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 colleagues¹). 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

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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 psychophysiological measures have been proposed as candidate trait markers in schizophrenia (for a review, see Javitt and colleagues¹¹). Examples include smooth pursuit eye movements,¹² P300 event-related potentials,¹³ sensory gating¹⁴ 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 pro-

posed 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 attention³⁵ 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 dorso-lateral 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 performance⁵⁶ 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 colleagues⁴⁹

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 non-clinical comparison groups. Matsushima and colleagues⁸⁵ 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 colleagues⁴⁵ 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. ⁸⁴	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 psychophysiological or neuropsychological measure.^{71,72} This work is currently in preparation for publication by our research group.

Despite the practical significance of the current classifica-

tion 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	Neutral face: state whether face is pleasant Chimeric faces: determine facial expression
Phillips and David ⁸⁸	12 pers. delusions 10 nonpers. delusions	10 healthy controls	Scenes depicting neutral, ambiguous or threatening activity	Recognition task
Phillips and David ⁸⁹				Recognition task
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	(i) Free-viewing (ii) Asked to attend to threatening areas
Phillips et al. ⁶⁶	19 pers. delusions 8 nonpers. delusions	18 healthy controls	Scene showing neutral, ambiguous or threatening activities	Free-viewing
Quirk and Strauss ^{92*}	20	10 addiction recovery patients	Emotional images	(i) Affect recognition (ii) Gaze direction discrimination
Rosse et al. ⁵⁸	16	38 cocaine users	Faces with direct and averted gaze	Varied by stimulus
Ryu et al. ^{59*}	60	30 healthy controls	Circles, faces symbols, landscape	Affect recognition
Schwartz et al. ⁹³	16	10 healthy controls	Upright and inverted faces	Affect recognition
Streit et al. ⁹⁴	16	18 healthy controls	Faces	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 = Wechsler 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	NR
Bestelmeyer et al. ³⁷	SC < controls	SC > controls	NR	SC < controls	NR	NR	Atypical
De Wilde et al. ⁶⁰	SC = controls	SC = controls	NR	NR	SC < controls	NR	Atypical for detailed cards
Gaebel et al. ⁸³	SC = controls	SC = controls	NR	NR	NR	NR	NR
Green et al. ³⁸	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	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. ⁶¹	SC < controls	SC > controls	NR	SC < controls	Raw: SC < controls Fixation: SC < controls	Atypical	
Loughland et al. ⁶²	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
Phillips and David ⁶⁶	Deluded SC < controls	NR	NR	NR	NR	Atypical for deluded SC but not nondeluded SC
Phillips and David ⁶⁰	SC < controls	NR	NR	NR	NR	Atypical
Phillips and David ⁶⁷	NR	NR	NR	NR	NR	Atypical
Phillips and David ⁶⁸	NR	NR	NR	NR	NR	Atypical
Phillips and David ⁶⁹	NR	NR	NR	NR	NR	Atypical
Phillips 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
Phillips and David ⁶⁰	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	NR	Atypical for affective but not neutral images
Ryu et al. ⁵⁹	SC < controls	SC > controls	NR	SC < controls	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 regions¹⁰³). 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 colleagues⁵² 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 colleagues⁸³ 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 (SANS¹¹⁵) 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 (BPRS¹¹⁶) 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 ef-

fect 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.

In contrast to the suggestion by Gaebel and colleagues⁸³ 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 schizophrenia⁴⁶ 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 colleagues⁶⁸ 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 colleagues⁶⁸ 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,

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.

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 colleagues⁹⁴ 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 colleagues⁴¹ 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 colleagues⁵³ found illness duration to correlate with scanpath length. Williams and colleagues⁶⁸ 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 hospital⁴⁵ 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 colleagues⁶⁸ found chlorpromazine equivalent dosage to correlate with fixation frequency, but not with fixation duration, distance between fixations or overall scanpath length. Hori and colleagues⁴⁰ 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 duration⁷⁴ 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 colleagues⁶² 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 colleagues⁶⁰ 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 symptomatology 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 visuo-cognitive 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 psychophysiological assessment in trait marker research.

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