Measurement in Clinical Trials of Schizophrenia: Promising Paradigms from CNTRICS

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Abstract

The third meeting of the Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia (CNTRICS) focused on selecting promising measures for each of the cognitive constructs selected in the first CNTRICS meeting. In the domain of perception, the two constructs of interest were *Gain Control* and *Visual Integration*. CNTRICS received five task nominations for *Gain Control* and three task nominations for *Visual Integration.* The breakout group for perception evaluated the degree to which each of these tasks met pre-specified criteria. For *Gain Control*, the breakout group for perception believed that two of the tasks (Prepulse Inhibition of Startle and Mismatch Negativity) were already mature and in the process of being incorporated into multisite clinical trials. However, the breakout group recommended that Steady State Visual Evoked Potentials be combined with contrast sensitivity to magnocellular vs. parvocellular biased stimuli, and that this combined task and the Contrast-Contrast Effect Task be recommended for translation for use in clinical trial contexts in schizophrenia research. For *Visual Integration*, the breakout group recommended the Contour Integration and Coherent Motion tasks for translation for use in clinical trials. This manuscript describes the ways in which each of these tasks met the criteria used by the breakout group to evaluate and recommend tasks for further development.

Keywords

perception; CNTRICS; sensory processes

Perceptual processes are viewed as being among the key domains for development of measures that can be used in clinical trials in schizophrenia. This topic was discussed at the first consensus meeting of CNTRICS (Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia, and summarized in *Biological Psychiatry* vol 64(1)[1]. At this initial meeting,

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the high priority constructs within perception were identified as: 1) gain control and 2) integration[2]. Gain control was defined as processes that allow sensory systems to adapt and optimize their responses to stimuli within a surrounding context. Integration was defined as processes linking the output of neurons that individually code local (typically small) attributes of a scene into global (typically larger) complex structure for guiding behavior. Both of these domains have features that make them attractive and valuable for clinical trials in schizophrenia [2]. Specifically, 1) both can be readily measured in humans, 2) both show evidence of impairment in schizophrenia, 3) both have moderately strong links to neural circuits, 4) both are partially understood in terms of the mechanisms, 5) animal models exist for gain control, but not for integration, 6) links to neuropsychopharmacology are present for both, but are stronger for gain control, 7) both can be applied to human neuroimaging, and 8) both have moderate links to functional outcome.

The goal of the third CNTRICS meeting was to identify promising paradigms within these two perceptual domains. The task was to take paradigms from these domains that were nominated by a broad group of experts, and to evaluate the paradigms according to a list of criteria to determine which ones are highly promising for immediate development. The criteria for evaluating paradigms include the following: 1) construct validity; 2) clarity of a link to neural circuit; 3) clarity of a link to cognitive mechanism; 4) availability of an animal model; 5) link to a neural system through neuropsychopharmacology; 6) amenable for use in human neuroimaging studies; 7) evidence of impairment in schizophrenia; 8) link to functional outcome in schizophrenia; and 9) good psychometric properties.

A breakout group was devoted to evaluating the nominated paradigms, which are shown in the table. The purpose of this paper is to briefly summarize some of the key decisions from this breakout group and then to provide more detailed descriptions of each of the recommended paradigms.

For the measures of gain control (see Table 1), it was decided that there were two distinctly different types of measures: those that are already well-established in the schizophrenia literature and used in multi-site trials versus those that are still largely unexplored. The breakout group thought that it would not be fair to evaluate both types of measures in the same exercise, so the two more mature measures (i.e. prepulse inhibition of startle and mismatch negativity) were separated from the less established measures (i.e. contrast-contrast sensitivity and steady state evoked potentials to magnocellular vs. parvocellular biased stimuli). The two mature tasks were considered to be reasonable measures of gain control because they involve neural adaptation to immediate context, despite the fact that neither was viewed as a prototypical measure of gain control. It was noted that an assessment of contrast sensitivity to magnocellular vs. parvocellular biased stimuli could be easily added to the steady state evoked potential assessment with little additional time or burden, and so the description below includes both elements.

The two measures of gain control that were recommended for immediate development (contrast-contrast sensitivity and steady state evoked potentials / contrast sensitivity to magnocellular vs. parvocellular biased stimuli) scored strongly across the key criteria. Two areas of limitations were noted, namely that there were not strong animal models, and there were few data on links to functional status in schizophrenia. The limitation for animal models was not an absence of models, but that these models typically involved cats or non-human primates, as opposed to rodents. Rodent models have clear advantages for preclinical drug development activities because they are much faster and cheaper to implement than cat or non-human primate models. Hence, these models are more feasible for screening a large number of compounds for pro-cognitive effects. It was also noted that the steady state evoked potentials involved electrophysiological methods that would present a substantial practical challenge for

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multi-site clinical trials. Nonetheless, practicality was not a criterion at this stage of paradigm evaluation.

For the construct of integration (see Table 1), two measures were listed as recommended for immediate development: the contour integration task and the coherent motion detection task. A third task, the babble task, was nominated as well. In this task, participants are presented with a dense array of voices in which it is difficult to detect coherent words or phrases. The experimenter then measures the degree to which individuals report hearing "spurious" words or phrases. Hoffman and colleagues have found that individuals who go on to develop schizophrenia are more likely to report hearing such spurious words or phrases[3]. Although the breakout group felt that this task was highly interesting, the group believed that more work was needed to establish its basic construct validity and neural basis before it was ready for translation for use in clinical trials contexts. The construct validity for the contour integration task was considered strong. Some ambiguity in construct validity was noted for the coherent motion detection task regarding whether the task is mainly conducted by global versus local processing. Also when evaluated by the criteria, both measures recommended for immediate translation had similar limitations, including questions about applications to rodent models, few data on links to outcome in schizophrenia, and few psychometric data such as test-retest reliability. In the section below, we provide descriptions of each of these tasks for each of the two constructs to provide guidance for future research that will facilitate the translation of these paradigms into use in clinical trials contexts in schizophrenia.

Gain Control: Task Recommended for Immediate Development Contrast-Contrast Effect (CCE) Task

Description

Contrast-Contrast Effect (CCE) Task is based on a well characterized visual illusion in which contrast sensitivity is strongly modulated by the visual properties of adjacent or surrounding stimuli[4–6] and follows closely the paradigm in a study by Dakin et al.[5]. In healthy subjects, the presence of a high contrast surround results in decreased contrast sensitivity, i.e. the same level of contrast is perceived as being lower when it is surrounded by a high contrast stimulus compared to when it is not surrounded by this stimulus. This illusion demonstrates contrast gain control, which is necessary for optimization of visual processing. Subjects view a circular patch (1.3° diameter) presented in the center of the field of view, which consists of blob-like shapes (8 c/deg. bandpass-filtered noise) with a contrast of 40%. This central patch is presented either with or without a high contrast (95%) surround for 1000 ms. Subjects then view a reference contrast patch and indicate which patch had a higher contrast. The contrast of the reference patch is varied to provide a psychometric function for contrast perception. An adaptive method of constant stimuli can be used[7]. This procedure has the advantage that one can simultaneously estimate accuracy and precision. The data from each subject can be fit with a cumulative Gaussian function to estimate the accuracy (bias/intercept) and precision (slope) of the subject's contrast perception.

Construct Validity

The large number of consistent and convergent behavioral and functional studies based on this and related tasks in humans and animals strongly support the construct validity of the CCE task as a measure of contrast gain control. By definition, gain control is a process in which the relative magnitude of input and output signals is dynamically modulated in an adaptive manner. From an ecological perspective, there is an obvious benefit to dynamically adjust contrast sensitivity in accordance to the visual qualities of a given visual scene. The varying need for contrast gain is effectively operationalized in this task by the presence or absence of a high contrast surround. Numerous electrophysiologic studies[8–15] and a recent human fMRI

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study[16] attest to the modulation of neural activity as a function of the presence of a high contrast surround. For example, in single unit studies, the response rate of neurons to a visual stimulus within its classic receptive field is strongly diminished in the presence of a high contrast surround, which is outside of the neuron's receptive field. Likewise, a human study by Zenger-Landholt and Heeger demonstrated strong correspondence between behavioral performance and V1 activity as a function of the presence of a high contrast surround[16].

Neural Systems

There have been a very large number of studies examining the neural basis of contextual modulation of contrast processing. While the specific neural mechanisms have yet to be clarified, there has been substantial progress in identifying candidate neural systems and pathways. Converging evidence from psychophysics and fMRI indicates that the contrast-contrast effect is linked to visual processing within the primary visual cortex (V1). The study by Zenger-Landolt found robust contextual modulation of the fMRI signal in V1, V2 and V3, but the best correlation with behavioral responses and, consequently, perceptual changes induced by contextual modulation, was with V1 signal changes[16]. Some investigators have hypothesized localized lateral inhibitory mechanisms via horizontal fibers within V1[17] while others have proposed feedback mechanisms ultimately acting on inhibitory neurons in V1[8]. The suppressive effects of both of these models are hypothesized to act through GABA neurotransmission of inhibitory interneurons. Alternatively, feedforward mechanisms, in which contextual modulation arises in the lateral geniculate nucleus of the thalamus have also been proposed[12,13]. In addition to these models, others have postulated that multiple mechanisms may account for the contrast-contrast effect[18,19].

Pharmacological or Behavioral Manipulation of Task Performance

The effects of pharmacological or non-pharmacological treatment on contrast gain control are unknown at present. However, prior studies have outlined the involvement of dopamine, GABA and acetylcholine systems in processes related to CCE Task performance. Consequently, these neurotransmitter systems are potential targets of pharmacological agents seeking to address deficits in contrast gain control. Dopamine modulation of visual contrast detection has been documented in animals and humans. It is thought that dopamine's primary locus of modulation is mediated by D2 receptors in the retina but some studies have also shown extra-retinal sites of action (for review see[20,21]). A recent study by Chen et al. suggests that the atypical neuroleptics, with relatively less dopamine activity compared to typical neuroleptics, are not associated with alterations in contrast sensitivity in subjects with schizophrenia[22]. One of the most commonly cited mechanisms for the contextual modulation of contrast sensitivity is through surround suppression. In turn, the predominant neurobiological mechanism thought to mediate surround suppression is lateral inhibition through GABA neurotransmission[17]. Ozeki and colleagues found a modest effect of application of GABA A receptor inhibition on the magnitude of contextual effects on contrast sensitivity[13]. A recent study in monkeys demonstrated anatomic and functional evidence of nicotinic receptors being a mediator of visual gain control. Nicotinic receptors were found to be expressed abundantly presynaptically on thalamocortical fibers, specifically in layer 4c of V1. Furthermore, the application of nicotine at these synapses resulted in response gain to contrast stimuli that prior to treatment were sub-threshold[23]. In addition to pharmacological interventions, some lines of evidence suggest a potential role for cognitive training in treating deficits in gain control. There is now compelling evidence that top down modulation acts on early stages of visual processing, even in V1[24] and for the role of attentional modulation of contrast gain[25].

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Animal Models

The contrast-contrast effect, alternatively referred to as surround suppression in the literature, has been one of the most replicated findings in visual neuroscience, having been studied abundantly in animals, mostly cats[10,12–14] and macaques[8,9,11,15]. Although, as alluded to above, the specific mechanism of the contrast-contrast effect has yet to be clarified, the large body of neuroanatomical and neurochemical knowledge in the visual system of these animals provide unparalleled opportunities for translational research. The vast majority of animal models, however, are based on electrophysiologic and not perceptual dependent measures. Therefore, the direct translation of animal results to human clinical studies must be done with this limitation in mind.

Performance in Schizophrenia

There is one published study that has applied the CCE Task to subjects with schizophrenia[5]. This study demonstrated notable robustness in detecting a group difference in performance and interpretive specificity. Healthy and psychiatric control subjects experienced significantly greater biasing effect of the high contrast surround on contrast perception, compared to patients with schizophrenia. The robustness of this difference was such that there was nearly complete separation between patients with schizophrenia and controls on this measure. One of the most compelling aspects of the CCE Task for schizophrenia research is that patients are predicted to actually perform better than control subjects. This result strongly argues against generalized deficits accounting for the results. In addition to the study by Dakin et al., there have been several other recent studies in schizophrenia that have either employed similar tasks or have examined contextual modulation of other visual processes[26–28]. Among these studies, there is consensus that subjects with schizophrenia demonstrate altered contextual modulation of visual processing. The convergence of results across multiple paradigms and laboratories strongly argue for the reliability and robustness of gain control deficits in schizophrenia.

Psychometric Data

An important limitation of this task is that there has not been extensive testing of its psychometric properties. Test-retest reliability has not been assessed. As a related matter, the impact of practice or training also requires investigation. An attractive feature of this task is that psychometric functions can be obtained for subjects. From these functions, separate indicators of precision (the minimum size of contrast differences that are detectable, which is indicated by the slope of the function) and bias (reflecting the amount of offset that is needed between the target and the surround to produce a perceptual match) can be obtained, allowing us to examine discrimination accuracy independent of response bias (as with other signal-detection analyses). This flexibility suggests the absence of floor/ceiling effects.

Future Directions

While the availability of well validated animal models of the CCE Task and the accrued knowledge about the basic neuroanatomical and neurochemical components of the neural systems and circuits related to this task present an excellent opportunity to identify the specific neural mechanisms giving rise to deficits in contrast gain control in schizophrenia, several challenges remain. First, some basic psychometric qualities of this task, such as test-retest reliability, practice effects, and ceiling/floor effects, must be assessed. Although the deficit in schizophrenia appears very robust, the CCE Task must be applied to independent samples by additional investigators in order to assess its reliability. Second, there is at present a paucity of knowledge on the efficacy of any interventions in schizophrenia. There are several potential pathways that may serve as targets for non-pharmacological and pharmacological treatments and present future opportunities of study. Finally, there is a great need, on a conceptual and empirical level, to incorporate contrast gain control deficits within a larger theoretical

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framework for the behavioral and higher-order cognitive deficits in schizophrenia. This effort may take the form of uncovering correlations between CCE Task deficits and clinical or cognitive features.

Steady-state visual evoked potentials and contrast sensitivity to magnocellular- and parvocellular-biased stimuli

Description

This particular steady-state visual evoked potential (ssVEP) task using magnocellular- (M) or parvocellular-biased (P) stimuli was developed by Zemon and Gordon[29]. This task is based on the differential response to contrast of the M and P pathways, which begin in the retina and project via the lateral geniculate nucleus (LGN) to primary visual cortex. The M pathway shows a steeply rising increase in response to increases in low contrast and then nearly saturates at about 16–32% contrast[30,31] (Figure 1A). The P pathway does not respond until about 10% contrast or greater and has a linear increase in response throughout the entire contrast range [30,32]. The slope of the linear portion of the contrast response curve is referred to as contrast gain, and it is about ten times greater for the M than P pathway.

To emphasize contributions from the M pathway to the ssVEP, isolated check stimuli (Figure 2) were kept within the low-contrast region [29]. To emphasize contributions from the P pathway to the ssVEP, checks were modulated around a high static contrast (pedestal) to avoid the low-contrast regions where magnitudes of M-pathway responses rise steeply with increase in contrast.

A key aspect of the procedure is that the same depths of luminance modulation (DOM) (0, 1, 2, 4, 8, 16, and 32%) are used for both the M- and P-biased conditions. To produce the M-biased conditions in which stimuli appear and disappear, the DOM of the checks is equal to the mean contrast (pedestal). Thus, the checks reach a peak contrast double that of the mean value. For example, if the mean of the checks is set at 4%, then the DOM is also 4% and the pattern reaches a peak contrast of 8% at one point in the cycle and 0% contrast a half cycle later. Under the P-biased condition, a high mean contrast (pedestal) of 48% is often used.

A second important feature is that data can be collected quickly. Responses are typically recorded from an electrode at a midline occipital site (O_z) referenced to a second electrode on the vertex of the head (C_z). Patterns are modulated quickly (e.g., at 12 Hz) in a contrast sweep such that DOM is increased in each second of a 7-second run. Thus, in a single run, all 7 DOMs are presented and there are 12 stimulus presentations per second. The M- and P-biased conditions are presented separately and there are 10 runs of each condition. Fourier analysis is used to obtain the response at the stimulus frequency for each 1-s EEG epoch in each run and mean amplitude and phase values are computed over the 10 runs. Signal-to-noise ratios (SNR) are also obtained [33–35] as are estimates of contrast gain and contrast gain control [33,34].

A second task that may be used to assess M- and P-pathway responses involves psychophysical contrast sensitivity. This is a classic behavioral task that has been used for over 50 years[36–38]. Sine-wave gratings presented at various spatial frequencies from low to high are the typical stimuli. Spatial frequency refers to the number of pairs of light and dark bars in a degree of visual angle such that lower spatial frequencies indicate wider bars and higher spatial frequencies indicate thinner bars. Different psychophysical methods have been used to measure contrast sensitivity functions (CSF)[37]. A preferred method is two-alternative forced-choice tracking in which, for instance, gratings are presented randomly to one half of a visual display, while the other half has a uniform field[33]. Participants are asked to state which side of the display contains the grating. Contrast is varied across trials using an up-down transform rule

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to determine the contrast threshold for each spatial frequency condition (e.g., the contrast at which the presence of the grating is correctly detected 70.7% of the time). Contrast sensitivity is the reciprocal of this threshold. High contrast sensitivity indicates good performance. CSFs are inverted U-shaped functions with a peak in the mid-range of spatial frequencies (4–6 cycles per degree) and fall-off at lower and higher spatial frequencies.

Construct Validity

Gain control, as defined in the CNTRICS initiative, refers to processes that allow sensory systems to adapt and optimize their responses to stimuli within a particular context [2]. The nonlinear response to contrast with steep gain at low contrast and amplitude compression and phase advance with increases in contrast was first described in cat retinal ganglion cells and termed "contrast gain control" [39,40]. Contrast gain control refers to the *change* in slope of the amplitude function as contrast increases. Contrast gain control is present in M, but not P, neurons[41] and divisive contrast gain control is operating at higher contrasts to limit the responses of the M pathway. The divisive contrast gain control in the M pathway is thought to arise from shunting inhibition, which appears to be $GABA_A$-mediated[29,42].

Thus, unlike the P response to contrast which shows low gain and is linear over the entire range of contrast, the M response to contrast is an example of adapting and optimizing responses by showing high gain (slope) at low contrast where it is needed in order to respond to low contrast and, given that responses cannot continue to rise at that rate, compression of responses at higher contrast so that the M pathway can still respond to high contrast, albeit with lower gain.

The psychophysical contrast sensitivity task generally produces thresholds that are in the low-contrast range (i.e., produces responses with high contrast sensitivity). High contrast sensitivity in the CSF indicates high contrast gain. In addition, the M pathway uses contrast gain control and CSFs reflect M-pathway responses under a variety of conditions.

Neural Systems

The contrast response functions obtained in healthy humans under M- and P-biased pedestal ssVEP conditions[29,33,43,44] (Figure 1C and 1D) are very similar to those recorded from M and P neurons in macaque retina (Figure 1A)[30,41,45,46] and LGN[30,41,45,46], supporting the concept that neural M and P responses are being examined. In psychophysical studies of contrast sensitivity, transient and sustained mechanisms have been posited to explain the resulting CSF. These psychophysical mechanisms appear to correspond to M and P activity, respectively. Changes in the shape of the CSF with manipulation of spatiotemporal stimulus conditions have led researchers to conclude that brief presentations of gratings over a wide range of spatial frequencies yield M-dominated responses, and long duration presentation of spatial frequency gratings yield P-dominated responses[47].

Pharmacological or Behavioral Manipulation of Task Performance

For the contrast response curve, microinfusion of NMDA antagonists into cat LGN and primary visual cortex reduce contrast gain as well as the maximum response (Figure 1B)[48,49]. NMDA may also be involved in the high contrast sensitivity seen in the psychophysical contrast sensitivity task. Dopamine[20,50] and nicotinic cholinergic receptors[23] appear to play a role in contrast sensitivity measurements.

Animal Models

Like humans, monkeys have M and P pathways and produce contrast response curves in electrophysiological studies that are very similar to the ssVEP functions described above for humans. Although cats do not have M and P divisions, they produce contrast response curves

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similar to those recorded from M cells in primates[48,49]. In addition, similar results were seen for monkeys, in which recordings were obtained from the dura mater above the brain, and humans using the same apparatus and ssVEP stimuli described above[51].

CSFs can be obtained psychophysically as well as electrophysiologically. CSFs have been obtained in a number of species including goldfish, cat, and falcon and can be obtained behaviorally in macaques[52,53].

Performance in Schizophrenia

To date, two studies in which the ssVEP task was used demonstrated preferential deficits in the M pathway in schizophrenia patients including decreased contrast gain[33,43]. A subset of patients were also found to have decreased shunting inhibition[54]. A number of studies [33, 55–59] though not all[60] show decreased contrast sensitivity in patients with schizophrenia. The high contrast sensitivity suggests M-pathway deficits, although others have argued for a P-pathway role in this deficit within the high spatial frequency region.

Psychometric Data

An advantage of the ssVEP task is that behavioral responses are not required and participants only have to fixate on the screen, which reduces the burden. The 95% confidence intervals for the ten runs per person demonstrate consistent data and good reliability within an individual[29]. In addition, Signal to Noise Ratios (SNRs) are typically high, indicating signals that are considerably larger than the variability within a condition[29,33,43]. Also, the large between-group effects observed using SNR indicate good reliability within a group[33,43]. A number of individuals were re-tested on another day and results show good reproducibility (Butler et al., unpublished observations). CSFs do not have a ceiling effect, but could have a floor effect because threshold can never be greater than 100% contrast (i.e., contrast sensitivity of 1 is a lower limit in performance). Practice effects are negligible with the 2-alternative forced choice tracking method[37]. In addition, there is good agreement in observers in the shape of the function and absolute values of contrast sensitivity.

Future Directions

For the ssVEP, a full study of reproducibility across days needs to be done. While a body of single-cell data exists to support the role of M and P pathways in the generation of both ssVEP and CSFs, additional single-cell investigations may serve to support the use of macaques as an animal model and the conclusion that there are distinct contributions from M and P cells to these response measures. This work would include examination of the specific pedestal conditions for ssVEP and a variety of spatio-temporal conditions for CSFs in single cell studies of M and P neurons. For both tasks, further patient, prodromal, and pharmacological studies are needed. In particular, the amenability of ssVEP and CSFs to modulation by pharmacological or behavioral interventions needs to be examined.

Gain Control: Already Mature Tasks Prepulse Inhibition of the eyeblink component of the startle blink

Description

The startle response is a set of reflexive responses to strong, sudden acoustic or tactile stimuli that can be studied in all mammals. Prepulse inhibition of startle (PPI) is considered a measure of “sensorimotor gating” because it involves both sensory stimuli and motor responses. In PPI, the startle response elicited by a startling stimulus is measured in the presence or absence of a weak prepulse stimulus, which can be in the same or a different modality. The weak prepulse strongly inhibits the response to the subsequent startling stimulus. PPI is not a form of

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habituation and is not correlated with auditory gating measured as event-related potentials elicited by pairs of identical clicks presented at 500 ms intervals[61]. In humans, startle is assessed in most cases via the eyeblink component of the startle reflex, using electromyographic recordings. In animals, the whole-body flinch aspect of the startle response is quantified using an accelerometer that is sensitive to dynamic movements.

Most studies use brief (20 – 40 ms) startle-eliciting acoustic stimuli, with intensities varying from 105 to 115 dB and presented for 20 to 50 ms. On some trials in a test session, the startle pulse is preceded at 30 ms to 500 ms by a prepulse, which is not thought to elicit a startle response by itself. PPI is usually expressed as the percentage of inhibition of the startle amplitude on prepulse trials relative to the amplitude during startle pulse trials, although difference scores and raw values should be assessed especially when group differences in startle reactivity are evident [62].

An extensive literature in both humans and animals has demonstrated the parametric responsiveness of PPI to many factors, including: stimulus intensities, rise-times, durations, and modalities; controlled vs. non-controlled background noise [63]; pure tone stimuli vs. white noise stimuli [64] instructions given to the participants regarding attending to the stimuli [65 66 67]; sex differences [68]; strain differences [69 70] and, in humans, differences in which eye is monitored as well as smoking behavior and personality factors.

Construct Validity

Gating functions are believed to be impaired in schizophrenia, which theoretically can lead to increased distractibility, cognitive fragmentation, and thought disorder [71 72 73 74]. PPI is thought to reflect a largely automatic, pre-attentional, and unlearned sensorimotor gating mechanism. Indeed, deficient PPI in schizophrenia has been observed with intervals between the prepulse and startle pulse being too short (e.g. 30 or 60 ms) to be influenced by the conscious allocation of attentional resources [75]. In some descriptions, PPI is seen as a mechanism to protect the processing of the first of successive stimuli. In other contexts, PPI has been considered as an operational measure of gain control impacting perception.

Neural Systems

The similarity of PPI across species supports the suggestion that the neurobiological mechanisms underlying the PPI in humans can be examined productively in animals [76 77 78]. Whereas structures at the level of the brainstem control the startle response *per se* [79 80] forebrain structures modulate the inhibitory functions of the prepulse via cortico-striato-pallido-pontine circuitry [81 80 77]. This modulatory system includes the limbic cortex (medial prefrontal cortex, amygdala, and ventral hippocampus), the thalamus, the ventral striatum (nucleus accumbens), the ventral pallidum, and the pontine tegmentum [80 82 78 77]. Most if not all of these structures have also been implicated in the pathophysiology of schizophrenia [77]. Furthermore, fMRI studies have shown that most of these regions are altered by startle and/or PPI in humans, some being affected differentially in schizophrenia patients relative to control subjects [66 83].

Pharmacological or Behavioral Manipulation of Task Performance

An extremely extensive literature describes the effects of pharmacological manipulations on startle and PPI in rats (summarized in Geyer et al., 2001 [84] and Jones et al., 2008 [85]). In mice, the literature on pharmacological effects is also substantial and is growing [86]. In addition, many of the genes implicated in schizophrenia have been examined in mice by studying the effects of relevant genetic manipulations on PPI [86 87]. In both rats and mice, strain differences and gene expression studies have also added to our understanding of the neurobiological substrates influencing PPI [69 70]. In humans, more limited pharmacological data are available

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(reviewed in [75,88] and [89]. It should be noted that some disparities between pharmacological effects on PPI have been noted when comparing mice with rats or rats with humans [90,91,78,77,92]. Recent work has begun to explore the ability of some atypical antipsychotics, and potentially other treatments, to increase PPI specifically in healthy volunteers who exhibit low baseline levels of PPI [93]. Such studies may enable the development of proof-of-concept studies for either antipsychotic or pro-cognitive agents.

Animal Models

The cross-species nature of startle and PPI enables the use of animal models of induced deficits that are extremely similar to the gating deficits seen in schizophrenia. Beginning with the initial demonstrations of the ability of dopamine agonists and glutamatergic antagonists to disrupt PPI in rats [94], the rodent PPI models have evolved into at least four distinct models [95,84,77]. These models have PPI measures in common but are differentiated by the manipulations used to disrupt PPI: 1) dopamine agonists; 2) serotonin agonists; 3) N-methyl-D-aspartate (NMDA) receptor antagonists; and 4) developmental manipulations such as isolation rearing or neonatal lesions of the ventral hippocampus [84]. In contrast to the first three models, which are based on changes induced by acutely administered psychotomimetic drugs, the fourth PPI model may help to assess environmental or developmental contributions to PPI deficits [96,97,98] . In addition to rodents, some work has begun to establish non-human primate models of PPI and pharmacological manipulations relevant to schizophrenia [99].

Performance in Schizophrenia

As first reported in 1978 [100] and confirmed subsequently in many laboratories (reviewed in [75,64]), PPI is reduced in schizophrenia patients. PPI deficits in schizophrenia patients are seen in patients treated with first generation antipsychotic drugs as well as in first-break patients who had never been treated with any antipsychotics [101]. Although schizophrenia was the original focus of psychiatric PPI studies, subsequent research has demonstrated that PPI is reduced in patients suffering from a variety of neuropsychiatric disorders [75,64]. For example, PPI deficits have also been found in OCD, Tourette's Syndrome, Huntington's Disorder, panic disorder, bipolar disorder, Asperger's syndrome, and others [102]. These disorders are all characterized by PPI deficits and by abnormalities of gating in sensory, motor, or cognitive domains.

Psychometric Data

The several reviews cited above include extensive information regarding the psychometrics of PPI. In addition, it should be noted that PPI is quite stable over time in rodents and in both healthy human volunteers and clinically stable patients with schizophrenia [103,104].

Mismatch Negativity

Description

Mismatch negativity (MMN) is an event-related potential (ERP) response that is elicited when a series of standard stimuli is interrupted periodically by deviant, or "oddball," stimuli. MMN can be elicited using auditory and visual deviant stimuli that differ in one type of physical property (e.g., pitch, duration, intensity) from the standard stimuli. Although MMN can be elicited with visual stimuli, it is most commonly recorded using auditory stimuli and there is more information on the neural subsystems and psychopharmacological effects on MMN with auditory stimuli. Thus, this brief review will focus largely on the auditory-elicited MMN. For a more in-depth review, including discussion on heritability and genes associated with MMN, see [105].

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In the typical auditory MMN paradigm, a standard auditory stimulus (e.g., a 1000 Hz, 50 ms tone) is presented repeatedly with a brief interstimulus interval (e.g., 500 ms). On approximately 10% of the trials, a deviant auditory stimulus that differs in one physical property (e.g., a 1000 Hz, 100 ms tone) is presented. Subjects are usually instructed to ignore the tones, are shown a silent movie, or perform a secondary visual processing task. Mismatch negativity is calculated as the difference between the ERP elicited by the deviant stimuli and the ERP elicited by the standard stimuli. Response onset can occur as early as 50 ms after the onset of the deviant stimuli and peaks at approximately 200 ms post-onset. Mismatch negativity elicited by auditory stimuli has its maximum response at fronto-central sites. In humans, MMN reflects a largely preattentive and automatic measure of change detection and is thought to represent an echoic memory process [106,107]. MMN is not under the voluntary control of the subject and does not require any overt response. Therefore, MMN is seen as an effective means to measure preattentional auditory mechanisms in neuropsychiatric populations in which there may be questions about whether subjects are fully able and motivated to perform active cognitive tasks.

Neural Systems

Several different studies, using varying methodologies, have been conducted to determine the neural source of the auditory MMN response. Source localization of the MMN ERP [108], magnetoencephalography [109] and functional MRI [110] studies have localized the auditory MMN to the primary and secondary auditory cortices. Specifically, this includes the superior temporal gyrus, while others find additional contributions from bilateral dorsolateral prefrontal cortices [111].

Pharmacological or Behavioral Manipulation of Task Performance

N-methyl-D-aspartate (NMDA) receptor-mediated glutamate dysfunction is thought to underlie MMN deficits in certain neuropsychiatric diseases, including schizophrenia [112]. NMDA antagonists have been shown to diminish MMN amplitude in primate models [112] as well as selectively diminish MMN amplitude in healthy control subjects while sparing other auditory-related ERP activity [113,114,115].

Animal Models

Animal models of MMN are very valuable in the neuroanatomical and psychopharmacological examination of normal and dysfunctional MMN. Reliable MMN data that closely match MMNs recorded in humans have been recorded from rats [116], cats [117], chimpanzees [118], as well as monkeys [112]. The results of these studies imply that animal models can be used to test newly developed pharmacological treatments to improve MMN in schizophrenia patients.

Performance in Schizophrenia

Deficits in mismatch negativity amplitude and latency have repeatedly been shown in schizophrenia patients using varying deviant stimuli, including duration deviants, frequency deviants, and intensity deviants [119,120,121,122]. A meta-analysis of MMN studies in schizophrenia patients [123] showed a mean effect size of approximately 1.0. Moreover, it appears duration deviant stimuli tend to result in a larger MMN deficit compared to frequency deviant stimuli, though the difference was not statistically significant. MMN also appears to be insensitive to antipsychotic medication in schizophrenia, as it is not affected by first-generation antipsychotic medications or risperidone, olanzapine or clozapine [124,125,126].

Mismatch negativity deficits in schizophrenia have recently been shown to be correlated with measures of functional outcome. In a sample of chronic schizophrenia patients, Light and Braff[121] found that MMN was significantly negatively correlated with the Global Assessment of Functioning (GAF) scale[127] as well as a measure of independent living[128], with MMN

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accounting for up to 42% of the variance in the functional status of the patients. Moreover, the relationship between MMN and functional status in schizophrenia patients has been shown to be stable over time [122]. These connections to functioning have been replicated. Kiang et al. [129] found that MMN elicited by duration-deviant tones was associated with GAF scores in a sample of 18 schizophrenia patients. Kawakubo and Kasai[130] found that poorer duration MMN, elicited using phonemes rather than pure tones, was correlated with lower GAF scores. This group[131] also found that better phoneme-deviant MMNs were associated with better scores on a social skills acquisition program after 3 months in a sample of 13 schizophrenia patients. Using a visual MMN task, Urban et al. [132] found that schizophrenia patients below the median on the GAF had significantly smaller MMN amplitudes than normal controls and patients who were above the median on the GAF.

Psychometric Data

In healthy controls, MMN has high test-retest reliability coefficients in the range of 0.60–0.80, with higher reliability seen using duration deviant stimuli [133]. In schizophrenia patients, MMN also appears to be stable over time, with one study finding no differences in MMN amplitudes recorded at least one year apart [122]. Mismatch negativity amplitude in frontal sties also appears to be stable in schizophrenia patients during acute and post-acute phases [134], suggesting that MMN amplitude deficits are a relatively stable trait characteristic of the disease.

Visual Integration Contour Integration Test

Description

In this task, the visual integrative mechanisms responsible for linking contour segments together are probed by employing stimuli with a continuous path of Gabor signals embedded in noise (see Figure 3). Participants are typically asked to either identify the location of the contour (e.g., a line or a circular shape, depending on the task) within the larger stimulus field, or to determine in which direction an egg-shaped contour is pointing (left or right) in a 2-alternative forced-choice task. Gabor elements are Gaussian-modulated sinusoidal luminance distributions that closely model the known spatial frequency processing properties of cells in area V1. Use of Gabor elements provides superior measurement of orientation sensitivity, and grouping of orientation cues, compared to stimuli with unknown effects on V1 neurons (e.g., arbitrarily constructed lines and dots). The embedded contours in stimuli employing Gabor elements cannot be detected by purely local filters or by the known types of orientation tuned neurons with large receptive fields[135]. The long-range orientation correlations along the path of the contour can only be found by the integration of local orientation measurements into an emergent shape representation (see Figure 3).

Construct Validity

Numerous studies using such tasks have explored the conditions under which human observers perceive or do not perceive contours (reviewed in[2]). These findings support Field et al.'s [136] concept of the "association field," in which neurons whose orientations are correlated in a manner that suggests the presence of a contour have facilitatory effects on each other, whereas neurons that encode elements whose orientation varies randomly with surrounding elements have an inhibitory effect on each other. Moreover, findings from psychophysical studies are consistent with computational models derived from information theory, in which receptive and contextual fields interact to enhance the salience of phenomena that can be grouped based on statistical regularities [137 138]. Validation of the concept of visual integration from psychophysical studies has come from tasks that manipulate one or more of the following 3 parameters: 1) signal noise ratio (Delta or Δ) which refers to ratio of the average spacing between adjacent background elements to the average spacing between adjacent contour elements; contours are more difficult to detect as the ratio decreases (see Figure 3); 2) the

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orientation of contour elements; contours are more difficult to detect as the elements are jittered and the correlation between the angles of adjacent elements decreases (see Figure 4); and 3) the spacing between contour elements; for children, but not healthy adults, contours are more difficult to detect as contour elements become further apart, even when Δ is kept constant by removing background elements as contour element spacing increases (see Figure 5).

Neural Systems

The behavioral findings using contour integration tasks are supported by microelectrode studies in animals that indicate facilitatory effects of flanker elements with orientations similar to, or strongly correlated with, a target element, and inhibitory effects of random orientation surrounds[139]. Moreover, behavioral findings fit closely with the predictions of the cortical processing model of visual integration proposed by Yen and Finkel[140] in which horizontal connections mediate context-dependent facilitatory and inhibitory interactions among neurons coding stimulus orientation. The contour integration task has demonstrated sensitivity to visual integration deficits in both anisometropic and strabismic ambyopia, disorders where integration deficits are limited to the early visual cortex regions subserving the disordered eye, showing clear differences between amblyopic and fellow eyes[141 142]. FMRI data in humans[143] and monkeys[144] indicate a visual cortex basis for contour integration, and a recent study in schizophrenia patients and healthy controls indicate that these same regions (e.g., V2–V4) are underactivated during contour perception in schizophrenia[145]. In addition, recent work suggests that contour integration mechanisms may be mediated by NMDA-mediated glutamatergic effects[146].

Pharmacological or Behavioral Manipulation of Task Performance

We are unaware of studies with these specific contour integration tasks that have examined whether performance can be modified through either pharmacological or behavioral interventions. However, as noted below, performance can improve during treatment in individuals with schizophrenia[147 148], suggesting that such deficits are amenable to modification. Given hypotheses about the mechanisms supporting contour integration described above, promising avenues for pharmacological manipulation would be agents that modulate NMDA receptor function[146].

Performance in Schizophrenia

The contour integration task has shown evidence of impairment in schizophrenia in all studies in which it has been used[145 149 148 150 151 152 153 154]. Performance on the contour integration test is related to level of disorganization, but not positive or negative symptoms in schizophrenia[147 155 149 148]. Moreover, among schizophrenia patients who demonstrate impairments on admission to acute-care-level treatment, test scores improve significantly over time, and the degree of change is related to improvement in disorganized symptoms[147 148].

Psychometric Data

Past studies have demonstrated adequate reliability and minimal practice effects. Silverstein et al[156] tested 87 people (including schizophrenia patients, other psychotic patients, and nonpatient controls) over two consecutive days using a signal-noise ratio (Δ) task variant. For controls only, across the first 2 days (collapsed across both conditions) the single measures ICC was .77, $p<.001$. For the entire sample the single measures ICC was .66, $p=.005$ (Footnote 1). In a study using a version of the task also employing a signal-noise ratio (Δ) manipulation, there were no significant differences in test-retest performance across 4 same-day administrations in children, or across 6 same-day administrations in adults[157]. In addition,

(1)These reliability estimates were calculated for the current paper and are not found in the original article cited.

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studies of practice effects in nonclinical and amblyopic samples indicate virtually no change in performance across repeated administrations in a single day, or two consecutive administrations on the same day[153 157] using a version of test that varies Δ only. When multiple administrations are used across multiple days, however, allowing for sleep-dependent perceptual learning, some minimal practice effects were observed[153 154]. For example, using the orientation manipulation variant of the test with 12 healthy controls for five consecutive days, Day 5 was the only day where scores differed significantly (p=.015) from Day 1[154]. Kovacs et al[158] reported that, when tested over three consecutive days, practice effects were not evident until the third day, and these were greater in children than in adults. Silverstein et al[153], using a version that varied Δ only, demonstrated the largest practice effects. However, in this study, the test was given twice a day for four consecutive days. To date, studies have not specifically assessed practice effects or test-retest reliability over periods greater than 5 days. However, in Uhlhaas et al.[148], non-disorganized schizophrenia patients, psychotic patients with disorders other than schizophrenia, and psychiatric controls did not perform differently when tested on admission and discharge to a psychiatric unit (mean length of stay was 23 (SD=22.2) days). Only the disorganized schizophrenia group demonstrated significant improvement, and this was significantly correlated with reduction in disorganized symptoms.

Future Directions

Future research will need to determine which of the three task versions described above are the most sensitive to visual integration deficits in individuals with schizophrenia. In addition, although each version of the task is relatively brief (20 minutes or shorter), work is needed to determine the minimum number of trials necessary both to discriminate patients from controls, and to be sensitive to treatment effects. In addition, work is needed to determine whether visual integration deficits as measured by contour integration are amenable to modulation by pharmacological or behavioral interventions.

Coherent motion detection

Description

Detection of coherent motion is a perceptual task used widely for assessing visual motion processing. Like many perceptual tasks, development of the coherent motion detection task [159 160] is based on the premise that, by systematically adjusting the signal strength of visual motion, one can quantitatively determine properties of the visual motion processing system. As one such property, perceptual performance during motion detection can be measured as a function of signal strength of the visual stimulus.

Coherent motion detection tasks utilize a specific motion stimulus called a random dot pattern (RDP) that consists of signal and noise components (Figure 6). The signal is an array of dots moving coherently in one direction (e.g. rightward) whereas the noise is another array of dots moving in random directions. These two arrays of moving dots interleave spatially within a certain region as well as temporally within a certain display time. The proportion of the signal dots in a RDP determines its motion signal strength – the greater the percentage of the signal dots, the stronger motion signal strength a random dot pattern possesses. The task, when applied in a behavioral domain, is to identify the direction of motion of the signal dots in the presence of the noise dots.

Construct Validity

Given the special spatial and temporal configurations in a RDP, the ability to detect the direction of motion provides an effective measure of visual integration. To perceive the direction of motion of the stimulus, one must integrate visual information about the signal dots that are distributed spatially in random locations and temporally at random times. Focus on

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one particular spatial location or one particular time would not lead to success in detecting the globally-defined direction of motion. The requirement of combining visual signals across space and time makes coherent motion detection a useful task for assessing integration, and therefore lends the task a high degree of construct validity. It has been used in studying a variety of populations – human and animal, young and elderly, healthy and diseased.

Neural Systems

Perceptual performance in coherent motion detection is mediated by neural computation in the visual motion systems. The primary neural computation includes direction selectivity and spatial integration – the former refers to a property that is characterized as the selective responsiveness of a neural unit to one specific direction of motion (but not to the opposite direction of motion), whereas the latter refers to a summation process that combines visual signals across space. Neurophysiological studies in monkeys have identified neural units that are responsive to coherent motion [161]. Robust neuronal responses to coherent motion in motion-sensitive brain areas such as the Middle Temporal (MT) Area have been directly linked to correct perceptual responses [162]. Neuroimaging studies in humans have shown that the same cortical regions (e.g., MT) are significantly activated in the presence of coherent motion [163], confirming the evidence found from neurophysiological studies. One important feature in these findings is that the magnitude of both neuronal responses and cortical activations at MT is proportional to the signal strength of coherent motion, mimicking the established relationship between accuracy of perceptual performance and signal strength of coherent motion.

Pharmacological or Behavioral Manipulation of Task Performance

Several types of neurotransmission appear to modulate detection of coherent motion. GABAergic activity plays an important role in forming and shaping direction selectivity, a neural property essential for motion detection[164]. Agonistic action of serotonin (via Psilocybin) can lead to a selective impairment in detection of coherent motion[165]. The impact of pharmacological modulations on detection of coherent motion is still an area that awaits further investigation.

Performance in Schizophrenia

Compared with healthy individuals, schizophrenia patients perform the task with significantly lower accuracies and require greater levels of signal strength in order to achieve similar levels of accuracies [166–169]. This result indicates that processing of coherent motion signals is deficient in this psychiatric disorder. On the other hand, a preliminary study showed that the relatives of schizophrenia patients and patients with bipolar disorder had normal performance on this task, suggesting specificity of coherent motion detection deficit in clinical schizophrenia [170]. This result, however, needs to be confirmed in larger and independent populations. The deficient performance in detecting coherent motion has been associated with smooth pursuit eye movement dysfunction in schizophrenia patients [166,171].

Cortical mechanisms underlying coherent motion detection have also been investigated in schizophrenia. Although normal detection of coherent motion primarily involves the occipital cortex, decreased neural activation in occipital areas such as MT (as expected), as well as increased neural activation in the frontal cortex, were found while schizophrenia patients performed this task [172]. This result suggests that coherent motion detection in schizophrenia involves not only sensory but also cognitive processing in the cortex.

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Psychometric Data

Many kinds of physiological (as well as behavioral) data are available to attest to the validity of the coherent motion detection task in measuring visual integration. Yet, the reliability of performance measurements in individuals, particularly in patients, still needs to be evaluated.

Future Directions

Thus far, this task has been used primarily within research laboratories. How to adapt this laboratory-based task in clinical settings is a future direction that merits effort. Additionally, the interaction between visual and cognitive processing remains an elusive topic in schizophrenia research. Detection of coherent motion may provide a probe into both visual and visual cognitive processes, in which the bottom-up and top-down mechanisms pertaining to visual integration can be concurrently and comprehensively evaluated in schizophrenia patients. Another prospective direction may be to evaluate the efficacy of antipsychotic agents on modulating behavioral performance during coherent motion detection tasks.

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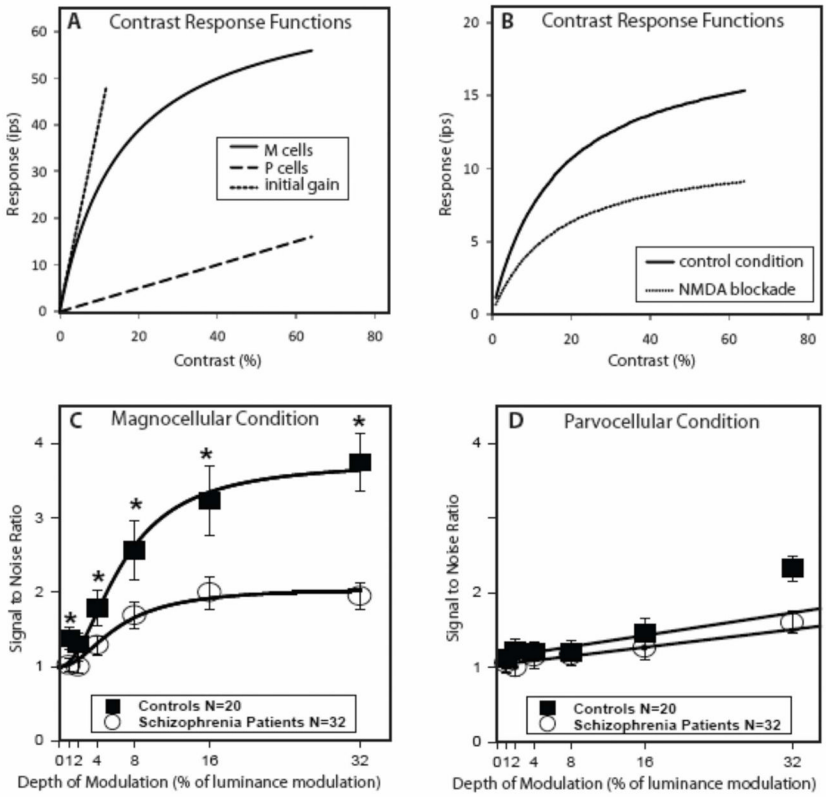

Figure 1.

(A) Contrast response functions recorded from macaque monkey retinal ganglion cells (adapted with permission from Kaplan and Shapley 1986). M cells show much higher gain (slope) than P cells at low contrasts. The initial gain of the M cells is shown in the dashed straight line derived from the M-cell curve. The gain of the P cells is the dashed line fitted to the P-cell function; (B) NMDA antagonists produce shallower gain at low contrast and a much lower plateau in visual evoked potential responses, indicating decreased signal amplification (adapted with permission from Kwon et al 1992); (C and D) Visual evoked potential responses (adapted with permission from Butler et al., 2005) using the M- and P-biased ssVEP technique described in this paper. The patient visual evoked potential contrast response curve in the M-biased condition shows similar decreased gain at low luminance contrast and decreased plateau as seen with NMDA antagonist administration, indicating decreased signal amplification.

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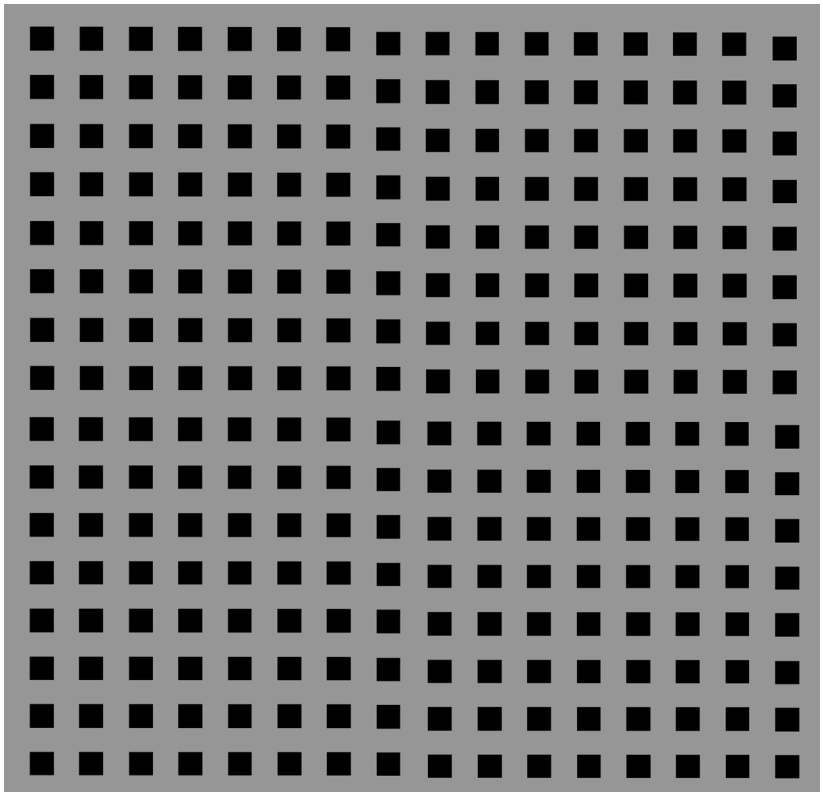

Figure 2.
Example of isolated check stimuli used in the ssVEP task.

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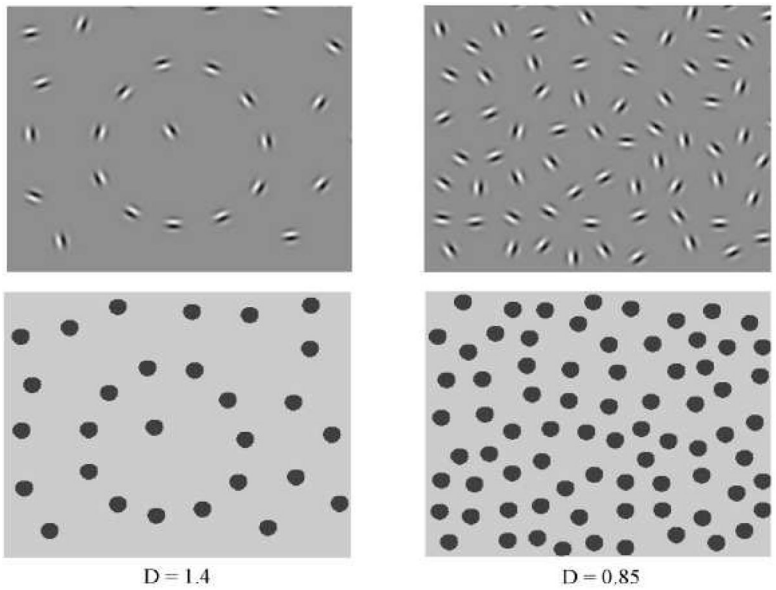

Figure 3.

Examples of Gabor-defined contours with different D values (top left: D=1.4, top right: D=0.85.). In the bottom panels, Gabor elements were replaced by disks to demonstrate the importance of correlated orientation cues in visual integration. Without orientation cues in these bottom panels, the contour remains invisible at D<1, and this is the range where visual integration depends on long-range spatial interactions. Note that these panels focus on the stimulus region containing the contour only. In the actual test stimuli the areas represented by the panels below would comprise about 1/8 of the total stimulus display.

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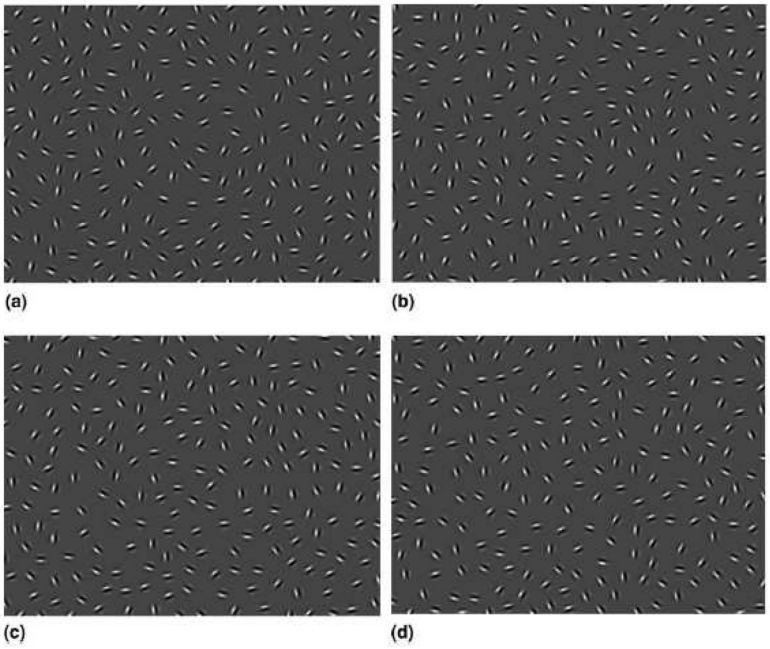

Figure 4.
Samples of images from the 2 alternative forced choice (2AFC) version of the task. Top left - 0 degree jitter, top right - 7–8 degree jitter, Bottom left - 15–16 degree jitter, Bottom right - 27–28 degree jitter. These panels show only the region of the display containing the contour. The actual stimuli contain approximately 75% additional space that contains only noise elements.

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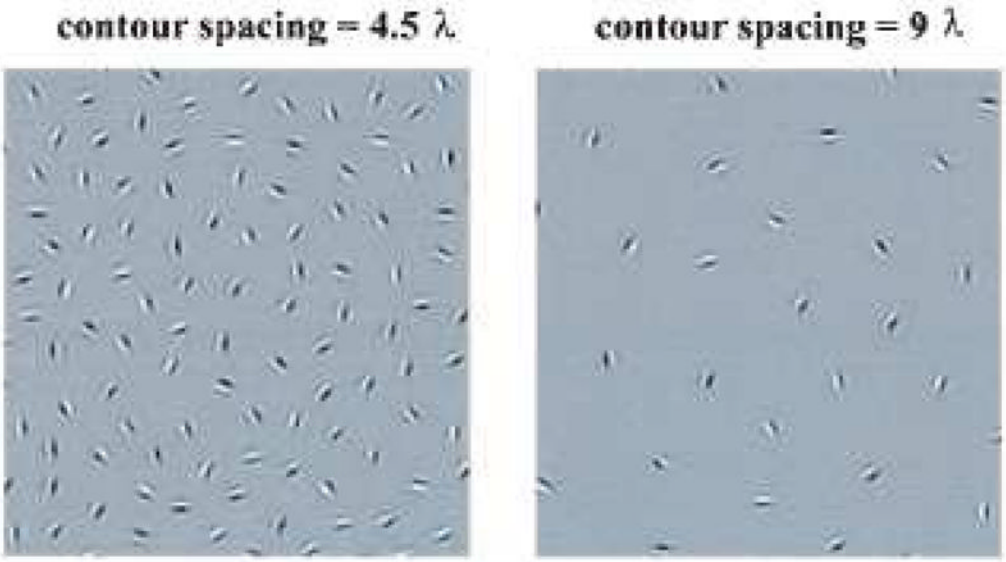

Figure 5.

Performance in the contour-integration task is determined by the relative noise density (D), and it might also be determined by the absolute (cortical) spatial range of interactions (i.e., the distance across which elements can be integrated into a single object). Left panel - contour spacing is small: 4.5λ (λ= wavelength of Gabor signal, or the width of the dark section of the stimulus). Right panel - contour spacing is large: 9 λ. These are partial presentations of the cards showing only the contour area. D=0.85 in both cases. Adult performance as defined by D at threshold does not vary significantly in the tested contour-spacing range, which means that adults are limited only by relative noise density. However, children integrate large-spaced contours with a greater difficulty, which indicates the possibility of shorter interaction ranges in their case, and also in cases of neuropsychiatric disorders with compromised contour integration.

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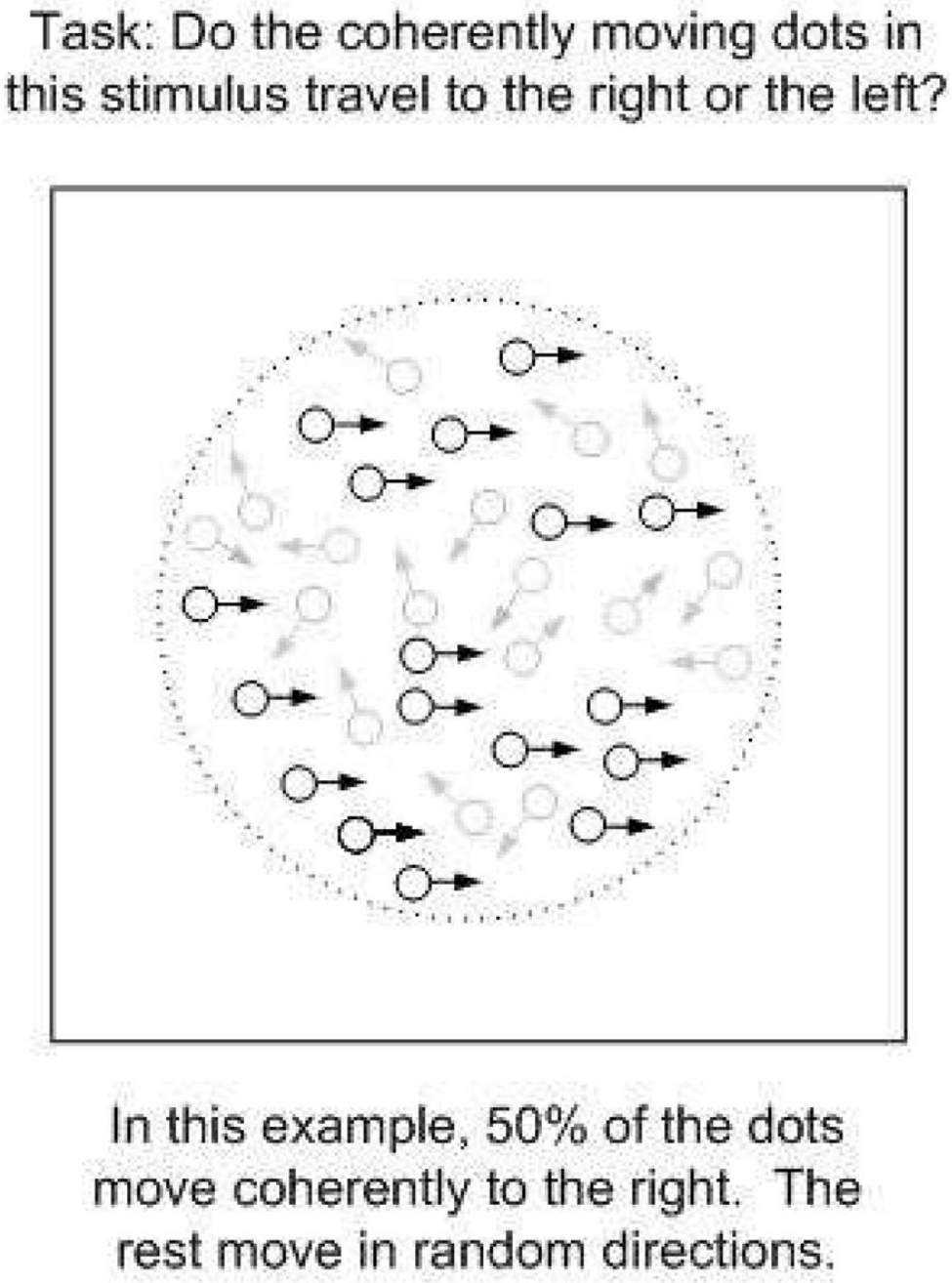

Figure 6.
Examples of stimuli from a coherent motion task.

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Table 1

Perception in Schizophrenia

Gain control: Neurons adapting their response levels to take into account their immediate context to make best use of a limited dynamic signaling-range.

Tasks Recommended for Immediate Development:

1. Contrast-Contrast Effect (CCE) Task
2. Steady state visual evoked potentials to magnocellular vs. parvocellular biased stimuli (with contrast sensitivity task)

Already Mature Tasks:

Prepulse Inhibition of Startle

Mismatch Negativity

Integration: The processes linking the output of neurons that code local attributes of a scene into global complex structure.

Tasks Recommended for Immediate Development:

1. Contour Integration Task
2. Coherent Motion Detection Task