Atypical scanpaths in schizophrenia: Evidence of a trait- or state-dependent phenomenon?

Sara A. Beedie, PhD; David M. St. Clair, MD, PhD; Philip J. Benson, PhD

Beedie, Benson — School of Psychology, College of Life Sciences and Medicine, University of Aberdeen, King's College; St. Clair — School of Medicine and Dentistry, Division of Applied Medicine, University of Aberdeen, Clinical Research Centre, Royal Cornhill Hospital, Aberdeen, Scotland

The development of trait markers of schizophrenia would represent an important advance in understanding the genetic architecture of the disease. To date, no candidate markers have satisfied all of the trait marker criteria, and many are not specific to the schizophrenia spectrum. Abnormalities in visual scanpaths are frequently reported in patients with schizophrenia and are emerging as a novel candidate for a schizophrenia biomarker. Here we review the suitability of scanpath measures as a target for trait marker research in schizophrenia. Papers reporting scanpath patterns in patients with schizophrenia were identified by PubMed and Google Scholar searches and by scanning reference lists in relevant articles. Search terms included "schizophrenia," "psychosis," "scanpath," "scan path," "fixation," "saccade" and "eye movement." Scanpath abnormalities afford impressive sensitivity and specificity and appear largely independent of psychotropic medications. Scanpaths may demonstrate some fluctuation with symptomatology and may be useful in illuminating illness state or subtypes. However, there is evidence that viewing behaviours remain atypical regardless of symptom remission and may be present in unaffected relatives of individuals with schizophrenia. This research is in its early stages, and further investigation regarding patterns of inheritance is required. Our findings support scanpath measures as a favourable topic for further investigation as a trait marker.

Introduction

Schizophrenia is a highly heterogeneous and complex disorder. Diagnosis of the disease is currently based on clinical criteria and lacks objective tests. Although there is much support for a genetic component in vulnerability to the illness, and a number of chromosome loci and candidate genes have been recognized, much about the genetic basis of schizophrenia remains unknown (for a recent review, see Williams and colleagues[1]). Several genes are likely to contribute to susceptibility, and patterns of inheritance are intricate and irregular. Further, the natural boundaries that may distinguish schizophrenia from other psychotic and affective disorders, such as bipolar disorder, are unclear.[2] Case–control studies of the underlying neuropathology or genetics of schizophrenia are limited by the inherent heterogeneity of the disease and the possibility that clinically similar phenotypes may also have different etiologic causes. The development of objective criteria and external markers would help to validate external boundaries that represent the underlying pathology of the disease.

One approach to furthering our understanding of the genetic architecture of schizophrenia involves the study of endophenotypes.[3] Endophenotypes are measurable characteristics, such as neuropsychologic or psychophysiologic traits, that are associated with genetic vulnerability for the disease. These characteristics are believed to reflect the action of genes associated with the illness, regardless of whether diagnosable pathology develops. The study of endophenotypes confers several benefits to genetic research in schizophrenia. First, if the phenotype is defined solely on the basis of the presence or absence of a schizophrenia diagnosis in genetic studies, false-negatives will occur where individuals carry the genetic vulnerability but do not display symptoms, and sensitivity will be reduced.[4] Second, the current classification of mental illness using psychiatric diagnoses does not lend itself to the dissection of diseases on the basis of their complex genetic architecture.[3] For example, the term "schizophrenia" may comprise several different disorders, each with its own genetic and non-genetic influences. Genetic analysis is made more difficult by the likely polygenic nature of schizophrenia.[5] Endophenotypes

Correspondence to: Dr. S.A. Beedie, School of Psychology, College of Life Sciences and Medicine, University of Aberdeen, William Guild Bldg., King's College, Aberdeen, Scotland, AB24 3FX; s.beedie@abdn.ac.uk

J Psychiatry Neurosci 2011;36(3)150-64.

Submitted Nov. 27, 2009; Revised June 14, Aug. 20, 2010; Accepted Sept. 1, 2010.

DOI: 10.1503/jpn.090169

help to dissect the disease phenotype into more biologically homogeneous subgroups of individuals, facilitating consideration of genetic underpinnings.[5,6] Although alternative terms such as "vulnerability marker," "trait marker" and "biomarker" have previously been used interchangeably with the term "endophenotype," recent authoritative reviews have clarified the distinctions between these concepts.[7,8]

Researchers have debated and refined the endophenotype concept in psychiatry. It is broadly accepted that a number of core criteria should be met. These include association with the disease under investigation, stability over time, relative independence from clinical state, evidence that the characteristic is under genetic control and cosegregation in families with probands and other affected family members.[3,7,9,10] Such measures must also show good psychometric or neurometric properties. Ideally, tests should be quick and inexpensive to administer to allow for high-powered studies. The original endophenotype approach assesses "intermediate phenotypes" that are proposed to constitute causal links between genes and disease. However, commentators have cautioned that not all putative endophenotypes meeting the above criteria will represent traits lying on the pathway between genes and disease. For example, a trait may comprise an epiphenomenon of a risk gene or may be associated with different genes than those predisposing to the disease.[8] Such traits may still confer substantial value in identifying more genetically homogeneous groups. Establishing that a trait truly lies on the gene–disease pathway may require longitudinal research and even intervention studies in addition to fulfilling the basic endophenotype characteristics.[8] Given that putative markers fulfilling the criteria of an endophenotype may provide valuable insight into a disease even when they have not been shown to constitute a causal link between genes and overt expression of the disease, in the present context we adopt the more operationally neutral term "trait marker" to refer to stable, heritable biological processes or abnormalities that are presumed to indicate disease vulnerability without the implication that the marker necessarily represents a causal link between gene and disorder.

A broad range of psychophysiologic measures have been proposed as candidate trait markers in schizophrenia (for a review, see Javitt and colleagues[11]). Examples include smooth pursuit eye movements,[12] P300 event-related potentials,[13] sensory gating[14] and antisaccade performance.[15] However, no measure to date has met the essential criteria required of an unequivocal marker of vulnerability for schizophrenia. For example, a deficit in smooth pursuit eye movements is one of the most promising potential markers. But there is evidence of heterogeneity in pursuit ability in both individuals with schizophrenia and healthy groups. Tracking deficits are not limited to nor uniformly present in schizophrenia. The proportion of individuals with schizophrenia presenting impaired tracking ranges from 12% to 96%, with most reports falling between 50% and 86%, compared with 1%–8% in controls.[5] Lack of diagnostic specificity is also a common limitation of endophenotype measures proposed to date.

A recently emerged candidate marker is the visual scanpath, the pattern of eye movements generated during free exploration of a visual scene. A number of researchers have proposed that scanpath measures may constitute a trait marker of vulnerability for schizophrenia, but few authors to date have reported the current state of scanpath research in this area. Investigations of the suitability of scanpaths as a marker are in their infancy compared with other more traditional measures. The purpose of this review was to draw together existing knowledge on state and trait characteristics of scanpath abnormalities in individuals with schizophrenia within the framework of the basic concepts widely accepted to be among the optimal characteristics for a trait marker. Papers reporting scanpath patterns in patients with schizophrenia were identified by PubMed and Google Scholar searches and by scanning reference lists in relevant articles. Search terms included "schizophrenia," "psychosis," "scanpath," "scan path," "fixation," "saccade" and "eye movement." We summarize findings relating to the association of scanpath deficits with schizophrenia, stability of these deficits over time and in parallel with fluctuations in disease state as well as evidence for genetic control of scanpath dysfunction in individuals with schizophrenia, as illustrated by family and genetic linkage studies.

Scanpaths as potential trait markers in individuals with schizophrenia

Eye movements provide a directly observable measure of visual orienting and attentional biases.[16,17] During visual exploration, patterns of visual scanning (scanpaths) are formed by successive periods of steady gaze (fixations) and intervening rapid movements (saccades).[18] Fixations allow salient areas of the scene to be concentrated on the fovea, providing the visual system with high-acuity information, while less detailed information is collected by parafoveal and peripheral retinal fields. Although it is possible to dissociate the point of gaze from the direction of visual attention,[19] under natural viewing conditions they are usually closely linked.[20,21] In healthy observers, the patterns of movements produced by the saccadic system are not random. Rather, saccades and fixations are subject to the influence of a number of variables, including the physical and semantic properties of the image and the demands of the viewing task.[22–30]

A variety of related measures are commonly used to study scanpaths. These include fixation and saccade frequency, fixation duration and saccade amplitude. Fixation measures reflect periods of detailed information acquisition and planning of subsequent distal fixations. Properties of ocular fixations may be influenced by difficulties in attentional disengagement or speed of information processing. Saccade measures may reflect the integrity of saccadic programming, the ability to execute saccadic sequences and fine oculomotor control. Clearly though, in any given measurement epoch, such variables will be highly interrelated, and an irregularity in any one stage of visual exploration is likely to be reflected by a number of variables. Therefore, the interpretation of eye movements arguably may be more valid when a number of measures are considered together, particularly when interpretation is to be made within frameworks of cognitive functions.

Experiments in human and nonhuman primates have isolated a fronto-parietal cortical complex that is active during

pursuit, intentional and reflexive saccades and scanpath formation. The frontal eye field (FEF) area receives extensive inputs from the extrastriate visual cortex and is involved in triggering and maintenance of saccadic and pursuit eye movements.[31,32] Frontal eye field activity coincides with transformation of cognitive decisions into motor signals to fixate a particular image location.[33] Some FEF activity is correlated with the frequency of saccadic eye movements.[34] The decisions and motivation for preparing and performing these saccades are controlled by the posterior cingulate cortex (the cingulate eye field). The parietal eye fields manage shifts in visual attention[35] and influence saccade target selection. Neural activity here dictates the latency of these reflexive, visually guided saccades. The supplementary eye fields receive motion and spatial information about image features via the dorsal visual pathway and prepare motor sequences for successive saccades. Saccade inhibition during fixation, short-term spatial memory and saccade prediction are orchestrated by the dorsolateral prefrontal cortex (DLPFC). The development, maturation and integrity of this cortical network are essential for triggering saccades generated by the superior colliculi and brain stem.

Atypical scanpaths in individuals with schizophrenia have been observed in response to a broad range of visual stimuli and in different tasks. In general, the literature has associated a restricted style of scanning with the illness, characterized by fewer fixations and saccades, increased average fixation durations, smaller saccades and shorter scanpath length compared with healthy viewers.[36–59] In contrast to the relatively extensive or holistic scanning strategies of healthy viewers, scanpaths in individuals with schizophrenia also tend to be less spatially dispersed, with less attention paid to perceptually and semantically informative areas.[36,39–42,44,46–48,50,51,54,55,59–69] Several researchers have employed scanpath techniques to examine face processing or emotion processing in individuals with schizophrenia, and a substantial proportion of reports of scanpath behaviour in this population are therefore based on findings from face stimuli presented centrally on a display. However, replication of similar scanning patterns with stimuli devoid of social content suggests that the phenomenon is not specific to faces or social scenes. Figure 1 illustrates fixation

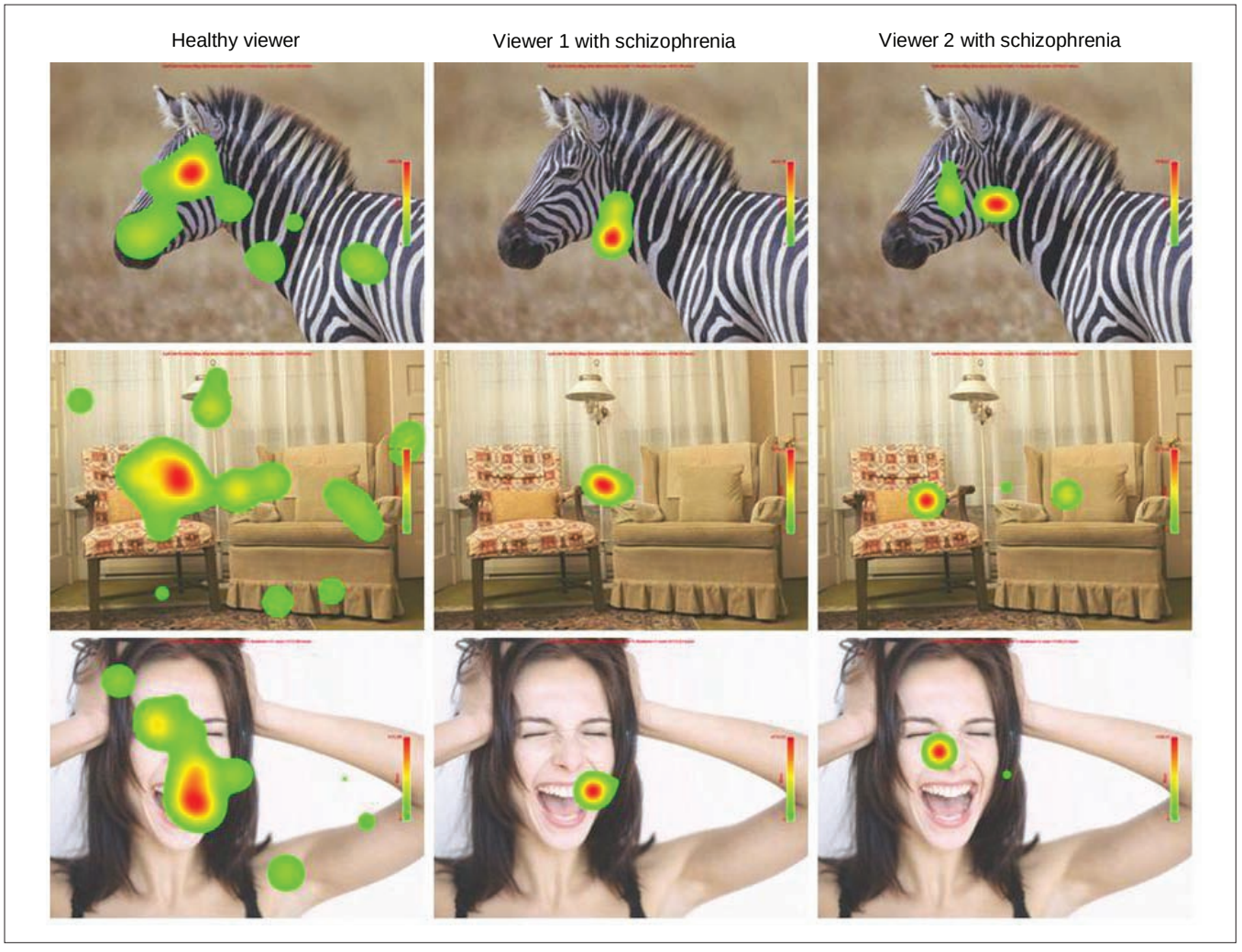

Fig. 1: Fixation heat maps for representative scanpaths of a healthy viewer and 2 individuals with schizophrenia. Red areas denote greater density of fixations. Image brightness and contrast have been reduced for clarity. Source: data reported in references 70–72.

patterns in individuals with schizophrenia and an unaffected control viewer.

A central role of frontal lobe pathologies in abnormal scanning is supported by neuroimaging findings,[73,74] similarities between scanpaths of patients with schizophrenia and individuals with frontal lobe lesions,[54,75,76] correlations with neuropsychological performance[56] and an association with negative symptoms, which in turn are linked with prefrontal dysfunction.[77] Scanpath abnormalities may represent an epiphenomenon of a more basic dysfunction in oculomotor control that is assessed by more established putative trait markers in individuals with schizophrenia. The possibility that the plethora of eye movement abnormalities arise from a common core deficit is worthy of further investigation. However, findings recently published by our group as conference abstracts suggest that scanpath and tracking deficits occur independently in patients with schizophrenia and nonclinical viewers.[70] This preliminary work has also found associations between scanpath measures and neuropsychologic performance in individuals with schizophrenia that were consistent with a role of DLPFC dysfunction in restricted scanning.[76] Previous studies have reported that although the DLPFC is implicated in smooth pursuit performance,[78–80] lesions in this area impair performance on saccadic tasks but do not disturb smooth pursuit performance.[81,82]

Methodologically, scanpaths confer a number of advantages over many alternative measures. Scanpath recording is inexpensive, objective and noninvasive and is not reliant on participants' compliance with complex task instructions. Scanpath abnormalities have been proposed as a putative marker for schizophrenia,[48,49,51,57,59,62,69] but whether scanpath deficits are a state- or trait-related phenomenon remains contentious. State markers of psychiatric disease are characteristics that appear and disappear with clinical episodes. Trait markers are phenomena that are present regardless of variation in clinical state.

Association of scanpath abnormalities with schizophrenia

Reliability and effect sizes

Scanpath abnormalities have been widely replicated in schizophrenia research, and results show high levels of consistency across studies, especially with regards to fixation number, saccade amplitude and scanpath length measures. Reports of null findings are infrequent. The robustness of the scanpath phenomenon is highlighted by the variations in task, stimuli and recording methods. Table 1 and Table 2 summarize published findings in individuals with schizophrenia and nonclinical comparison viewers.

We calculated effect sizes for all studies in Table 1 and Table 2 reporting group means and standard deviations for any of the fixation or saccade measures of interest (frequency and duration of fixations and saccades, amplitude of saccades and total scanpath length) for individuals with schizophrenia and nonclinical comparison groups. The 28 studies meeting these criteria and included in the effect size calculations are denoted by asterisks in Table 1. When data for more than 1 condition were reported, such as data for individual stimuli, schizophrenia subgroups or test sessions, individual effect sizes were calculated for each condition, resulting in 202 individual effect sizes. A summary of effect sizes for individual measures is presented in Table 3. Medium to large effect sizes were found for each of the 5 scanpath measures, with a mean Hedges' unbiased population estimate (g*) ranging from 0.98 (fixation frequency) to 0.64 (fixation duration). Standard deviations for the mean effect sizes suggest that a high variation across studies is also present. To date, studies of scanpath dysfunction in patients with schizophrenia have varied considerably in both task and stimulus conditions and methods of data analysis. Task selection can alter the cognitive and neural mechanisms implicated in viewing behaviour (e.g., free-viewing tasks compared with visual search), and it is vital to consider such issues during study design. Further sources of variation arise in the operationalization of dependent measures between studies. For example, some studies define scanpath length as the sum of the distance between successive fixations, whereas other studies measure the true path of the point of gaze. Methodologic variation may not only impact on the potential for generalization across studies but may constitute an important consideration in the accurate interpretation of viewing behaviours and perceptual experience. Stimulus size and interest need to be sufficient to elicit eye movements and visual exploration.[95] It is important to provide adequate reason to make fixations and saccades around the image to allow researchers to make inferences about cognitive processes involved during integration of perceptual information. If scanpath measures are to provide a potential target for trait marker research, it will be critical to consider standardization of practices. The magnitude of the preliminary effect sizes here support the potential value of scanpath measures as a discriminatory tool, and further analysis of the sources of variation across studies will help to build an optimized protocol for the identification of the scanpath deficit in future studies.

Sensitivity and specificity

Numerous trait markers may be associated with a given disorder. As each trait is hoped to reflect the actions of a more discrete genetic profile than the disease phenotype, each marker may represent only part of the risk for that disorder. It may be argued, therefore, that weak associations between disorder and marker should not automatically result in discounting of the candidate trait measure.[9] Nevertheless, attempts to use scanpath parameters to distinguish individuals with schizophrenia from other clinical samples have demonstrated promising levels of sensitivity and specificity, beyond those of more traditional candidate markers, such as smooth pursuit deficits.[5] Sensitivity denotes the proportion of individuals correctly identified as belonging to the affected group (true positives). Specificity refers to the proportion of individuals correctly identified as not belonging to the affected group (true negatives). Kojima and colleagues[49]

reported responsive search score (RSS; a measure of the spatial distribution of visual attention) to provide 71%–80% sensitivity and 80%–88% specificity in distinguishing individuals with schizophrenia from those with unipolar depression, epilepsy and amphetamine psychosis and nonclinical comparison groups. Matsushima and colleagues[85] found similar efficiency (76.7% sensitivity and 81.4% specificity) using discriminant analysis to separate outpatients with schizophrenia from individuals with depression, methamphetamine psychosis (MAP), anxiety disorders, temporal lobe epilepsy or frontal lobe lesions and healthy controls. Predictor variables in the discriminant function were RSS and fixation frequency. Applying this same discriminant function, Kojima and colleagues[45] found even higher levels of sensitivity (89.0%) and specificity (86.7%) in groups of individuals with schizophrenia and depression. Scanpaths may be a valuable addition to more traditional eye movement trait markers in discriminating between patients with

Table 1: Methods of studies examining scanpath behaviour in individuals with schizophrenia (part 1 of 2)

Study	Schizophrenia group, no. and type	Comparison group	Stimuli	Task†
Benson et al.[36]*	11 paranoid	22 healthy controls 6 cannabis-induced psychosis	Faces, landscapes, fractals	Free-viewing
Bestelmeyer et al.[37]*	22	37 healthy controls 19 bipolar disorder	Faces, fractals, landscapes, noise	Free-viewing
De Wilde et al.[60]*	50	36 healthy controls 23 siblings‡	Images from Thematic Apperception Test	Thematic Apperception Test
Gaebel et al.[83]	20	20 healthy controls	Drawings depicting proverbs	Free-viewing
Green et al.[39]*	24	26 healthy controls	Faces (context-free and context-embedded)	"Decide what the person is feeling or thinking"
Green et al.[38]*	11 deluded 8 nondeluded	22 healthy controls	Faces	"Think about how the person seems to be feeling"
Hori et al.[40]*	37	36 healthy controls	Rorschach stimuli	Eye movements recorded during free response period in Rorschach test
Kojima et al.[49]	105	50 healthy controls 30 unipolar depression 28 amphetamine psychosis 50 epilepsy	S-shaped figures	S-shaped figures procedure§
Kojima et al.[46]*	25	25 healthy controls 25 unipolar depression 10 obsessive–compulsive disorder	S-shaped figures	S-shaped figures procedure§
Kojima et al.[47]*	80	50 healthy controls 25 methamphetamine psychosis 21 temporal lobe epilepsy (L) 12 temporal lobe epilepsy (R)	S-shaped figures	S-shaped figures procedure§
Kojima et al.[45]*	145	124 healthy controls 116 depression	S-shaped figures	S-shaped figures procedure§
Kojima et al.[48]*	29	23 healthy controls	S-shaped figures	S-shaped figures procedure§
Kurachi et al.[94]	12	12 healthy controls	Picture completion test of the WAIS	WAIS picture completion test
Leonards et al.[61]	8 paranoid 1 disorganized 9 undifferentiated	28 healthy controls	Faces, fractals, landscapes	
Loughland et al.[51]*	65	61 healthy controls 52 affective disorder	Faces, degraded faces	(i) Face recognition (ii) Affect recognition
Loughland et al.[52]*	65	61 healthy controls	Faces	Affect recognition
Loughland et al.[62]*	63	61 healthy controls 37 first-degree relative‡	Faces, degraded faces	(i) Face recognition (ii) Affect recognition
Manor et al.[53]*	25	25 healthy controls	Neutral face, Rey Complex Figure	
Matsukawa et al.[63]	15	19 healthy controls 20 systemic lupus erythematosus	S-shaped figures	S-shaped figures procedure§
Matsushima et al.[54]*	20	20 healthy controls 18 frontal lobe lesion	S-shaped figure	S-shaped figures procedure§
Matsushima et al.[85]*	30	10 healthy controls 10 unipolar depression 10 methamphetamine psychosis 10 alcohol psychosis 10 anxiety disorder 10 temporal lobe epilepsy 10 frontal lobe lesion	S-shaped figures	S-shaped figures procedure§
Mikami et al.[55]*	30	30 healthy controls 48 methamphetamine psychosis	S-shaped figures	S-shaped figures procedure§
Minassian et al.[56]*	38	30 healthy controls	Rorschach stimuli	Viewing for subsequent Rorschach response period
Moriya et al.[64]	24	20 healthy controls	Human figures, S-shaped figures	Free-viewing

schizophrenia and healthy controls. Recent findings have shown that a multivariate eye movement phenotype combining scanpath with tracking and fixation stability measures may accurately distinguish cases from controls at a rate approaching 100%, far beyond the accuracy rate of any single traditional psychophysiologic or neuropsychologic measure.[71,72] This work is currently in preparation for publication by our research group.

Despite the practical significance of the current classification system of psychiatric diagnoses, it is widely acknowledged that these hypothetical categorizations are unlikely to reflect the natural boundaries of the disorders. One of the benefits of the endophenotype approach is that external markers may be used to validate and refine these boundaries. Trait markers may thus be shared across disorders, reflective of shared genetic pathways or common biological bases. Equally, however, it is important to develop markers with sufficient specificity to support genetic analysis for a

Table 1: Methods of studies examining scanpath behaviour in individuals with schizophrenia (part 2 of 2)

Study	Schizophrenia group, no. and type	Comparison group	Stimuli	Task†
Nishiura et al.[57]*	28 paranoid 16 nonparanoid	72 healthy controls	Faces with emotion-congruent sound, circles	Judge whether current picture differs from previous
Obayashi et al.[42]*	27	20 healthy controls	Geometric figures (from Benton Visual Retention Test)	Benton Visual Retention Test
Obayashi et al.[41]*	18 paranoid 7 disorganized 2 undifferentiated 1 catatonic	29 healthy controls	S-shaped figures	S-shaped figures procedure§ 2test sessions 6 months apart
Philips and David[86]	7 deluded 7 nondeluded	10 healthy controls	Single faces, face pairs	Face recognition
Phillips and David[50]	7 deluded 7 minimally deluded	10 healthy controls	Single faces, face pairs	Face recognition
Phillips and David[87]	8	9 healthy controls	Neutral faces, chimeric faces	
Phillips and David[88]	12 pers. delusions 10 nonpers. delusions	10 healthy controls	Scenes depicting neutral, ambiguous or threatening activity	
Phillips and David[89]				Neutral face: state whether face is pleasant Chimeric faces: determine facial expression
Philips and David[65]*	7 deluded 7 nondeluded	10 healthy controls	Single faces and face pairs (from Recognition Memory Test)	Recognition task
Philips and David[90]*	6 deluded 5 minimally deluded	9 healthy controls	Single faces and face pairs (from Recognition Memory Test)	Recognition task
Phillips et al.[91]	19 pers. delusions 8 nonpers. delusions	17 healthy controls	Scene showing neutral, ambiguous or threatening activities	
Phillips et al.[66]	19 pers. delusions 8 nonpers. delusions	18 healthy controls	Scene showing neutral, ambiguous or threatening activities	(i) Free-viewing (ii) Asked to attend to threatening areas
Quirk and Strauss[92]*	20	10 addiction recovery patients	Emotional images	Free-viewing
Rosse et al.[58]	16	38 cocaine users	Faces with direct and averted gaze	(i) Affect recognition (ii) Gaze direction discrimination
Ryu et al.[59]*	60	30 healthy controls	Circles, faces symbols, landscape	Varied by stimulus
Schwartz et al.[93]	16	10 healthy controls	Upright and inverted faces	Affect recognition
Streit et al.[94]	16	18 healthy controls	Faces	Affect recognition 2 test sessions 4 weeks apart
Takahashi et al.[43]	38	37 parents‡ 47 siblings‡	S-shaped figures	S-shaped figures procedure§
Takahashi et al.[44]*	23	43 healthy controls 23 siblings‡	S-shaped figures	S-shaped figures procedure§
Tsunoda et al.[74]	39¶		S-shaped figures	S-shaped figures procedure§
Tsunoda et al.[73]*	32	32 healthy controls	Benton Visual Retention Test	Viewing for stimulus reproduction
Williams et al.[68]*	63	60 healthy controls	Faces, degraded faces	Free-viewing for later recognition
Williams et al.[67]*	28	28 healthy controls	Faces	Viewing for subsequent affect recognition
Xia et al.[69]	14	41 healthy controls 23 parents‡	S-shaped figures	S-shaped figures procedure§

(L) = left-side spike focus; nonpers. = nonpersecutory; pers. = persecutory; (R) = right-side spike focus; WAIS = Weschler Adult Intelligence Scale.
*Study included in effect size calculations.
†In most of these studies, it is not clear whether participants were aware of affect recognition tasks, reproduction tasks, etc., before viewing or whether they completed a free-viewing task and were then informed of the additional task.
‡First-degree relatives, parents and siblings were all unaffected relatives of patients with schizophrenia.
§In these tasks, participants are shown an S-shaped figure (target figure) and asked to state whether the figure differs from a similar figure presented previously. The question "Are there any other differences?" is then repeated until the participant states that no further differences are present. Eye movements are recorded during each viewing period and during questioning.
¶Both schizophrenia and schizotypal disorder.

Table 2: Results of studies examining scanpath behaviour in individuals with schizophrenia (part 1 of 2)

Study	Variable of interest*					Region of interest
	No. of fixations	Mean duration of fixations	No. of saccades	Avg. saccade amplitude	Scanpath length	
Benson et al.[36]	SC < controls	SC > controls	SC < controls	SC = controls	NR	NR
Bestelmeyer et al.[37]	SC < controls	SC > controls	NR	SC < controls	NR	Atypical
De Wilde et al.[60]	SC = controls	SC = controls	NR	NR	SC < controls	Atypical for detailed cards
Gaebel et al.[83]	SC = controls	SC = controls	NR	NR	NR	NR
Green et al.[39]	Context-free: SC < controls (NS) Context-embedded: SC = controls	Context-free: SC = controls Context-embedded: SC > controls	Context-free: SC < controls Context-embedded: SC = controls	NR	NR	Atypical
Green et al.[38]	SC < controls	SC = controls	NR	SC = controls	Fixation: SC < controls (NS) Raw: SC = controls	% No. of fixations to features: SC = controls % Fixation duration to features: SC < controls
Hori et al.[40]	SC < controls	SC > controls	NR	SC < controls	SC < controls	Atypical
Kojima et al.[49]	NR	NR	NR	NR	NR	NR
Kojima et al.[46]	SC < controls	NR	NR	SC < controls	NR	NR
Kojima et al.[47]	SC < controls	NR	NR	Chronic SC < controls	NR	NR
Kojima et al.[45]	SC < controls	NR	NR	SC < controls	NR	NR
Kojima et al.[48]	NR	NR	NR	NR	NR	NR
Kurachi et al.[84]	1st 10 s: SC = controls 2nd 10 s: SC < controls	NR	NR	NR	1st 10 s: SC = controls 2nd 10 s: SC < controls	NR
Leonards et al.[61]	NR	SC > controls	SC < controls	SC < controls	NR	Atypical
Loughland et al.[51]	SC < controls	SC > controls	NR	SC < controls	Raw: SC < controls Fixation: SC < controls	Atypical
Loughland et al.[52]	NR	SC > controls	NR	SC < controls	Raw: SC < controls Fixation: SC < controls	Atypical for happy and neutral but not sad faces
Loughland et al.[62]	SC < controls	Face recognition: SC < controls Affect recognition: SC > controls	NR	SC < controls	Fixation: SC < controls Raw: SC < controls	Atypical
Manor et al.[53]	Face: SC < controls (NS) Rey: SC = controls	SC = controls	NR	NR	Face: SC < controls Rey: SC = controls	NR
Matsukawa et al.[63]	NR	NR	NR	NR	NR	NR
Matsushima et al.[54]	SC < controls	NR	NR	SC < controls	SC < controls	NR
Matsushima et al.[85]	NR	NR	NR	NR	NR	NR
Mikami et al.[55]	SC < controls	NR	NR	NR	SC < controls	NR
Minassian et al.[56]	NR	SC > controls	NR	SC = controls	SC < controls	NR

Table 2: Results of studies examining scanpath behaviour in individuals with schizophrenia (part 2 of 2)

Study	Variable of interest*					Region of interest
	No. of fixations	Mean duration of fixations	No. of saccades	Avg. saccade amplitude	Scanpath length	
Moriya et al.[64]	NR	NR	NR	NR	NR	Atypical
Nishiura et al.[57]	Smiling face: SC < controls Circles: SC < controls Crying face: SC = controls	NR	NR	NR	Smiling face: SC < controls Circles: SC < controls Crying face: SC = controls	NR
Obayashi et al.[42]	SC < controls	NR	NR	SC < controls	SC < controls	Atypical
Obayashi et al.[41]	SC < controls	NR	NR	T1: SC < controls	NR	NR
Philips and David[86]	Deluded SC < controls	NR	NR	NR	NR	Atypical for deluded SC but not nondeluded SC
Phillips and David[50]	SC < controls	NR	NR	NR	NR	Atypical
Phillips and David[87]	NR	NR	NR	NR	NR	Atypical
Phillips and David[88]	NR	NR	NR	NR	NR	Atypical
Phillips and David[89]	NR	NR	NR	NR	NR	Atypical
Philips and David[65]	Deluded SC < controls Nondeluded SC = controls	Deluded SC > controls Nondeluded SC = controls	NR	NR	NR	Atypical for deluded SC but not nondeluded SC
Philips and David[90]	SC = controls	SC = controls	NR	NR	NR	(T1) Single faces: atypical in deluded SC but not nondeluded SC Face pairs: atypical in deluded SC and nondeluded SC (T2) normal
Phillips et al.[66]	NR	NR	NR	NR	NR	Atypical in SC with persecutory delusions
Quirk and Strauss[92]	NR	SC > controls (NS)	NR	NR	SC = controls	Atypical for affective but not neutral images
Ryu et al.[59]	SC < controls	SC > controls	NR	SC < controls	SC < controls	Atypical
Schwartz et al.[93]	NR	NR	NR	NR	NR	NR
Streit et al.[94]	NR	SC < controls (NS)	NR	SC < controls	NR	Atypical
Takahashi et al.[44]	SC < controls	NR	NR	NR	NR	Atypical
Tsunoda et al.[73]	SC < controls	SC > controls	NR	SC < controls	NR	NR
Williams et al.[68]	SC < controls	SC > controls	NR	SC < controls	SC < controls	Faces: atypical Degraded: normal
Williams et al.[67]	SC < controls	SC = controls	NR	NR	SC < controls (risperidone-treated, but not haloperidol-treated, SC patients)	Atypical in haloperidol-treated SC patients, but not risperidone-treated SC patients (happy and neutral but not sad faces)
Xia et al.[69]	SC < controls	NR	NR	SC = controls	SC < controls	NR

Fixation = scanpath length as measured by total distance fixation points; NR = not reported; NS = nonsignificant trend; Raw = true scanpath length; Rey = Rey complex figure; SC = schizophrenia; T1 = first test session; T2 = second test session.
*Patterns of attentional assignment to regions of interest. Only results of comparisons with healthy, nonclinical and nonrelative groups are reported. Results do not differ between tasks or stimuli unless otherwise stated.

particular illness.[96] Atypical visual scanning in itself is not specific to the schizophrenia spectrum. Scanpath abnormalities have been demonstrated in individuals with other psychiatric disorders, including social phobia,[97,98] autism,[99–103] bipolar affective disorder,[37,52] attention-deficit/hyperactivity disorder (ADHD),[104] generalized anxiety disorder,[16] obsessive–compulsive disorder[46,105] and Alzheimer disease.[106] Importantly, these abnormalities differ from those found in individuals with schizophrenia, suggesting that scanpath dysfunction as seen in schizophrenia may have value as a disorder-specific marker.

Other psychotic disorders

Differential scanpath patterns in patients with other forms of psychosis suggest that restricted scanpath behaviour in those with schizophrenia is not simply the result of psychosis itself, nor does it inevitably lead to such symptoms. For example, patients with MAP show symptoms highly similar to those in patients with schizophrenia, including paranoid psychosis with persecutory delusions and hallucinations. Although patients with MAP and those with schizophrenia do not differ in terms of fixation frequency or scanpath length, the spatial distribution of attention is substantially less impaired in those with MAP. Similarly, individuals with systemic lupus erythematosus, manifestations of which include schizophreniform psychosis, show more widespread dispersion of fixations than patients with schizophrenia,[63] and patients with cannabis-induced psychosis reveal fixation clustering and restricted scanning that is more pronounced than that associated with schizophrenia.[36] Investigation of saccade and smooth pursuit performance in chronic ketamine use, which is associated with psychotic symptoms and cognitive deficits similar to those of schizophrenia-spectrum disorders, has also suggested that ketamine administration is not a suitable model for oculomotor deficits in individuals with schizophrenia.[107]

Developmental disorders

Autism is linked with an erratic, disorganized pattern of visual exploration.[102] As in schizophrenia, individuals with autism demonstrate impairments in face processing and social functioning. Some similarities in scanning styles have been found between schizophrenia and autism groups. During face viewing, both individuals with schizophrenia and those with autism assign less attention to the eyes and attend more to the mouth and nonface areas than do healthy groups[68,94,99,101,102,108,109] (although a different study found no difference between autism and control groups in the proportion of time spent viewing the mouth and eye regions[103]). Also mirroring viewing patterns in individuals with schizophrenia, adolescents and young adults with autism have demonstrated diminished visual attention to social contextual information when judging mental state.[39,100] Despite these similarities in scanning styles, individuals with autism do not show the deviant temporal parameters that are characteristic of scanning behaviours in patients with schizophrenia.[102,110]

Reduced attention to salient scene regions in individuals with schizophrenia is also more extreme than that recorded in people with ADHD.[104] Attention-deficit/hyperactivity disorder has been linked with a more extensive visual scanning style, characterized by increased scanpath lengths compared with healthy groups.[111] Therefore, patients with schizophrenia and those with ADHD may show distinguishable scanpath behaviours despite the presence of social functioning and attention deficits in both groups.

Affective disorders

Bipolar affective disorder (BPAD) almost certainly shares a common genetic basis with schizophrenia spectrum disorders.[2,112,113] Individuals with BPAD produce exploratory eye movements similar to those of patients with schizophrenia, but BPAD is nevertheless distinguishable as an illness using certain measures. Loughland and colleagues[52] investigated scanpath formation during face viewing in individuals with bipolar and unipolar depression. Whereas individuals with schizophrenia had scanning behaviour that was atypical in both spatial and temporal domains, patients with affective disorders differed from controls in reduced attention to facial features.[52] A second study involving patients with bipolar disorder found this group to occupy an intermediate position between healthy observers and viewers with schizophrenia with regards to a range of temporal scanpath variables during free-viewing.[37] This second study found that spatial distribution of fixations differed significantly between patients with bipolar disorder and healthy controls for fractals, noise patterns, landscapes and faces. Compared with healthy viewers, individuals with unipolar depression demonstrate diminished fixation frequency and decreased cognitive search scores (an index of attention to predetermined regions of interest during a figure comparison task). However, in contrast with the scanning behaviours of patients with schizophrenia, unipolar depression is also associated with normal saccade amplitude and RSS (an index of the overall fixation dispersion).[45,46]

Anxiety disorders

Patients with generalized anxiety disorder fixate a similar number of image regions as controls during scene viewing.[16] This viewing pattern contrasts that in patients with schizophrenia, who allocate attention to a restricted spatial area. Individuals with generalized social phobia demonstrate a form of hyperscanning to faces, characterized by increased scanpath length compared with healthy viewers.[97,98] Responsive search scores (indexing attentional distribution during a figure comparison task) and fixation frequency are also reported to be lower in individuals with schizophrenia than in patients with obsessive–compulsive disorder.[46]

Alzheimer dementia

Individuals with Alzheimer dementia have been reported to show increased fixation duration and smaller saccade amplitude and decreased attention to salient regions during clock reading compared with controls.[106] However, data directly comparing scanpath behaviours of schizophrenia groups and individuals with Alzheimer disease or other forms of dementia are not yet available.

Stability and relation with clinical state

Association with clinical symptoms

In an early study, Gaebel and colleagues[83] found that restricted scanning behaviour was related to negative symptoms in schizophrenia, whereas positive symptoms were linked with extensive scanning styles (or hyperscanning). Although not unequivocal, more recent studies have reported that scanpath variables correlate with measures of negative clinical symptoms. Two studies have reported significant correlations with the Positive and Negative Syndrome Scale (PANSS)[114] negative symptom subscore with small-to-medium effect sizes for fixation frequency (R^2 = 0.22 and 0.08) and duration (R^2 = 0.14 and 0.11), saccade amplitude (R^2 = 0.17 and 0.16) and scanpath length (R^2 = 0.21).[59,73] Although effects of larger magnitude (R^2 for significant correlations ranging from 0.20 to 0.32) were found for fixation frequency and scanpath length in a third study, patterns were not consistent across stimuli.[57] One report found no correlation of scanpath measures with PANSS scores, with the exception of a small correlation with scanpath length (R^2 = 0.09).[52] Studies using individual Scale for the Assessment of Negative Symptoms (SANS[115]) subscales have found that restricted scanning can be associated with dimensions of avolition/apathy[46,56,73] and affective flattening or blunting.[46,73,94] Restricted scanning is less often associated with alogia and anhedonia subscales.[56] There have also been reports of associations between restricted scanning and Brief Psychiatric Rating Scale (BPRS[116]) subscales of blunted affect,[40,46,48,54] motor retardation,[40] emotional withdrawal[46,48,54] and unusual thought content.[40] However, null findings have also been reported in each instance.[40,48] No single eye movement measure or clinical state measure has consistently linked scanpath dysfunction with negative symptoms. Other studies have found no relation between scanpath measures and negative symptoms.[53,67,90] Meta-analysis is also problematic since most of these studies only report effect sizes for significant correlations.

The exception to these inconsistent findings is the association of negative symptoms with RSS, which indexes the distribution of visual attention during a visual comparison task. The RSS has been repeatedly linked with measures of blunted affect and emotional withdrawal with moderate effect sizes (blunted affect: mean R^2 = 0.30; emotional withdrawal: mean R^2 = 0.28).[46–48,54] In studies using RSS, the viewer is presented with a simple geometric shape and asked to describe in what way the figure differs from a similar stimulus presented previously. After the viewer's response, the experimenter asks whether there are any further differences, and RSS is measured during the viewer's response period at this stage. Given that the viewer has already answered the initial question, the degree of visual exploration during the RSS period is likely to reflect an interpersonal component and an ability to engage in conscious, internally motivated visual exploration that is not required under the free-viewing conditions of many other studies.

Table 3: Scanpath measures in individuals with schizophrenia compared with nonclinical groups across 28 studies

Measure	Hedges' g*	SD	95% CI	No.†
Fixation frequency	0.98	0.54	0.85–1.11	68
Fixation duration	0.64	0.52	0.48–0.80	40
Saccade frequency	0.73	0.41	0.26–1.19	3
Saccade amplitude	0.74	0.51	0.56–0.92	30
Scanpath length	0.77	0.48	0.65–0.89	61
Overall	0.81	0.53	0.74–0.88	202

CI = confidence interval; SD = standard deviation.
*Studies included in the calculation of effect sizes are marked with an asterisk in Table 1.
†Number of comparisons for which effect sizes were calculated. When data were available for more than 1 condition within a study (e.g., for individual stimuli, schizophrenia subgroups or test sessions), effect sizes were calculated independently for each condition.

In contrast to the suggestion by Gaebel and colleagues[83] that positive symptoms are associated with an extensive scanning style, findings suggest that scanpath dysfunction occurs relatively independently of positive symptomatology. Studies have found no evidence of association between scanpath measures and positive symptom scores, either with regard to PANSS subscales,[52,59,73] individual BPRS items[40,46,48] or BPRS composite scores for positive symptom items.[40,94] Only one study since that of Gaebel and colleagues has reported significant correlations between extensive hyperscanning and positive symptom scores.[48] Positive associations linking fixation frequency with somatic concern (R^2 = 0.16) and excitement (R^2 = 0.22) on the BPRS have not been replicated. In a second study, a negative correlation between PANSS positive symptom scores and scanpath length linking increased positive symptoms with more restricted scanning also revealed only a small effect (R^2 = 0.09) and was seen for only 1 of 3 stimuli. Similarly, a finding of more restricted distribution of visual attention in a final study was seen for only 1 of 4 stimuli. Such findings suggest that scanpath dysfunction is not associated with positive symptomatology. Additional reports have failed to find evidence of extensive scanning in patients with schizophrenia[46] or have linked groups with predominantly positive symptoms with a range of viewing styles from restricted to extensive scanning behaviours.[61] One possibility is that that restricted scanning is more specifically linked with delusional symptoms,[38] at least with respect to face viewing, although scanpaths still remain atypical in patients with only minimal delusional symptoms.

Investigations of associations between scanpath anomalies and symptom clusters identified by factor analytic methods have found the candidate marker to be relatively independent of symptom profiles. Williams and colleagues[68] examined associations of scanpath behaviours with symptoms of psychomotor poverty, assessing blunted affect, social withdrawal and poor rapport, disorganization, tapping positive and negative aspects of thought disorder and reality distortion, which denotes delusions and grandeur.[117] Williams and colleagues[68] suggested that scanpath behaviour showed only minimal associations with symptom factors and that most patients may be characterized by restricted scanning styles. Only subtle associations between symptom dimensions and scanpath variables were found in other studies by the same group.[51,52]

Association with particular symptoms does not constitute a shortcoming in the use of scanpaths as a trait marker. In fact,

links between symptom dimensions and particular scanpath styles may suggest possible lines for investigation in attempting to partition schizophrenia into natural subtypes. However, the question of whether scanpath abnormalities remain constant during changes in symptom severity is central to ascertaining whether eye movement measures comprise state or trait markers. Three studies have asserted that scanpath idiosyncrasies do not remain stable over time. Phillips and David[50,90] reported that viewing abnormalities diminished with improvements in delusional symptoms. Individuals with schizophrenia have been found to be significantly more impaired in visual exploration during inpatient treatment periods than during outpatient treatment in cross-sectional research.[59] Importantly, neither of these studies demonstrated a complete recovery of "normal" scanning behaviour in remitted groups. Therefore, whereas changes in symptom severity may generate some fluctuation in scanpaths, it appears that at least some degree of scanpath deficit remains, regardless of clinical state.

Eye movements generally show no association with global symptom ratings in individuals with schizophrenia in correlational analyses.[45,55,56,67,83] Moreover, other studies have revealed stability of scanpath abnormalities, regardless of symptom changes. Streit and colleagues[94] found that idiosyncrasies of scanpath length, fixation duration and feature selection in patients with schizophrenia persisted across testing sessions 4 weeks apart, regardless of a decline in symptom severity. Positive, but not negative, symptoms declined between testing sessions, supporting a lack of association between restricted scanning and positive symptoms. In another study, patients demonstrated relatively stable eye movement behaviours over an 8-month period despite partial remission of both positive and negative symptoms.[41] In contrast, patients in this study who showed no reduction in symptoms across the course of the research demonstrated a reduction in saccade amplitude between testing sessions.[41] The authors argued that exploratory eye movements are influenced by both trait and mental state factors. That eye movement idiosyncrasies do not improve with reductions in symptoms may support the use of scanpath parameters as a vulnerability marker, whereas saccade amplitude may model illness chronicity in patients with schizophrenia.

Association with other clinical features

Although Obayashi and colleagues[41] suggested that saccade amplitude may model chronicity in patients with schizophrenia, other reports of the relation between scanpath patterns and illness duration are inconsistent. Evidence for a lack of association of scanpath variables with illness duration has been documented,[42,45,54,58] although Manor and colleagues[53] found illness duration to correlate with scanpath length. Williams and colleagues[68] reported significant correlations between illness duration and scanpath variables in patients with schizophrenia, with longer duration associated with diminished scanning, although patterns of association were inconsistent across stimuli. Those few studies assessing other clinical characteristics in relation to scanning have found no association between scanpath variables and number of clinical episodes,[45] duration of current stay in hospital[45] or total number of hospital admissions.[56]

A further question is whether atypical scanning is a consequence of pharmacologic treatment. Evidence of a subtle relation between neuroleptic dose and restricted scanpath behaviour in patients with schizophrenia has been reported in 2 studies. Williams and colleagues[68] found chlorpromazine equivalent dosage to correlate with fixation frequency, but not with fixation duration, distance between fixations or overall scanpath length. Hori and colleagues[40] found a negative correlation between fixation frequency and neuroleptic daily dose, although this relation became nonsignificant when they controlled for negative symptom ratings in the analysis.

In contrast, numerous studies have found no significant associations between scanpath variables and neuroleptic dosage in patients with schizophrenia.[38,42,45,46,51,53,54,56,58,59,73,74,90] Although many of these reports are based on post hoc analyses, the findings are supported by comparisons of neuroleptic-naïve patients with patients receiving regular neuroleptic treatment in both cross-sectional and longitudinal study designs. In 2 studies, the scanpaths of individuals with schizophrenia receiving neuroleptics did not differ from those of never-medicated patients (cross sectional design,[48] longitudinal design[41,48]). Other researchers have found no influence of medication type (typical v. atypical neuroleptics[51,62]) or duration[74] on scanpath variables. Evidence that antipsychotic medications may reduce abnormalities in viewing behaviour also suggests that restricted scanning is not a consequence of neuroleptic treatment.[60,89] In some instances, correlations between neuroleptics and eye movements may be due to higher neuroleptic doses being associated with more pronounced positive symptoms (and thus a tendency toward a more extensive scanning style).[83]

Few studies have directly assessed the effects of specific neuroleptic medications on scanpath behaviours in patients with schizophrenia. A study examining face viewing in outpatients with schizophrenia receiving either risperidone or haloperidol found that the 2 treatment groups did not differ on fixation frequency, overall fixation duration or scanpath length.[67] However, patients treated with haloperidol showed reduced attention to facial features compared with healthy viewers. The authors argued that the spatial distribution of attention may be subject to medication effects, whereas temporal variables are not.

Genetic control

Compared with other putative candidate trait markers currently under investigation, few studies have examined scanpath anomalies in relatives of schizophrenia probands. Even fewer studies have looked at genetic linkage. However, evidence of linkage of exploratory eye movement behaviours (specifically number of fixations) to chromosome 22q11.2-q12.1 has been reported.[43] Chromosome 22q is associated with several candidate genes for schizophrenia, and microdeletions in this region have been linked with increased risk for the disease. Further, characteristics of restricted scanpath behaviours

have been demonstrated in healthy relatives of individuals with schizophrenia. Such findings support the use of scanpath measures as a marker of genetic liability for schizophrenia.[62] Parents of schizophrenia probands have been found to demonstrate reductions in fixation frequency, scanpath length and indices of the distribution of visual attention compared with nonrelative groups, suggesting that viewing behaviours may be at least partly under genetic control.[69] Loughland and colleagues[62] examined face-viewing patterns in patients, healthy first-degree relatives of patients with schizophrenia and unrelated controls. Relatives' viewing behaviour was unusual, with temporal measures of fixation patterns falling between those of controls and the atypical patterns seen in probands. Relatives also showed an atypical distribution of fixations to face stimuli that was even more extreme than that observed in the schizophrenia group. Similarly, healthy siblings of schizophrenia probands have been found to occupy an intermediate position between patients with schizophrenia and healthy controls with regards to fixation frequency and spatial dispersion of fixations.[44]

Findings to the contrary have been reported in a study by de Wilde and colleagues.[60] They found that healthy siblings of individuals with schizophrenia did not differ from age-matched controls on several scanpath measures, including scanpath length, fixation number and fixation duration, during viewing of complex scenes. Shorter scanpath length was found in patients with schizophrenia but not siblings, and the authors suggested that scanpath length is not a suitable candidate for a vulnerability marker of schizophrenia. Previous reports of scanpath abnormalities in healthy sibling groups were argued to be attributable to a failure of previous studies to match sibling and nonsibling groups on age. Also of note, however, is that the study by de Wilde and colleagues[60] failed to find the prominent scanpath abnormalities in their group of schizophrenia patients that may be expected on the basis of numerous previous studies. Specifically, patients did not differ from healthy controls with regards to frequency of fixations or average duration of fixation. Sampling biases or insensitivity of this particular protocol in identifying restricted scanning behaviours may explain these differences between studies. Another possibility is that scanpath behaviours in relatives of patients with schizophrenia may be highly heterogeneous.

Summary and future directions

At this early stage in research, measures of visual scanpath formation appear to constitute an appealing opportunity for trait marker investigation in individuals with schizophrenia. Although the findings are still far from clear, scanpaths are beginning to show promise as a candidate trait marker, at least in those areas studied to date.

Atypical scanning behaviours are a widely replicated and apparently robust finding in individuals with schizophrenia and are not specific to face stimuli. Scanpath measures show exciting levels of sensitivity and specificity in distinguishing case from control groups and may address the problem of poor diagnostic specificity posed by other candidate trait markers. In parallel with this, current findings on scanpaths in individuals with BPAD suggest that these measures may also include sufficient information to illuminate overlap in genetic vulnerability or clinical features between related disorders.

There is some suggestion that restricted scanning may be linked with the negative symptoms of schizophrenia, or alternatively with delusional symptoms, at least with regard to face viewing. This may point to the possibility of scanpaths as a specific marker for particular symptomatologies that may help to stratify subtypes or indicate state. Some studies have reported state-related changes in scanpath behaviour in patients with schizophrenia. However, there is evidence that viewing behaviours still remain atypical to some extent despite symptom remission, supporting the argument that scanpath deficits are likely to be a constant feature in these individuals.

Genetic control of scanpath abnormalities is supported by initial findings of linkage analysis and relative studies.

Additional research is clearly merited to further define the state and trait characteristics of atypical scanning in individuals with schizophrenia, particularly with regard to the heritability and genetic control of the deficit.

The present review has not discussed cosegregation of scanpath abnormalities in the families of patients with schizophrenia, as studies in this area have not yet been reported. Studies of scanpath behaviours in relatives of individuals with schizophrenia are not entirely unequivocal. Substantive investigation of familial patterns of scanpath abnormalities will be necessary before such measures may be defined as trait markers.

Standardization in scanpath methodology across studies is required. Although scanpath deficits appear reasonably robust to detect differences in task and stimuli between research groups, variance in the selection and definition of dependent measures to date create difficulties in comparability between studies. Such investigation should also provide further information on the psychometric properties of scanpath dysfunction such as test–retest statistics, which are not yet available, and separate meta-analyses will be useful in delineating the impact in sources of variation in methodology across studies.

Arguably, the most useful biological markers should be well understood mechanisms that will augment understanding of the disease.[10] However, little is understood about the underlying etiology of atypical scanning in individuals with schizophrenia at present. Patterns of visual exploration may reflect a more complex interplay of neurobiologic mechanisms and cognitive functions compared with the more discrete mechanisms tapped by tasks such as smooth pursuit tracking or inhibition of the P50 auditory evoked response.[96] That is not to say, however, that the impaired mechanism reflected by the restricted scanning phenomenon must also be affected by such variables. It may be that restricted scanning represents an anomaly in a low-level oculomotor or visuocognitive mechanism. A number of lines of inquiry have pointed to a role of the frontal lobes, and scanpath abnormalities appear to comprise a generalized deficit in visual behaviour. Additional impacts of cognitive and emotional deficits on scanpath behaviours have also been demonstrated in face viewing studies. Further exploration of the

underlying neuropathologic and cognitive etiologies of scanpath abnormalities will clarify how scanpath abnormalities can further inform our understanding of schizophrenia. Although it could be suggested that scanpath deficits reflect prefrontal control mechanisms that are common to other psychiatric disorders, the relative specificity of restricted scanning styles to schizophrenia suggests that this is not the case. Clearly, further consideration of the cognitive and neurologic pathologies underlying the scanpath deficit is essential to build a biological explanation of the specific physiologic mechanisms assessed here. Deficits in the processing of real-world visual information, as measured by the scanpath paradigm, may be highly informative with regard to cognitive or neurologic function and subjective experience in individuals with schizophrenia. Indeed, this phenomenon appears to merit further consideration in its own right, besides any potential role in genetics or novel intervention studies.

Understanding potential association with specific genes will require further linkage studies or candidate gene designs. More work is required in relatives of individuals with schizophrenia. Furthermore, understanding whether those deficits tapped by scanpath methodologies represent a causal link between genetics and diagnosable pathology is likely to require longitudinal work and intervention studies.

Limitations

This review is unable to give a definitive answer as to which tasks (e.g., feature search, free viewing) or stimuli are the most appropriate for measuring scanpath dysfunction in individuals with schizophrenia or whether it matters. Mitigating cognitive and unknown perceptual disturbances may yet influence conformation. Until further work is done with families of schizophrenia probands, it is difficult to assess how similar unaffected family members' scanpaths are to those of patients. Whereas there is evidence to suggest that simple spatiotemporal measures of scanpaths during viewing capture some sense of the abnormality, it is not yet clear whether one of these measures, a combination of these measures or alternative higher order statistics will be best suited to discriminate between the scanpaths of individuals with schizophrenia and those of individuals with other illnesses and nonclinical comparison groups. Nevertheless, scanpaths are unarguably affected in individuals with schizophrenia.

Conclusion

Although a number of questions are still to be addressed, eye movements during scene inspection are emerging as a powerful and informative discriminatory tool in the study of schizophrenia. Some studies have reported state-related fluctuation in the degree of scanpath dysfunction present in individuals with schizophrenia. However, evidence of the deficit in healthy relatives of individuals with schizophrenia and findings that some degree of dysfunction remains regardless of symptom remission also suggest that restricted scanning may pre-empt the clinical manifestation of the disease. Scanpath dysfunction does not appear to be a consequence of neuroleptic medication. It is possible that scanpath dysfunction may represent a stable, heritable trait marker of disease vulnerability, which is exaggerated with deterioration in clinical state. Further, evidence for a strong association with schizophrenia and high levels of sensitivity and specificity warrants further investigation of scanpath behaviours as a trait marker for schizophrenia and suggests that such measures may constitute a promising avenue of research to understand the pathophysiology of the disease. At the least, scanpaths may address the limited specificity of other more traditional biomarker targets and serve as an invaluable addition to alternative measures, such as smooth pursuit eye movements or sensory gating indices, to substantially improve the diagnostic specificity of psychophysiologic assessment in trait marker research.

Acknowledgements: This review is partly based on a doctoral dissertation completed by Dr. Beedie under the supervision of Dr. Benson and Professor St. Clair. During the preparation of this manuscript, salary support for Dr. Beedie was provided by the Chief Scientist Office (CZB-4-734, awarded to Dr. Benson) and previously by the European Commission (SGENE, awarded to Professor St. Clair).

Competing interests: As above.

Contributors: Drs. Beedie and Benson acquired the data and wrote the article. All authors designed the review, analyzed the data, reviewed the article and approved its publication.

References

1. Williams HJ, Owen MJ, O'Donovan MC. New findings from genetic association studies of schizophrenia. *J Hum Genet* 2009;54:9-14.
2. Lichtenstein P, Yip B, Björk C, et al. Common genetic determinants of schizophrenia and bipolar disorder in Swedish families: a population-based study. *Lancet* 2009;373:234-9.
3. Gottesman II, Gould TD. The endophenotype concept in psychiatry: etymology and strategic intentions. *Am J Psychiatry* 2003;160:636-45.
4. Clementz BA, Grove WM, Iacono WG, et al. Smooth-pursuit eye movement dysfunction and liability for schizophrenia: implications for genetic modeling. *J Abnorm Psychol* 1992;101:117-29.
5. Calkins ME, Iacono WG, Ones DS. Eye movement dysfunction in first-degree relatives of patients with schizophrenia: a meta-analytic evaluation of candidate endophenotypes. *Brain Cogn* 2008;68:436-61.
6. Cadenhead KS, Braff DL. Endophenotyping schizotypy: a prelude to genetic studies within the schizophrenia spectrum. *Schizophr Res* 2002;54:47-57.
7. Ritsner M, Gottesman I. Where do we stand in the quest for neuropsychiatric biomarkers and endophenotypes and what next? In: Ritsner M, editor. *The handbook of neuropsychiatric biomarkers, endophenotypes and genes: neuropsychological endophenotypes and biomarkers*. New York (NY): Springer; 2009. p. 3-21.
8. Walters JT, Owen MJ. Endophenotypes in psychiatric genetics. *Mol Psychiatry* 2007;12:886-90.
9. Cannon TD, Keller MC. Endophenotypes in the genetic analyses of mental disorders. *Annu Rev Clin Psychol* 2006;2:267-90.
10. Turetsky BI, Calkins ME, Light GA, et al. Neurophysiological endophenotypes of schizophrenia: the viability of selected candidate measures. *Schizophr Bull* 2007;33:69-94.
11. Javitt DC, Spencer KM, Thaker GK, et al. Neurophysiological biomarkers for drug development in schizophrenia. *Nat Rev Drug Discov* 2008;7:68-83.
12. Calkins ME, Iacono WG. Eye movement dysfunction in schizophrenia: a heritable characteristic for enhancing phenotype definition. *Am J Med Genet* 2000;97:72-6.
13. Blackwood DH, St Clair DM, Muir WJ, et al. Auditory P300 and eye tracking dysfunction in schizophrenic pedigrees. *Arch Gen Psychiatry* 1991;48:899-909.

14. Myles-Worsley M, Ord L, Blailes F, et al. P50 sensory gating in adolescents from a pacific island isolate with elevated risk for schizophrenia. *Biol Psychiatry* 2004;55:663-7.
15. Clementz BA, McDowell JE, Zisook S. Saccadic system functioning among schizophrenia patients and their first-degree relatives. *J Abnorm Psychol* 1994;103:277-87.
16. Freeman D, Garety P, Phillips M. An examination of hypervigilance for external threat in individuals with generalized anxiety disorder and individuals with persecutory delusions using visual scan paths. *Q J Exp Psychol A* 2000;53:549-67.
17. Mogg K, Bradley BP, Field M, et al. Eye movements to smoking-related pictures in smokers: relationship between attentional biases and implicit and explicit measures of stimulus valence. *Addiction* 2003;98:825-36.
18. Noton D, Stark I. Eye movements and visual perception. *Sci Am* 1971;224:35-43.
19. Posner MI. Orienting of attention. *Q J Exp Psychol* 1980;32:3-25.
20. Corbetta M, Akbudak E, Conturo T, et al. A common network of functional areasfor attention and eye movements. *Neuron* 1998;21:761-73.
21. Findlay JM, Walker R. A model of saccade generation based on parallel processing and competitive inhibition. *Behav Brain Sci* 1999;22:661-721.
22. Antes JR. The time course of picture viewing. *J Exp Psychol* 1974; 103:62-70.
23. Henderson JM, Hollingworth A. High-level scene perception. *Annu Rev Psychol* 1999;50:243-71.
24. Henderson JM. Human gaze control during real-world scene perception. *Trends Cogn Sci* 2003;7:498-501.
25. Just MA, Carpenter PA. Eye fixations and cognitive processes. *Cognit Psychol* 1976;8:441-80.
26. Krieger G, Rentschler I, Hauske G, et al. Object and scene analysis by saccadic eye movements: an investigation with higher-order statistics. *Spat Vis* 2000;13:201-14.
27. Lofthus G, Macworth N. Cognitive determinants of fixation location during picture viewing. *J Exp Psychol Hum Percept Perform* 1978;4: 565-72.
28. Molnar F. About the role of visual exploration in aesthetics. In: Day HI, editor. *Advances in intrinsic motivation and aesthetics*. New York (NY): Plenum Press; 1981
29. Rayner K. Eye movements in reading and visual information processing; 20 years of research. *Psychol Bull* 1998;124:372-422.
30. Yarbus A. *Eye movements and vision*. New York (NY): Plenum Press; 1967.
31. Gaymard B, Ploner C, Rivaud-Pechoux S, et al. The frontal eye field is involved in spatial short-term memory but not in reflexive saccade inhibition. *Exp Brain Res* 1999;129:288-301.
32. Fukushima K. Frontal cortical control of smooth-pursuit. *Curr Opin Neurobiol* 2003;13:647-54.
33. Burman DD, Segraves MA. Primate frontal eye field activity during natural scanning eye movements. *J Neurophysiol* 1994;71:1266-71.
34. Schmidt D, Krause B, Wiss P, et al. Visuospatial working memory and changes of the point of view in 3D space. *Neuroimage* 2007;36: 955-68.
35. Müri RM, Nyffeler T. Neurophysiology and neuroanatomy of reflexive and volitional saccades as revealed by lesion studies with neurological patients and transcranial magnetic stimulation (TMS). *Brain Cogn* 2008;68:284-92.
36. Benson PJ, Leonards U, Lothian RM, et al. Visual scanpaths in first-episode schizophrenia and cannabis-induced psychosis. *J Psychiatry Neurosci* 2007;32:267-74.
37. Bestelmeyer PE, Tatler BW, Phillips LH, et al. Global visual scanning abnormalities in schizophrenia and bipolar disorder. *Schizophr Res* 2006;87:212-22.
38. Green MJ, Williams LM, Davidson D. Visual scanpaths to threat-related faces in deluded schizophrenia. *Psychiatry Res* 2003;119:271-85.
39. Green MJ, Waldron JH, Simpson I, et al. Visual processing of social context during mental state perception in schizophrenia. *J Psychiatry Neurosci* 2008;33:34-42.
40. Hori Y, Fukuzako H, Sugimoto Y, et al. Eye movements during the Rorschach test in schizophrenia. *Psychiatry Clin Neurosci* 2002;56:409-18.
41. Obayashi S, Matsushima E, Okubo Y, et al. Relationship between exploratory eye movements and clinical course in schizophrenic patients. *Eur Arch Psychiatry Clin Neurosci* 2001;251:211-6.
42. Obayashi S, Matsushima E, Ando H, et al. Exploratory eye movements during the Benton Visual Retention Test: characteristics of visual behaviour in schizophrenia. *Psychiatry Clin Neurosci* 2003;57:409-15.
43. Takahashi S, Ohtsuki T, Yu S, et al. Significant linkage to chromosome 22q for exploratory eye movement dysfunction in schizophrenia. *Am J Med Genet B Neuropsychiatr Genet* 2003;123B:27-32.
44. Takahashi S, Tanabe E, Yara K, et al. Impairment of exploratory eye movement in schizophrenia patients and their siblings. *Psychiatry Clin Neurosci* 2008;62:487-93.
45. Kojima T, Matsushima E, Ohta K, et al. Stability of exploratory eye movements as a marker of schizophrenia — a WHO multi-center study. *Schizophr Res* 2001;52:203-13.
46. Kojima T, Matsushima E, Ando K, et al. Exploratory eye movements and neuropsychological tests in schizophrenic patients. *Schizophr Bull* 1992;18:85-94.
47. Kojima T, Matsushima E, Nakajima K, et al. Eye movements in acute, chronic, and remitted schizophrenics. *Biol Psychiatry* 1990; 27:975-89.
48. Kojima T, Potkin S, Kharazmi M, et al. Limited eye movement patterns in chronic schizophrenic patients. *Psychiatry Res* 1989;28:307-14.
49. Kojima T, Ando K, Ando H, et al. Eye movements as a marker of schizophrenia. *Schizophr Res* 1988;1:178-9.
50. Phillips M, David A. Understanding delusions in schizophrenia using visual scan paths. *Biol Psychiatry* 1996;39:549-50.
51. Loughland CM, Williams LM, Gordon E. Schizophrenia and affective disorder show different visual scanning behaviour for faces: A trait versus state-based distinction? *Biol Psychiatry* 2002;52:338-48.
52. Loughland CM, Williams LM, Gordon E. Visual scanpaths to positive and negative facial emotions in an outpatient schizophrenia sample. *Schizophr Res* 2002;55:159-70.
53. Manor BR, Gordon E, Williams LM, et al. Eye movements reflect impaired face processing in patients with schizophrenia. *Biol Psychiatry* 1999;46:963-9.
54. Matsushima E, Kojima T, Ohbayashi S, et al. Exploratory eye movements in schizophrenic patients and patients with frontal lobe lesions. *Eur Arch Psychiatry Clin Neurosci* 1992;241:210-4.
55. Mikami T, Naruse N, Fukura Y, et al. Determining vulerability to schizophrenia in methamphetamine psychosis using exploratory eye movements. *Psychiatry Clin Neurosci* 2003;57:433-40.
56. Minassian A, Granholm E, Verney S, et al. Visual scanning deficits in schizophrenia and their relationship to executive functioning impairment. *Schizophr Res* 2005;74:69-79.
57. Nishiura S, Morita K, Kurarkake K, et al. Characteristics of left and right scanning in schizophrenia patients using exploratory eye movements: comparison with healthy subjects. *Psychiatry Clin Neurosci* 2007;61:487-94.
58. Rosse RB, Schwartz BL, Johri S, et al. Visual scanning of faces correlates with schizophrenia symptomatology. *Prog Neuropsychopharmacol Biol Psychiatry* 1998;22:971-9.
59. Ryu H, Morita K, Shoji Y, et al. Abnormal exploratory eye movements in schizophrenic patients vs healthy controls. *Acta Neurol Scand* 2001;104:369-76.
60. de Wilde O, Bour L, Dingemans P, et al. Visual scan paths in young patients with schizophrenia, healthy siblings and controls. *Schizophr Res* 2007;89:362-3.
61. Leonards U, Duhoux S, Rey-Bellet P, et al. Do disturbances in social interaction influence visual scene exploration in psychotic patients? [abstract] *Perception* 2002;31(Suppl);182.
62. Loughland CM, Williams LM, Harris AW. Visual scanpath dysfunction in first-degree relatives of schizophrenia probands: Evidence for a vulnerability marker? *Schizophr Res* 2004;67:11-21.
63. Matsukawa Y, Takahashi S, Aoki M, et al. Patients with systemic lupus erythematosus show a normal responsive search score in exploratory eye movement analysis: comparison with schizophrenia. *Ann Rheum Dis* 2002;61:748-50.
64. Moriya H, Anod K, Kojima T, et al. Eye movements during perception of pictures in chronic schizophrenia. *Psychiatry Clin Neurosci* 1972;26:189-99.
65. Phillips ML, David AS. Visual scan paths are abnormal in deluded schizophrenics. *Neuropsychologia* 1997;35:99-105.
66. Phillips ML, Senior C, David AS. Perception of threat in schizophrenics with persecutory delusions: an investigation using visual scan paths. *Psychol Med* 2000;30:157-67.
67. Williams LM, Loughland CM, Green MJ, et al. Emotion perception in schizophrenia: an eye movement study comparing the effectiveness of risperidone vs. haloperidol. *Psychiatry Res* 2003;120:13-27.
68. Williams LM, Loughland CM, Gordon E, et al. Visual scanpaths in

schizophrenia: Is there a deficit in face recognition? *Schizophr Res* 1999;40:189-99.
69. Xia M, Takahashi S, Tanabe E, et al. Eye movement studies on schizophrenics and their parents. *Eur Neuropsychopharmacol* 1996;6 (Suppl 3):64.
70. Beedie SA, St.Clair DM, Rujescu DP, et al. Smooth pursuit and visual scanpaths: Related or independent deficits in schizophrenia? *Schizophr Res* 2010;117:247-8.
71. Benson P, Beedie SA, Giegling I, et al. A classification model of schizophrenia using a multivariate eye movement phenotype [abstract]. *Eur Psychiatry* 2010;5(Suppl 1):611.
72. Benson PJ, Beedie SA, Giegling I, et al. Multivariate eye movement psychophysiology accurately differentiates schizophrenia cases from unaffected controls. *Schizophr Res* 2010;117:248-9.
73. Tsunoda M, Kurachi M, Yuasa S, et al. Scanning eye movements inschizophrenic patients: relationship to clinical symptoms and regional cerebral blood flow using 123I-IMP SPECT. *Schizophr Res* 1992;7:159-68.
74. Tsunoda M, Kawasaki Y, Matsui M, et al. Relationship between exploratory eye movements and brain morphology in schizophrenia spectrum patients. *Eur Arch Psychiatry Clin Neurosci* 2005;255:104-10.
75. Luria A, Karpov B, Yarbuss A. Disturbances of active visual perception with lesions of the frontal lobes. *Cortex* 1966;2:202-12.
76. Beedie S, St.Clair D, Rujescu D, et al. Frontal brain function and visual exploration of natural scenes in schizophrenia [abstract]. *Eur Psychiatry* 2010;25(Suppl 1):1104.
77. Roberts JK. Brain structure and function in the schizophrenias: a neurobehavioural approach. *Psychiatr J Univ Ott* 1983;8:67-80.
78. Schmid A, Rees G, Frith C, et al. An fMRI study of anticipation and learning in smooth pursuit eye movements in humans. *Neuroreport* 2001;12:1409-14.
79. Pierrot-Deseilligny C, Müri R, Nyffeler T, et al. The role of the human dorsolateral prefrontal cortex in ocular motor behavior. *Ann N Y Acad Sci* 2005;1039;239-51.
80. Burke MR, Barnes GR. Brain and behaviour: a task-dependent eye movement study. *Cereb Cortex* 2008;18:126-35.
81. Gooding DC, Iacono WG, Hanson DR. Smooth pursuit and saccadic eye movement performance in a prefrontal leukotomy patient. *J Psychiatry Neurosci* 1999;24:462-7.
82. Heide W, Kurzidim K, Kompf D. Deficits of smooth pursuit eye movements after frontal and parietal lesions. *Brain* 1996;119:1951-69.
83. Gaebel W, Ulrich G, Frick K. Visuomotor performance of schizophrenic patients and normal controls in a picture viewing task. *Biol Psychiatry* 1987;22:1227-37.
84. Kurachi M, Matsui M, Kiba K, et al. Limited visual search on the WAIS picture completion test in patients with schizophrenia. *Schizophr Res* 1994;12:75-80.
85. Matsushima E, Kojima T, Ohta K, et al. Exploratory eye movement dysfunction in patients with schizophrenia: possibility as a discriminator for schizophrenia. *J Psychiatr Res* 1998;32:289-95.
86. Phillips ML, David AS. A cognitive neuropsychiatric approach to the study of delusions in schizophrenia using visual scan paths. *Schizophr Res* 1996;18:216-7.
87. Phillips ML, David AS. Abnormal perception of simple and chimeric facial stimuli in schizophrenia: investigation of underlying attentional mechanisms using visual scan paths. *Schizophr Res* 1997;24:120-1.
88. Phillips ML, David AS. Attention to threat in schizophrenia: investigation of the cognitive processes underlying paranoia using visual scan paths. *Schizophr Res* 1997;24:121.
89. Phillips ML, David AS. Viewing strategies for simple and chimeric faces: an investigation of perceptual bias in normals and schizophrenic patients using visual scan paths. *Brain Cogn* 1997;35:225-38.
90. Phillips ML, David AS. Abnormal visual scan paths: a psycho - physiological marker of delusions in schizophrenia. *Schizophr Res* 1998;29:235-45.
91. Phillips ML, Senior C, David AS. Investigation of the cognitive processes underlying paranoia using visual scan paths. *Schizophr Res* 1998;29:61.
92. Quirk SW, Strauss ME. Visual exploration of emotion eliciting images by patients with schizophrenia. *J Nerv Ment Dis* 2001;189:757-65.
93. Schwartz BL, Rosse RB, Johri S, et al. Visual scanning of facial expressions in schizophrenia. *J Neuropsychiatry Clin Neurosci* 1999;11: 103-6.
94. Streit M, Wölwer W, Gaebel W. Facial-affect recognition and visual scanning behaviour in the course of schizophrenia. *Schizophr Res* 1997;24:311-7.
95. Beedie S, Shephard E, Giegling I, et al. Visual scanpaths as a generalised deficit in schizophrenia [abstract]. *Perception* 2010;30(Suppl):34.
96. Adler LE, Freedman R, Ross RG, et al. Elementary phenotypes in the neurobiological and genetic study of schizophrenia. *Biol Psychiatry* 1999;46:8-18.
97. Horley K, Williams L, Gonsalvez C, et al. Face to face: visual scanpath evidence for abnormal processing of facial expressions in social phobia. *Psychiatry Res* 2004;127:43-53.
98. Horley K, Williams L, Gonsalvez C, et al. Social phobics do not see eye to eye: a visual scanpath study of emotional expression processing. *J Anxiety Disord* 2003;17:33-44.
99. Dalton KM, Nacewicz BM, Johnstone T, et al. Gaze fixation and the neural circuitry of face processing in autism. *Nat Neurosci* 2005;8: 519-26.
100. Klin A, Jones W, Schultz R, et al. Defining and quantifying the social phenotype in autism. *Am J Psychiatry* 2002;159:895-908.
101. Klin A, Jones W, Schultz R, et al. Visual fixation patterns during viewing of naturalistic social situations as predictors of social competence in individuals with autism. *Arch Gen Psychiatry* 2002;59:809-16.
102. Pelphry KA, Sasson NJ, Reznick JS, et al. Visual scanning of faces in autism. *J Autism Dev Disord* 2002;32:249-61.
103. Rutherford MD, Towns AM. Scan path differences and similarities during emotion perception in those with and without autism spectrum disorders. *J Autism Dev Disord* 2008;38:1371-81.
104. Karatekin C, Asarnow J. Exploratory eye movements to pictures in childhood-onset schizophrenia and attention-deficit hyperactivity disorder. *J Abnorm Child Psychol* 1999;27:35-49.
105. Shephard S, Beedie SA, Kuriakose J, et al. Perseverative eye movements in obsessive-compulsive disorder and schizophrenia [abstract]. *Perception* 2010;39(Suppl):37.
106. Mosimann UP, Felblinger J, Ballinari P, et al. Visual exploration behaviour during clock reading in Alzheimer's disease. *Brain* 2004; 127:431-8.
107. Morgan CJ, Huddy V, Lipton M, et al. Is persistent ketamine use a valid model of the cognitive and oculomotor deficits in schizophrenia? *Biol Psychiatry* 2009;65:1099-102.
108. Neumann D, Spezio M, Piven J, et al. Looking you in the mouth: abnormal gaze in autism resulting from impaired top-down modulation of visual attention. *Soc Cogn Affect Neurosci* 2006;1:194-202.
109. Spezio ML, Adolphs R, Hurley RS, et al. Analysis of face gaze in autism using "Bubbles." *Neuropsychologia* 2007;45:144-51.
110. van der Geest JN, Kemner C, Camfferman G, et al. Looking at images with human figures: comparison between autistic and normal children. *J Autism Dev Disord* 2002;32:69-75.
111. Marsh PJ, Williams LM. ADHD and schizophrenia phenomenology: Visual scanpaths to emotional faces as a potential psychophysiological marker? *Neurosci Biobehav Rev* 2006;30:651-65.
112. Craddock N, O'Donovan MC, Owen MJ. Psychosis genetics: modeling the relationship between schizophrenia, bipolar disorder, and mixed (or "schizoaffective") psychoses. *Schizophr Bull* 2009;35: 482-90.
113. International Schizophrenia Consortium; Purcell SM, Wray NR, Stone JL, et al. Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. *Nature* 2009;460:748-52.
114. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull* 1987;13:261-76.
115. Andreasen NC. The Scale for the Assessment of Negative Symptoms (SANS): conceptual and theoretical foundations. *Br J Psychiatry Suppl* 1989;(7):40-58.
116. Overall JE, Gorham DR. The Brief Psychiatric Rating Scale. *Psychol Rep* 1962;10:790-812.
117. Liddle PF. The symptoms of chronic schizohrenia. A re-examination of the positive-negative dichotomy. *Br J Psychiatry* 1987;151:145-51.