Table 75: Cognitive processes required for the successful completion of neuropsychological measures used in this study

<table>
<thead>
<tr>
<th>Cognitive Processes Required</th>
<th>Psychomotor Speed</th>
<th>Processing Speed</th>
<th>Visual Search</th>
<th>Perceptual Analysis</th>
<th>Working Memory</th>
<th>Sequencing</th>
<th>Inhibition</th>
<th>Set Maintenance</th>
<th>Set Shifting</th>
<th>Planning</th>
<th>Vigilance</th>
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<tr>
<td>Processing Speed</td>
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<td>Digit Symbol</td>
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<td>Letter-Number Sequencing</td>
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<td>Sustained Attention</td>
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<td>Continuous Performance</td>
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<td>Stroop Task</td>
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<td>Verbal Fluency Tasks</td>
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Note: blank cell refers to limited or no use of this process during the task, with increasing “+” referring to relative demand of the given component during performance of the task.
Symptom Groupings

Part of the logic behind the current study was that, since there was substantial evidence suggesting that many of the symptom dimensions proposed under the three- and five-factor models of symptomatology were heterogeneous, then if only a small number of the symptoms within these were broad groupings related to external neuropsychological measures, these correlations would be diluted when made at a group level. As such, it was proposed that the use of the more refined symptom groupings identified in the eleven-factor model would enhance any relationships that exist. However, if the groupings defined under the eleven-factor model were themselves also heterogeneous, then this problem would still remain, and relationships with external measures would still be obscured.

It is unlikely, however that this is the underlying cause of the lack of identification with external measures. Firstly, the clustering procedure and the detailed examination of symptom intercorrelation applied in the first study produce highly internally consistent symptom groupings that were also clinically logical. Secondly, where the broad groupings of symptoms (in the 3- or 5- factor models) showed any useful predictive relationship with the target variables, the correlations between all of the individual symptom measures in this factor and the neuropsychological variable were examined. This did not reveal any in which a subset of symptoms within the combinations defined under the eleven-factor model showed strong external relationships (>10% of shared variance) yet were excluded from predictive equations.

Alternatively, if the symptom groupings defined under the eleven factor model represented un-necessary over-splitting of symptom dimensions, this would not have
obscured any external relationships as all of the sub-groupings in question would have been identified as significant correlates of the measure in question in the initial correlation matrix. Although there was evidence that some of the eleven factor model groupings that reflected sub-divisions of the simple model factors exhibited uniformly poor relations with external variables (as was the case with the ‘bizarre behaviour’ and ‘conceptual disorganisation’ groups), there was no case where it could be suggested that over-splitting of symptom dimensions that were strongly related with the target variables had occurred.

**Participant Characteristics**

Correlations between variables will be attenuated if there is a poor spread of performance on one of both of the measures under examination (Nunnally, 1967). There are a number of characteristics of the current cohort that may have contributed to the lack of identification of any relationships between the neuropsychological measures and measures of symptoms. Firstly, the current participant sample, although accessed from a number of sources, was predominantly chronic in nature, with many of those interviewed accessed through community-based treatment services rather than in-patient services. As such, it could be argued that the range of symptomatology experienced among the cohort may have been attenuated. While this was certainly the case for a number of variables (such as the ‘somatisation’, ‘visual hallucination’, ‘excitement’, and ‘inappropriate affect’ symptom groups), these symptom groupings were excluded from analysis in the current study, and there was a reasonable range of severity of experience for each of the included variables (with distribution tables provided in Study 1).
Secondly, the largely chronic nature of the sample may have introduced variables that indirectly affected any relationship between symptoms and performance on neuropsychological measures, such as the dampening effect that social disengagement, institutionalisation, long term medication, and the experience of multiple psychotic episodes may have had on performance. In an attempt to control for the variance associated with many of these factors, variables such as duration of education, duration of illness, and medication levels were entered into the regression models prior to the stepwise inclusion of symptom measures. However, this did not address the deleterious effect of many of the aforementioned factors (institutionalisation, long term medication effects), and indeed granted these control measures a greater level of importance in the analysis procedure than the presence of symptoms themselves (i.e. despite the fact that the hypotheses under study were in reference to the relationships between symptoms and neuropsychological performance, before any particular symptom groups could enter the predictive models, they were required to explain a significant amount of variance beyond that contributed by the control measures). While this hurdle may have had the potential to inhibit the identification of symptom-task performance relationships, examination of raw correlations regardless of the control measures clearly showed that, other than the ‘cognitive dysfunction’ grouping, relationships between symptom groupings and neuropsychological performance were almost uniformly slight (displaying less than 12% shared variance).

Finally, given that the participant sample, as a whole, performed at a much lower level to comparison control groups (Table 44) it is possible that floor effects in some of the neuropsychological measures may have produced a reduction in the range of performance, which, in turn, would lead to attenuated correlations with these variables. As could be seen on inspection of Table 49, however, the variability of performance
amongst the clinical cohort was at least equivalent to that seen in the control group across all measures, and as such this is unlikely to have produced a marked impact on correlation values.

The optimal environment for the current study would have been a diagnostically-broad, recent-onset, neuroleptic-naïve, population-based sample. While replication of the findings identified within the current cohort in such a sample would be recommended, it is extremely unlikely that the lack of identification of poor relationships between those symptoms at the conceptual ‘core’ of schizophrenia and measures of neuropsychological performance is simply an artefact of the characteristics of the participants that contributed to this study. As shown in the literature overview at the start of this chapter, while this is the first study to have systematically examined the relationship between performance of all of the components of an eleven-factor model of symptomatology, consistent with the findings of the current study, symptom-task relationships identified in the literature to date for all measures remained relatively slight regardless of the refinement of the symptom groupings or the characteristics of the participants involved.

*Analysis Logic*

It is worthwhile considering whether the logic of the analytic approach adopted in the current study itself may have contributed to the lack of identification of symptom-task relationships. Green and Nuechterlein (1999) discuss potential interpretative challenges when a study seeks to identify relationships between two variables, X and Y, while controlling for variable C. In the case where variable C is an effect of X rather than an independent intervening variable, then removing the variance of C may remove possible
explanatory variance from the relationship between X and Y. Such a scenario had the potential to occur in the current study if increases in symptomatology were related to increases in medication level, which was a variable that was controlled for in the analyses. While this variable was included as a control measure in three of the regression models, its inclusion only explained an extremely small amount of variance in each instance (1% or less) and as such would not have been likely to have disrupted any pairwise relationships.

*Item Set Artefacts*

One final criticism that could be levelled at the methodology here employed may be the inclusion of items within the ‘symptom’ set which were reflective of clinical assessments of neurocognitive function, such as ‘inattentiveness during mental status assessment’, ‘disorientation’ and ‘difficulty in abstract thinking’. It may seem almost blantly obvious that, in an investigation of the relationship between symptomatology and performance on a series of neuropsychological measures, that if proxy clinical ratings of neurocognitive function are included in that symptom set, then these clinical ratings will necessarily relate strongly with the more objective measures of such functioning. However, these variables were included in the current item set as these form part of the symptom batteries of the SANS and the PANSS, instruments which are commonly used in the derivation of the three- and five- factor models of symptomatology. This being so, variance from such items has necessarily contributed to any study using these instruments to examine relationships with neuropsychological variables.
While retaining these ratings in the item set used here allowed an unbiased comparison to previous studies using the SANS/SAPS and PANSS/BPRS scales, their explicit differentiation from other symptoms in the eleven-factor model may have undermined the potential for other symptom groupings to contribute to the regression model, given the use of the stepwise procedure for symptom entry. That is, if the clinical ratings of neurocognitive function were excellent proxy measures of the dependant measure, then their inclusion in the equation would have consumed all the variance available for explanation, and hence no other symptom groupings would have been able to enter the equations. Inspection of the raw correlations between symptoms and the neuropsychological measures of attention (Table 62) clearly show that this was not the case: firstly, the ‘cognitive dysfunction’ symptom trio was strongly, but certainly not perfectly, related to performance on each of the measures, a finding supported by recent independent studies (Good et al., 2003). Secondly, the raw correlation matrix (Table 62) clearly showed that the other symptom groupings in the eleven-factor model generally had poor correlations with task performance even when the variance associated with the ‘cognitive dysfunction’ items was not considered, and that those symptom groupings that could contribute to the explanation of performance variance beyond the variance contributed by other groupings (Table 63: regardless of whether ‘cognitive dysfunction’ was included or otherwise) also entered the predictive regression models (Table 64).

In sum, it would appear that, with the exception of the matter of the cognitive complexity of the neuropsychological measures applied in the current study, most of the methodological criticisms have been largely addressed or may not have produced effects of sufficient magnitude to have caused negative results (or Type 2 errors) in the search for relationships between symptom groupings and components of attention. In the current study, correlations between clinical ratings of ‘cognitive dysfunction’ and not
symptoms within the conceptual core of schizophrenia were identified with neuropsychological measures of attention. Given that relationships, albeit moderately weak ones, between these same measures and symptom factors have been identified by other research using different groupings of the same items adopted in the current study (the three- and five-factor models), the findings here appear to suggest that many of the associations seen in the extant literature may simply reflect secondary relationships or artefacts of models that combine proxy measures of neurocognitive function with measures of actual symptoms (such as hallucinations, delusions, negative signs, thought disorder and the like).

It would appear that the identification of the processes underlying the manifestations of particular symptoms may best be gained through the application of the careful and precise approaches such as those adopted within the methodology of cognitive neuropsychology. The findings of the current study show that the relatively coarse clinical neuropsychological measures of attention may be largely unrelated to the presence of those symptoms commonly associated with a diagnosis of schizophrenia. Instead, these formal neuropsychological measures appeared to be best predicted by brief clinical assessments of cognitive dysfunction. The independence of these clinical ratings of cognitive dysfunction from other symptom groups identified within the SANS/SAPS/PANSS/BPRS item set, and their validation through the presence of independent relationships with external measures is, firstly, supportive of the validity of these ratings made in the clinical context. Secondly, and more pertinently, this shows the importance of separating clinical symptoms from proxy measures of neurocognitive functioning in symptom batteries used in the assessment of schizophrenia. As the role of ‘cognitive dysfunction’ within the experience of the current participant cohort has proven so important in this study, a more detailed discussion of the role of neurocognitive function
for the understanding of both the nature of the diagnosis, and the approach to its treatment is detailed below, along with a framework for conceptualising the findings identified in the current study.

**Symptoms, Neurocognition and Outcome: A framework for reconciling these findings**

*Schizophrenia as a Neurocognitive Disorder?*

The finding of an apparent dissociation of global measures of cognitive deficits from symptomatology leads to the question of whether there is any special role for the presence of neurocognitive dysfunction in the understanding of the disorder as a whole. The findings here could simply be interpreted as a validation of the clinical ratings of ‘inattentiveness during mental status testing’, ‘disorientation’ and ‘difficulty in abstract thinking’, as, in a general reflection of an inverse linear relationship between these and more formal assessments, those that received high clinical ratings on these items also performed poorly on the formal clinical neuropsychological assessments. However, the consistent finding of group-level deficits in performance of participants diagnosed with schizophrenia on a range of neuropsychological measures (Heinrichs & Zakzanis, 1998) clearly suggests that neurocognitive deficits are a particularly important piece of the puzzle of schizophrenia.
In an interesting return to some of the initial conceptions of early investigators such as Kraepelin, in recent years an increasing body of literature has suggested that neurocognitive dysfunctions may be a core feature of schizophrenia. Evidence supporting such a view has been derived from studies showing that certain neurocognitive deficits can be identified prior to the onset of florid symptoms (Caspi et al., 2003; Erlenmeyer-Kimling et al., 2000), appear relatively stable over the course of the illness (Heaton et al., 2001; Hoff et al., 1999; Russell et al., 1997; Stirling et al., 2003), and remain even when symptoms are in remission (Nuechterlein & Dawson, 1984). Moreover, deficits on particular neuropsychological measures have been shown to be useful predictors of eventual development of schizophrenia in those at high genetic risk (Erlenmeyer-Kimling et al., 2000; Freedman et al., 1998), and unaffected relatives of individuals diagnosed with schizophrenia show impairments on some neuropsychological measures which are reflective of their relative genetic risk of developing the disorder (Egan et al., 2001; Toomey, et al., 1998). These findings have led to the proposal that those cognitive dysfunctions most associated with schizophrenia could be used as endophenotypes in genetic studies of the disorder (Egan et al., 2001; Hoff & Kremen, 2002).

One of the major challenges to the view that neurocognitive dysfunction lies at the core of schizophrenia is that such an assertion would require that all individuals receiving this diagnosis would, by definition, experience cognitive impairment. Certainly, in the current study, the sample of those diagnosed with schizophrenia performed below the average achieved by neurologically-intact comparison groups on practically every neuropsychological measure examined. However, 55% of the participants performed within the normal range in terms of general intellectual function (WAIS-III full-scale IQ), and even on measures considered to be good predictors of genetic risk for the disorder,
substantial proportions still performed within a range that would not be differentiable from performance of unaffected individuals: if performance within one standard deviation of the control group mean is taken as a reference frame of normal performance, 53% of clinical participants attained normal performance on modified WCST perseverative errors, 41% produced antisaccade inhibition errors within this range; and 27% produced d’ sensitivity measures on the Continuous Performance Task at this level. Independent studies have identified similar results, with some suggesting that up to 55% of their patient sample performed within a normal range on neuropsychological measures (Bryson, Silverstein, Nathan & Stephen, 1993; Strauss & Silverstein, 1986), although many have suggested more moderate levels of 11% (Torrey, Bowler, Taylor & Gottesman, 1994), 15% (Heinrichs & Awad, 1993), or 23% (Kremen, Seidman, Faraone, Toomey & Tsuang, 2004) of cohorts with schizophrenia performing within a ‘neuropsychologically normal’ range. It is possible that these findings may partially reflect the differing degrees of sensitivity of the neuropsychological tests employed (Zakzanis, 1998). However, in a very careful study using a comprehensive battery of neuropsychological tests encompassing eight major ability areas, 28% of a sample of 171 clinically stable outpatients with schizophrenia performed within a normal range in a general performance profile, and 11% did not display performance deficits on any of the measured neuropsychological domains (Palmer et al., 1997). Such results would seem inconsistent with the proposal of neurocognitive dysfunction being a core trait of schizophrenia.

These findings may be reconcilable if the presence of schizophrenia produces a downward shift in an individual’s neurocognitive performance when compared to premorbid levels. For example, similar to the case in dementia (Naugle, Cullum & Bigler, 1990) those individuals with schizophrenia performing in the normal range may have
achieved high-average or greater performances if it was not for the presence of the disorder. Some evidence for this type of effect has emerged: Kremen (et al., 2000) showed that participants with schizophrenia identified by blind raters as neuropsychologically normal had significantly greater estimated premorbid ability than a neuropsychologically-matched control group. Similarly, studies of neuropsychological performance in monozygotic twins discordant for schizophrenia have shown that even when the affected member performs within the normal range, this tends to be below that of their unaffected twin (Goldberg et al., 1990; Torrey et al., 1994). However, consistent with the findings of the Palmer (et al., 1997) study, 11% of the affected twins in the Torrey (et al., 1994) study showed minimal or no neuropsychological impairment, even in comparison to their unaffected twin.

Similarly, while the majority of those with a diagnosis of schizophrenia may display performance deficits across a neuropsychological battery, there is evidence to suggest that this pattern of deficits is not uniform for all patients (Heinrichs & Awad, 1993; Kremen et al., 2004). This has led some authors to suggest that the heterogeneity of schizophrenia may be reduced through the use of subgroups defined on the basis of the neurocognitive deficits or multiple cognitive phenotypes (Heinrichs, Ruttan, Zakzanis & Case, 1997; Hoff & Kremen, 2002; Joober et al., 2002; McDermid & Heinrichs, 2002).

The findings to date appear to suggest that, while extremely promising, neurocognitive deficits are not necessary associates of the diagnosis of schizophrenia. This is consistent with the position held in the current study that ‘schizophrenia’ itself is not a homogeneous diagnostic entity. While it remains, then, an open question as to whether neurocognitive dysfunctions may be at the core of a more narrowly-defined ‘schizophrenia’, the crucial role of cognitive function in the mediation of functional
outcome of patients is becoming increasingly apparent. It is the recent findings in this area which provide a framework through which the findings of the current study may be understood.

Neurocognition and Outcome: A framework

The practical importance of the independence between symptoms and neurocognitive factors is becoming increasingly apparent in regard to functional outcomes of schizophrenia (Green, 1998; Sharma & Harvey, 2000). It was noted in earlier sections above that several of the neurocognitive measures applied in the current study showed much stronger relationships than did symptoms with measures of functional outcome, such as social and vocational functioning, social problem solving and psychosocial skill acquisition (Green, 1996; Velligan et al., 1997). Meta-analysis of research in this area showed that neurocognitive measures such as working memory, Continuous Performance Task and card sorting task performance all displayed robust relationships with measures of functional outcome, individually explaining 20-40% of outcome variance (with composite measures explaining 20-60% of outcome variance: Green et al., 2000).

Clearly these important associations hold great promise for potential enhancements to outcome for individuals diagnosed with schizophrenia if research can pry apart these findings to better understand the mechanisms behind the underlying relationships. One of the steps in this process is the identification of mediating factors that might intervene in this relationship. While this specific line of research in schizophrenia is an emerging one (Green & Nuechterlein, 1999), there is a substantial body of pre-existing research
that is relevant to this issue, although the studies in question may not have been specifically designed with this purpose in mind. With a view to providing some integration of the existing knowledge in this area, Green and Nuechterlein (1999) have summarised this literature into a conceptual framework (Figure 24). This model accounts for a number of findings including the potential beneficial effects of cognitive remediation and adjunctive pharmacotherapy (such as glycine agonists) on neurocognitive functioning; the fact that antipsychotic medications have strong ameliorating effects on symptoms, yet only weak effects on neurocognitive function (in the case of typical neuroleptics) or emerging evidence of beneficial effects that may themselves be indirect (the ‘cognitive sparing’ effect of atypical antipsychotics may arise from reductions in extrapyramidal side effects, which remove the need for anticholinergic adjunctive treatments that are known to have deleterious effects on cognition); the independence of psychotic symptoms and neurocognitive measures, but weak relationships between negative symptoms and both neurocognition and outcome (although the direction of causation between these remains unclear); and the inclusion of social cognition as a possible mediating factor between the identified relationship between neurocognition and functional outcome.
Figure 24: Possible mediating factors in the relationship between neurocognition and functional outcome (from Green & Nuechterlein, 1999).

Recalling that the major findings of this second study were: firstly, the independence of clinical measures of cognitive dysfunction from symptom measures, and the strong relationships of these ratings with formal neuropsychological assessments; secondly, the independence of the ‘social dysfunctions’ symptom grouping as a predictor of the ‘flexibility’ composite measure of executive function assessments (the modified Wisconsin Card Sorting Test, the Antisaccade task, and verbal fluency); and thirdly, the relationship between the symptom grouping of ‘hostility’ and performance on this same neuropsychological composite measure of ‘flexibility’. The relationships described in the Green and Nuechterlein (1999) model, and by extension, the studies contributing to it, provide a framework for understanding the outcomes of the current study, and placing the present results within a context of existing research.
The finding of the relative independence of cognitive dysfunction from other symptoms assessed by the SANS/SAPS and PANSS/BPRS is consistent with the proposals in Green and Nuechterlein’s (1999) model. Evidence in support of this independence both in terms of phenomenology and relations with external neuropsychological variables has been discussed at length in previous sections above, and summarised in Table 74.

The Green and Nuechterlein (1999) model is particularly helpful in clarifying the finding that ‘social dysfunctions’ and not ‘negative signs’ emerged as an independent predictor of performance on the ‘flexibility’ composite measure. The Niewenstein (et al., 2001) meta-analysis of studies in this area showed small but significant correlations between the degree of ‘negative’ symptoms under the two- and three-factor models of symptomatology and perseverative errors on the Wisconsin Card Sorting Task (r=0.27, p<0.05, 8% shared variance). Green and Nuechterlein (1999: Figure 24) build this relationship into their model, noting that the literature tends to suggest small levels of shared variance (10-15%) between ‘negative’ symptoms (broadly defined) and neurocognitive function. However, the series of findings from the first and second studies here helps decompose this relationship. Firstly, the ‘negative’ symptom group used in studies of symptom-neurocognition relationships is typically derived from the entire SANS scale, which was shown in the first study to be a composite of three distinguishable symptom groupings: ‘negative signs’, comprising all the blunting and alogia symptoms; ‘social dysfunctions’, comprising apathy and asociality-type symptoms; and the ‘cognitive dysfunction’-type symptoms (attention). While the ‘cognitive dysfunction’ grouping was clearly independent of other symptoms, the ‘negative signs’ and ‘social dysfunctions’ groupings were moderately inter-correlated in the current cohort (r=0.51, 26% shared variance). When the symptom items combined into the
‘social dysfunction’ group are examined carefully, it is clear that these are exactly the types of variables that are included in studies of functional outcome, including: social functioning (social withdrawal, recreational interests), occupational functioning (impersistence at work or school), community outcome or caregiver burden (grooming and hygiene), and patient satisfaction (relationships with peers and ability to feel intimacy, among other items). As has been discussed, there is substantial evidence of strong relationship between neurocognitive measures and outcome in general (Addington & Addington, 2000; Liddle, 2000; Spaulding et al., 1999) and that card sorting tasks (one of the core measures of the ‘flexibility’ variable used here) in particular have shown relationships with social functioning (Dickerson, Boronow, Ringel & Parente, 1996; Jaeger & Douglas, 1992; Lysaker, Bell, Zito & Bioty, 1995); occupational functioning (Bellack, Gold & Buchanan, 1999; Lysaker, Bell & Beam-Goulet, 1995; Meltzer, Thompson, Lee & Hankan, 1996) and community outcome (Penn, Mueser & Spaulding, 1996). Combining these lines of evidence, the findings here suggest two conclusions: firstly, the weak relationships between the ‘negative signs’ grouping and the neurocognitive measures may have arisen from shared correlations with intermediate variables, in this case the ‘social dysfunctions’ symptoms, which showed moderate relationships with both the neurocognitive measures and with the ‘negative signs’ grouping. This is consistent with the weak relationship identified between the ‘negative signs’ and neuropsychological variables. Such a finding is further in support of the need for decomposition of the broad ‘negative’ symptom group proposed in the three-factor model of symptoms, as this is again evidence that relationships with external measures may be caused through the inclusion of ‘cognitive dysfunction’ or ‘social dysfunction’ items in this single rating, neither of which is fundamentally associated with the symptoms that are at the core of this concept (here labelled as ‘negative signs’). Secondly, studies such as that of Spaulding, Fleming, Reed, Sullivan, Storzbach and Lam (1999),
which have shown that improvements in card sorting performance through psychiatric rehabilitation are related to improvements in interpersonal problem solving ability suggest that the direction of causation runs from the neuropsychological variable to the ‘social dysfunction’ measure in the relationship identified here. As such, while this will not have changed the resulting analyses, the regression models applied in the current study were making predictions in the wrong ‘direction’, as ‘social dysfunctions’ were used to predict performance on the neuropsychological ‘flexibility’ variable. This is an example, then, of the problem of ‘horizontalisation’ of diagnoses, as termed by van Praag (1997): in the aim of deriving a full clinical picture of those experiencing schizophrenia, measures of what appear to be primary dysfunctions (the ‘cognitive dysfunctions’ symptoms) have been combined with secondary, or consequential symptoms (the ‘social dysfunction’ symptoms).

A similar interpretation may be suggested for the relationship between the ‘hostility’ grouping and performance on the neuropsychological measure of ‘flexibility’. While the presence of clinically significant symptoms of hostility in up to 20% of the current sample would suggest that this is clearly not an insignificant part of a description of a patient’s presentation, clinical wisdom would suggest that these are likely to be secondary expressions of other problems. Examining the individual symptoms contributing to the ‘hostility’ grouping, ‘aggressive and agitated behaviour’ and ‘poor impulse control’, the view of these symptoms as more secondary in nature can be better understood. Problems with impulse control are a common behavioural manifestation of damage to frontal lobe regions, which are the exact functions assessed through the Antisaccade task errors and Wisconsin Card Sorting perseverative errors, here combined into the measure of ‘flexibility’ (Lezak, 1995). Moreover, neurocognitive rehabilitation interventions have also been shown to have beneficial effects on symptoms of hostility (Brenner, Kraemer,
Hermanutz & Hodel, 1990). As such, the finding of a relationship between the ‘hostility’ symptoms and the neuropsychological measure of ‘flexibility’ here may be both a validation of the accuracy of the clinical rating and also an indication that the degree of hostility may be a secondary effect of some particular aspects of those cognitive dysfunctions experienced by patients – rather than, as might have been suggested by the predictive regression models presented here, a causative agent in this relationship.

While the findings here require replication and examination in more targeted studies, they are clearly consistent with the framework offered by the Green and Nuechterlein (1999) model of relationships and mediating factors between neurocognition and functional outcome in schizophrenia (Figure 24). Moreover, this model has been shown to be particularly useful in providing suggestions in regard to the direction of causation of the findings of the current study.

**Summary:**

Disorders of attention have been long been reported among individuals diagnosed with schizophrenia, and they have been proposed as possible associates of the schizophrenia genotype. However, ‘attention’ itself is a complex concept, a composite outcome of the functioning of multiple sub-systems, and there have been indications that deficits in specific components of attention may share moderate correlations with the presence of particular symptoms of schizophrenia, rather than being characteristic traits of the diagnosis itself. In this study, we set out with the implicit hypothesis that the weak to moderate correlations identified between aspects of attention and symptoms were due to
the use of coarse psychopathological models which apply heterogeneous groupings of symptoms as dependent measures, hence obscuring potential relationships. Using findings from the existing literature, explicit hypotheses were defined for the relationships between each of six components of attention measured by common neuropsychological tests and the symptom groupings defined according to the eleven-factor model of schizophrenia identified in the first study. However, instead of identifying stronger relationships between these components of attention and symptoms when these more homogeneous symptom groupings were applied, instead, weaker relationships with symptoms were shown. It was clear that a small group of three items from the SANS and PANSS (‘inattentiveness during mental status testing’, ‘disorientation’, and ‘difficulty in abstract thinking’) were strongly correlated with all of the target dependent measures. This symptom trio, grouped as ‘cognitive dysfunction’ in the eleven-factor model, were identified as independent from other groupings in the item set during the first study. However, in the popular three-factor model of symptomatology, these were combined within the ‘negative’ symptom grouping, and were similarly combined into the ‘cognitive’ dimension in the five-factor model. While both the ‘negative’ component in the three-factor model and the ‘cognitive’ dimension of the five-factor model were related to the neuropsychological measures of attention, examination of the correlations between each of the individual symptoms in these factors and performance on the dependent measures clearly showed that the group correlations were almost entirely due to the presence of the trio of ‘cognitive dysfunction’ symptoms alone. This was interpreted as suggesting that the correlations between these symptom dimensions and neuropsychological measures may have arisen from the combination of genuine clinical symptoms/signs (unrelated with the neuropsychological variables) with proxy clinical ratings of cognitive dysfunction (strongly related with the neuropsychological variables). As such, this validated the independence of the
SANS/PANSS ‘cognitive dysfunction’ items from other components of the eleven-factor model, and was consistent with the expanding body of literature suggesting that gross neuropsychological deficits are independent of symptomatology in schizophrenia.

Applying the eleven-factor model of symptomatology, two other symptom groupings, namely ‘hostility’ and ‘social dysfunctions’ were shown to contribute significantly to the prediction of neuropsychological performance independent of others. However, careful examination of these relationships in light of the existing literature in regard to neurocognition and functional outcome suggested that the experience of symptoms in these two groupings were likely to be consequences of neuropsychological dysfunction, rather than the cause of these relationships flowing in the opposite direction. As such, to the extent that the ‘cognitive dysfunction’ dimension of the eleven-factor model is a valid index of neurocognition, the ‘hostility’ and ‘social dysfunction’ groupings in this model may simply be secondary factors: important for a description of the full clinical picture of patients but not as targets in biological research.

The neuropsychological measures employed in the current study were relatively coarse measures of functioning, requiring the functioning of multiple systems for their successful completion. If schizophrenia is to be considered a ‘brain disease’, then there must, by definition, be identifiable linkages between the expressed symptoms and the functioning of underlying brain systems. However, these impairments are likely to be highly specific, and perhaps too subtle to be identified using clinical neuropsychological measurement at a group level. The validity of the remaining symptom groupings proposed in the eleven-factor model remains an open question, and it would seem likely that the most illuminating approach will require targeted investigations of these groupings using highly specific cognitive measures.
Study Three: Validation of Symptomatological Models of ‘Schizophrenia’: II. Relationships with Pursuit Eye Tracking Performance

History of eye movement research in the context of schizophrenia

The capacity to maintain sharp focus on a moving target is clearly an important skill for survival in a complex environment. The ability of humans to follow a moving target by means of extremely steady movements of the eyes (while keeping head position stable) was not discovered until late in the nineteenth century (Eckmiller, 1987). Hering (1891) first examined these smooth eye movements (langsae Augenfolgebewegungen), and also noted (as did others such as Landoldt, 1891) that these could not be voluntarily generated by most individuals in the absence of a moving target (Eckmiller, 1987). Such findings led Dodge (1903) to suggest that these continuous tracking movements represented the function of a distinct oculomotor subsystem. He termed these as ‘pursuit’ movements, and suggested that this system was distinct from movements such as ‘saccades’ where rapid, discontinuous, movements of the eye are used to quickly relocate visual fixation. Diefendorf and Dodge in 1908 conducted a photographic study of the eye movements of psychiatric patients following the swing of a pendulum, and while their initial interest directed towards the ocular motility of bipolar (‘maniaca-depressive insanity’) patients, they noted that the pursuit eye movements of patients with dementia praecox were particularly disrupted. Instead of smooth eye movements, those with dementia praecox showed ‘a marked hesitation to fall into the swing of the pendulum’ (Diefendorf & Dodge, 1908, p. 468), producing eye movements that were
more step-like than fluid (Figure 25). While such disruptions of pursuit eye movement were not restricted to those with dementia praecox, Diefendorf and Dodge (1908) identified this pattern among patients with other diagnoses “only where the disease process [had] produced marked deterioration” (p. 468), while it was apparent among even the “mildest cases” (p. 468) of dementia praecox. Moreover, as the saccadic eye movements of dementia praecox patients in this study were unaffected, and the photographic records showed that the participants were clearly trying to follow the movement of the pendulum, Diefendorf and Dodge (1908) suggested that the disrupted pursuit was in some way typical of the disease process in dementia praecox, rather than an artefact of wholesale disruption of ocular motility or of inattention (Clementz & Sweeney, 1990; Holzman, 1983).
While Kraepelin discussed the Diefenforf and Dodge (1908) findings in the 1919 revision of his textbook of psychiatry (relating the faltering eye tracking to the faltering patterns of attention in dementia praecox patients), their findings attracted little subsequent research attention. Two studies in the 1930s (Couch & Fox, 1934; White, 1938) replicated the presence, but not the specificity, of this pursuit deficit in dementia praecox/schizophrenia. Subsequently, research in this area again lay dormant until Holzman, in a 1969 review of perceptual aspects of psychopathology, noted several
reports scattered across the previous five decades of diminished vestibular response to stimulation among those with schizophrenia. As part of the methodological protocol of an attempted replication of this effect, saccadic performance and pursuit eye movements in response to a pendulum stimulus were recorded (Holzman, 1983), and serendipitously, the disturbance of smooth pursuit among participants with schizophrenia was rediscovered (Holzman, Proctor & Hughes, 1973). The importance of this effect was subsequently clear when Holzman and colleagues (Holzman, Proctor, Levy, Yasillo, Meltzer & Hurt, 1974) identified smooth pursuit eye movement deficits in approximately 52% of recently hospitalised patients with schizophrenia, 85% of chronically hospitalised schizophrenia patients, compared with approximately 22% of manic-depressive, and 21% of non-psychotic psychiatric patients, suggesting a degree of specificity of this deficit to schizophrenia. Moreover, the study also identified smooth pursuit deficits in around 45% of clinically- unaffected first degree relatives of patients with schizophrenia, compared with 10.5% of relatives of other psychiatric patients, and 8.3% of a control population, suggesting some degree of genetic component to the deficit (Holzman et al., 1974).

These early studies by Holzman and colleagues reinvigorated research in this area. The presence of defective pursuit in a substantial proportion of those diagnosed with schizophrenia has proven to be an extremely robust finding, identifiable even with very crude stimuli, eye movement recordings, and interpretation techniques (Grawe & Levander, 1995). By 1993, the deficit had been replicated more than 80 times in studies of patients in the United States, Europe, Asia, and Oceania (Levy, Holzman, Matthysse & Mendell, 1993). More than being simply an easily replicable disorder, following the findings of the Holzman (et al., 1974) study, multiple lines of evidence suggest that pursuit eye movement deficits in schizophrenia have great potential as a biological marker, or an endophenotype (Gottesman & Gould, 2003) for the diagnosis (Calkins &
Firstly, disordered eye tracking appears to be quite stable among those with schizophrenia, as it has been identified among first-episode (Hutton et al., 1998; Katsanis, Iacono & Beiser, 1996) and chronic (King, Mills, Mannion & Green, 1999) patients, and remains while individuals are in an acute (Iacono, Moreau, Beiser, Fleming & Yin, 1992), stabilised (Gooding, Iacono & Beiser, 1994) or remission phase (Arolt, Teichert, Steege, Lencer & Heide, 1998), as well as among drug-naïve (Campion et al., 1992) and subsequently medicated patients (Siever et al., 1986). Secondly, the presence of eye tracking disorder appears to be largely specific to schizophrenia: while prevalence estimates of the presence of pursuit dysfunction vary depending on the exact definition of ‘disorder’ and whether gross or specific measures are used (Avila, Adami, McMahon & Thaker, 2003), inflated occurrences of pursuit disorder have consistently been shown in schizophrenia populations (44-86%: Holzman, et al., 1974; 1977; 1980; 1984; 50%: Allen, 1997 using global measures; 20% using specific measures: Iacono, Morreau, Beiser, Fleming & Lin, 1992) relative to neurologically-intact control populations (8%: Holzman, Solomon, Levin & Watermaux, 1984; 10%: Allen, 1997; 0-16%: Clementz & Sweeney, 1990) and other psychiatric diagnoses such as bipolar disorder (41%: Holzman et al., 1984, using global measures; 7% using specific measures: Amador et al., 1991; Iacono et al., 1992; Muir, St Clair, Blackwood, Roxburgh & Marshall, 1992) or major depression (Lencer et al., 2004). This degree of specificity (0.20-0.86) is substantially greater than that of Schneider’s first rank symptoms (average 0.21, range 0.04-0.42: Andreasen & Flaum, 1991). Moreover, disorders of pursuit also appear more commonly among those with schizophrenia-spectrum disorders, such as delusional disorder (Campana, Gambini & Scarone, 1998) or schizotypal personality disorder (Keefe et al., 1989) than control populations, and the presence of eye tracking disorders among neurologically-intact populations is often associated with increased levels of schizotypal personality traits.
Thirdly, disordered pursuit occurs at an increased rate among unaffected first-degree relatives of individuals with schizophrenia diagnoses (34-58% using global measures: Holzman et al., 1974; 1977; 1980; 1984; 20% using specific measures: Iacono et al., 1992), in comparison to relatives of patients with other psychiatric disorders (such as affective disorders: 10-13% using global measures: Holzman et al., 1974; 1977; 1980; 1984; 8-14% using specific measures: Iacono et al., 1992) and the general population (8% using global measures: Holzman et al., 1974; 1977; 1980; 1984; 5% using specific measures: Iacono et al., 1992). Similarly, pursuit dysfunction occurs more commonly in children of mothers with schizophrenia than control populations (Ross, Hommer, Radant, Roath & Freedman, 1996). Finally, eye tracking disorder appears to be at least partly under genetic control, as twin studies of both neurologically-intact individuals (Katsanis, Taylor, Iacono & Hammer, 2000) and twins discordant for schizophrenia (Holzman, Kringlen, Levy, Proctor, Heberman & Yasillo, 1977; Holzman, Kringlen, Levy & Haberman, 1980) have shown much greater concordance rates for qualitative and quantitative measures of eye tracking performance in monozygotic than dizygotic twins. The current state of the literature, however, suggests that, while tantalising, only around two-thirds of the variance in the pursuit deficit associated with schizophrenia may be genetically determined (Grove, Clementz, Iacono & Katsanis, 1992; Katsanis, Taylor, Iacono & Hammer, 2000). Such findings demand a deeper understanding of the nature of pursuit eye movements themselves, and of the exact nature of the pursuit deficit in schizophrenia specifically.
Oculomotor systems involved in eye tracking

The metrics and neurology of the systems involved in eye tracking have been extensively characterised over the past century (see, for example: Robinson, 1965; Eckmiller, 1987). In terms of the mechanics of the process, there is a delay of approximately 100-150 milliseconds after the local motion of a target stimulus (Preibe, Churchland & Lisburger, 2001) before the initialisation of the pursuit system (Morrow & Sharpe, 1995). In the subsequent 100-125 milliseconds, an eye movement is initiated in the direction of the target movement at a velocity only loosely related to that of the target (often referred to as ‘open loop’ pursuit: Ciuffreda & Tanner, 1995). Following this period, information in regard to any discrepancy between the position or velocity of the target and that of the eye is used to guide eye movements (a ‘closed loop’ feedback system: Hutton et al., 2001; Stark, 1983). During this component of pursuit, the movement of the eye is under dual-mode control: position and velocity errors are corrected independently by the saccadic and pursuit systems respectively (MacCavoy & Bruce, 1995). While independent (Rashbass, 1961), these systems work interactively in order to maintain the image of the stimulus on the retina (Hutton & Kennard, 1998). Early studies used global ratings of the quality, or smoothness, of eye tracking performance to identify deficits in participants with schizophrenia (Levy, Holzman, Matthysse & Mendell, 1994). The ‘praecox pursuit’ noted by Diefendorf and Dodge (1908) was characteristically step-like when compared with the more fluid performance of other participants when following the swing of a pendulum (Figure 25). These jagged movements represent saccadic activity during tracking (Clementz & Sweeney, 1990). Clearly, then, specific characterisation of the contribution of both saccadic and pursuit systems to eye tracking performance is required to understand the exact nature of the disorder in schizophrenia.
Several precise quantitative measures of pursuit and saccadic activity during tracking have been defined (Abel & Zigler, 1988; Friedman et al., 1992), based on the function of the movement. The role of the smooth pursuit system is to match the velocity of the eye to that of the target in order to stabilise the image of the target on the retina. The success of this performance can be quantified by the ratio of eye velocity to target velocity, or ‘gain’, where a value of 1.0 reflects a perfect match of velocities (Clementz & Sweeney, 1990). Saccadic involvement in eye tracking may be either compensatory or intrusive (Levy, Holzman, Matthisse & Mendell, 1993). Compensatory saccades are direct reflections of the interaction between the two eye movement systems during tracking, serving to reduce position error when gain is imperfect. When the velocity of the eye is lagging behind the target (low gain), a saccade in the direction of the target can be made to ‘catch-up’ to the target (a ‘catch-up saccade’: CUS). If the velocity of the eye is greater than that of the target (high gain), a saccade made in the opposite direction to the motion of the target will reduce eye position error (a ‘back-up saccade’: BUS). Saccades occurring during eye tracking that do not serve any position-error-reducing function are classed as ‘intrusive’ (Abel & Zigler, 1988). These are usually inhibited during eye tracking among neurologically-intact individuals, but the most common of these are ‘square-wave jerks’ (SWJ), ‘anticipatory saccades’ (AS), and ocular flutter (Figure 26: Clementz & Sweeney, 1990). SWJ (originally ‘gegenrucke’: Abel & Ziegler, 1988) are pairs of small saccades in opposite directions (between 1° and 5°), where the first saccade takes the eye away from the target, and the second returns it. These are separated by an interval of around 150-400 milliseconds, during which time the eye continues pursuit (Levy et al., 1993). Very large SWJ, with saccadic amplitudes of 10° or greater and usually brief (100-125 millisecond) intersaccadic intervals, are distinguished by some authors as macro-SWJ (Clementz & Sweeney, 1990). The second type of saccadic intrusions, AS, are generally 5°
or greater saccades made in the same direction as, but ahead of, the target, producing an increase in position error (Ross, Olincy, Zerbe & Radant, 2002). These can be differentiated from the first component of a SWJ as the eye subsequently tends to remain stationary or drift only slightly (hence, producing a post-saccadic period of extremely low gain), either waiting for the target to reach this new position before continuing pursuit, or making a BUS to refoveate the target after an extended interval period (500-1500 msec: Abel & Ziegler, 1988; Clementz & Sweeney, 1990; Levy et al., 1993). In recent years, some researchers have subdivided AS on the basis of minimum amplitude criteria, defining those with an initial saccade of 4° or greater as AS (Ross, Olincy & Radant, 1999), and saccades that follow this general pattern (a forward-directed saccade that increases position error and is followed by a period of extremely low gain) but with small initial amplitude (1°-4°) as a ‘leading’ saccade (LS: Ross et al., 2002). Finally, ocular flutter refers to a number of saccades (5-10 degrees in amplitude) in succession without an intersaccadic interval (Clementz & Sweeney, 1990).
The nature of the eye tracking deficit in schizophrenia

In light of the combined involvement of saccadic and pursuit systems during eye tracking, the hesitant, step-like movements that Diefendorf and Dodge (1908) characterised as ‘praecox pursuit’ could be understood as tracking with low-gain pursuit (the hesitance) along with the presence of saccades (the ‘step-like’ movements: Figure 25). This is indeed the nature of the eye tracking deficit described in the modern literature: as a group, participants with schizophrenia exhibit an eye tracking deficit with
low gain, and an increased frequency of saccades, when compared to neurologically-
intact participants (Allen, 1997; Campion et al., 1992; Friedman, Jesberger & Meltzer,
1991; Friedman et al., 1995; Gambini, Colombo, Cavallaro & Scarone, 1993; Nkam et al.,
2001). Indeed, given that much of the early literature in this area simply used qualitative
assessments to dichotomously identify eye tracking as ‘normal’ or ‘disordered’, recent
studies have attempted to identify which of the specific eye tracking measures account
for the majority of variance in such descriptions. These have shown that the variables
most closely related to this differentiation in schizophrenia are gain, CUS, and, to a lesser
extent, AS; but not other measures such as BUS or SWJ frequency (Levy et al., 2000;
Ross et al., 1998). Evidence for the presence of between-group differences on each of
these variables will be considered separately below.

Investigations of eye tracking in neurologically-intact populations suggest that for slow
target velocities (up to 20°/sec), pursuit gain is maintained at approximately 1.0, but this
ratio steadily decreases with increasing target velocity (0.90-0.95 up to 40°/sec and
rapidly declining at higher velocities: Ciuffreda & Tannen, 1995; Lisberger, Evinger,
Johanson & Fuchs, 1981). This general pattern of declining gain with increasing velocity
holds true among observers with schizophrenia (Hutton et al., 2001). However, gain in
these participants has consistently been shown to be reduced relative to neurologically-
intact observers even at low target velocities (4°-20°/sec) in medication-free; first-
episode; acute; and chronic patients (Clementz, Sweeney, Hirt & Haas, 1990; Flechtnier,
Steinbacher, Sauer & Mackert, 1997; Friedman, Jesberger & Meltzer, 1991; Friedman et
al., 1995; Levy et al., 1993; Sweeney et al., 1994; Ross, Olincy, Harris, Sullivan & Radant,
2000). A recent study has also shown that, while first-episode and chronic observers
exhibit equally deficient gain compared to controls at low target speeds (10°-20°/sec), at
higher target speeds (30°-36°/sec), medicated, chronic patients perform more poorly
than first-episode participants, who themselves produce lower gain than controls at these velocities (age, which is known to affect gain was included as a covariate in these analyses: Hutton et al., 2001). While schizophrenia-control differences are robust at a group level, it is clear that the gain deficit is not homogenous amongst all observers with schizophrenia (Ross, Ochs, Pandurangi, Thacker & Kendler, 1996). In a large sample (n=101) of consecutively-admitted participants with schizophrenia-spectrum disorders (Sweeney et al., 1994), 47% of the patient sample produced gain that was two standard deviations beneath that of a the mean of a neurologically-intact comparison cohort following a 9°/sec target. In a subsequent study, using a faster target speed (17°/sec), an even smaller proportion of observers with schizophrenia produced such deficits in gain (34% two standard deviations below a control-group mean: Ross et al., 2002). Similarly, Levy (et al., 2000) found that just half of their patient sample could be qualitatively classed as poor eye-trackers, with only those participants so classified displaying any deficiencies in gain when compared to neurologically-intact participants.

At low to moderate target speeds (10°-20°/sec), CUS represent approximately 70-80% of all saccadic activity occurring during eye tracking among neurologically-intact participants and a similar (Levy et al., 2000) or slightly lower proportion (Friedman et al., 1992) among observers with schizophrenia. Amongst both groups, however, the rate of occurrence of CUS increases with increasing target speed (Mather, Neufeld, Merskey & Russell, 1992; Ciuffreda & Tannen, 1995). As would be expected given the finding of reduced gain at a group level amongst participants with schizophrenia, multiple studies have shown an increase in the number of CUS in these participants, whether acute, chronic, medicated or medication-free, compared to neurologically-intact controls at low to moderate target speeds (up to 20°/sec: Flechtner et al., 1997; Friedman, Jesberger & Meltzer, 1991; Levy et al., 1993; Ross et al., 1996; 2001; Sweeney et al., 1994). The few
dissenting studies from this trend, have suggested lower CUS frequency, but increased CUS amplitude, amongst observers with schizophrenia when compared with controls at low target speed (Abel, Friedman, Jesberger, Malki & Meltzer, 1991). In contrast to the general trend of an increased CUS frequency among observers with schizophrenia at low to moderate target speeds (up to 20°/sec), at faster target speeds, there appears to be little difference in the rate of CUS in schizophrenia and control cohorts (at 20-66°/sec: Abel et al., 1991; Mather et al., 1992). This may help clarify recent findings by Hutton et al (2001) who reported no difference in CUS frequency of first-episode patients compared with control observers, averaged across target speeds between 10°/sec and 36°/sec, despite an overall lower gain. However, while the finding of increased CUS frequency at target speeds lower than 20°/sec among observers with schizophrenia appears robust at a group level, such findings obscure a degree of heterogeneity within patient cohorts: Levy (et al., 2000) could classify just half of their patient sample as having qualitatively poor eye tracking, with only the poor trackers displaying any significant increase in CUS frequency when compared with control observers (at a target frequency of 16°/sec). Moreover, the large Sweeney (et al., 1994) study of consecutively-admitted participants with schizophrenia-spectrum disorders (n=101), identified just 17% of the patient sample with a CUS frequency that was two standard deviations above that of the mean of a neurologically-intact comparison cohort following a 9°/sec target.

The other form of compensatory saccade, BUS, appears much less frequently than CUS, comprising 12-20% of all saccadic activity during 16°/sec eye tracking in both control and schizophrenia populations (Levy et al., 2000). This component of performance has attracted little research attention, however, several studies suggest that there is no difference in the frequency of BUS among observers with schizophrenia when compared to neurologically-intact control cohorts at low to moderate target velocities (up to
When following a 9°/sec target, 7% of a sample of observers with schizophrenia, as well as 7% of control participants (n=42 and 43 respectively) produced BUS frequencies that were two standard deviations above the mean of a control group (Flechtner et al., 1997). However, when BUS frequency is averaged across a wide range of target frequencies (10°/sec to 36°/sec), Hutton (et al., 2001) found a lower rate of BUS among observers with schizophrenia in comparison to a matched control group, which was consistent both for first-episode and chronic patients.

Of the saccade types classed as intrusive during eye tracking (SWJ, AS and LS), SWJ are the most common. For moderate target speeds (16°/sec) these have been estimated as comprising between 4 to 6 percent of all saccadic activity, both for neurologically-intact and schizophrenia observers (Levy et al., 2000). These occur at an approximate frequency of 5 per minute during fixation and during tracking of a 5°/sec and 16°/sec target (Abel & Ziegler, 1988; Levy et al., 2000). Multiple investigations have suggested that there is no difference in frequency of SWJ between observers with schizophrenia and neurologically-intact controls at low to moderate target speeds (up to 20°/sec: Arolt, Teichert, Steege, Lenc er & Heide, 1998; Clementz et al., 1990; Friedman et al., 1992; 1995; Flechtner et al., 1997; Levy et al., 2000). Indeed, some studies have reported a lower frequency of SWJ among observers with schizophrenia in comparison to controls at low target speeds (9°/sec: Sweeney et al., 1992; 1994), or for first-episode but not chronic patients across a wide target velocity range (10°/sec to 36°/sec, Hutton et al., 2001). The weight of findings in the current literature, however, suggest no difference in SWJ frequency between those with schizophrenia diagnoses and controls. In support of this, the large study of Sweeney (et al., 1994) showed an equal proportion of schizophrenia and control participants (4% of samples of n=101 and 55 observers respectively) exhibiting SWJ.
frequencies greater than two standard deviations above the mean of neurologically intact controls when following a low-speed target (9°/sec), with very similar findings identified in a subsequent independent study (Flechtner et al., 1997).

Anticipatory saccades (AS) are very infrequent, comprising between 0-2% all saccades occurring during tracking at low to moderate speeds (5°/sec to 20°/sec: Friedman et al., 1992; Levy et al., 2000). Practically, this rate is in the order of 1-2 AS per minute among schizophrenia and control observers while tracking a 16°/sec target (Levy et al., 2000). Findings in regard to between-group differences in AS frequency have been more mixed than for other saccade types: with multiple studies reporting equal AS frequency in schizophrenia and control observers at low to moderate target speeds (9°/sec to 17°/sec: Arolt et al., 1998; Clementz et al., 1990; Levy et al., 2000; Ross et al., 2002; Sweeney et al., 1994); however, other studies at similar target velocities have reported an increased AS frequency among observers with schizophrenia (Friedman et al., 1992; Flechtner et al., 1997; Ross, Olincy & Radant, 1999; Ross et al., 2001). The large study by Sweeney (et al., 1994) reported 16% of schizophrenia-spectrum observers, compared with 6% of controls exhibited AS frequencies greater than two standard deviations above the mean of neurologically intact controls when following a low-speed target (9°/sec), with very similar findings identified in a subsequent independent study (12% of clinical observers, 7% of controls: Flechtner et al., 1997). Part of the reason for the discrepant findings in research to date may be methodological in nature, as a recent study has suggested that eye tracking recordings made using the predominant technique, infra-red reflection (IR), may be susceptible to misclassifying eye blinks as AS (Calkins et al., 2001). Eye blinks during pursuit occur at greater frequency among observers with schizophrenia than neurologically-intact participants (Amador et al., 1991), and, through comparison of electro-oculograph (EOG) recordings (where eye blinks provide a clearly characteristic
trace) with IR recordings of eye movement, Calkins (et al., 2001) showed that up to one third of EOG-identified blinks were classified as saccades when the IR trace was used, with this effect inflating AS rates in observers with schizophrenia, but not among control observers. However, while this methodological challenge may be responsible for some of the variance in between-group findings for AS frequency, and the rate of AS themselves is very low, this aspect of saccadic activity during pursuit eye tracking may be quite important for understanding the nature of the disorder in schizophrenia, as amongst a range of eye tracking variables, AS rate has been shown to be useful in differentiating first-degree relatives of individuals with schizophrenia from control populations (Ross, et al., 1998).

Ross and colleagues have investigated small-amplitude (1°-4°) AS, defining these as leading saccades (LS). In several studies, this group have identified higher rates of LS in observers with schizophrenia compared with controls, with the magnitude of this effect reaching to an effect size of up to 1.6 depending on the definition applied for identification of LS, despite the infrequent occurrence of such saccades (approximately 15 per minute among observers with schizophrenia, 4 per minute in controls with a 17°/sec target: Ross et al., 1999; 2001; 2002). While such findings are extremely promising for future investigations, the extremely small size of these saccades (1°-4°) means that they may be easily misidentified if there occurs any slight shift in the calibration of the recording process (such as a bump of IR glasses used in recording: Ross et al., 1999), and the precise definition of these movements (in terms of amplitude, change in position error, and post-saccadic slowing) requires an extremely detailed analysis of the eye tracking record which is not currently easily available to research groups in the field.
In summary, the literature in regard to the specific nature of the eye tracking deficit in schizophrenia suggests that, at a group level and low to moderate target velocity (5°/sec to 20°/sec), observers with schizophrenia display a reduction in gain, with a concomitant increase only in positively-directed (CUS) but not negatively-directed (BUS) compensatory saccades. There also appears to be no difference in the presence of the most common form of intrusive saccade (SWJ), but findings have been mixed in regard to less prevalent saccadic intrusions, with an increased, but still infrequent, presence of AS suggested by some studies, particularly for those of small amplitude (LS). At higher target velocities (above 20°/sec), there remain deficits of gain, with these exacerbated further in chronic patients when compared to those experiencing a first episode, however there appears to no longer be any increase in CUS frequency among those with schizophrenia. Complicating these results is the repeated finding that the use of between-group experimental designs masks the presence of a heterogeneous eye tracking performance among participants with schizophrenia, where a substantial proportion of patients (perhaps even half) display pursuit eye tracking which is indistinguishable from neurologically-intact control participants using these specific measures.

What do these findings mean for the understanding of the nature of the eye tracking dysfunction in schizophrenia? The two most prominent theories suggest that the characteristic ‘praecox pursuit’ could arise from a compensatory mechanism or a disinhibitive mechanism. A compensatory process is the most immediately intuitive: the inflated frequency of saccades in schizophrenia at a group level simply reflects an increased number of compensatory CUS in order to reduce the position error arising from the low gain experienced in these observers. If this is the case, a strong inverse relationship between the presence of CUS and gain would be anticipated. However, such an explanation appears not to tell the full story: in control participants, CUS frequency is
strongly inversely correlated with average gain ($r \approx -0.6$ at target speeds from 5°/sec to 20°/sec: Abel et al., 1991; Allen, 1997). However, among observers with schizophrenia, this relationship appears to be markedly reduced at low velocities (5°/sec: $r \approx -0.4$) and absent at moderate velocities (20°/sec: $r \approx -0.2$: Abel et al., 1991; Allen, 1997; Levy et al., 2000). While these findings argue against a compensatory process being the full cause of the eye tracking disorder in schizophrenia, they do not take into account the possibility that the gain-CUS frequency relationship among participants with schizophrenia may differ from that in neurologically intact participants in terms of the amplitude of the CUS made in these groups, and as such, further evaluation of the role of a compensatory mechanism is deserved. The suggestion that an increased saccade rate among observers with schizophrenia at a group level is caused by a failure of inhibition of the saccadic system is led by findings that, when asked to fixate on a single, static, target, participants with schizophrenia demonstrate a much increased rate of saccades away from the target in comparison to neurologically-intact participants (Abel & Ziegler, 1988; Mialet & Pichot, 1981; Pivik, 1991). If such disinhibition is the cause of the increased saccade rate in schizophrenia, then a relationship between the degree of saccadic disinhibition during a static fixation task with the frequency of saccades during eye tracking would be anticipated. Several investigations have found no such relationship (Matsue et al., 1986; Mather, Neufeld, Merskey, & Russell, 1989; Clementz, McDowell & Zisook, 1994), although Matsue (et al., 1986) identified a moderate correlation between the number of saccades during eye tracking and those during static fixation, only when the participant was asked to fixate on an imagined target, not when fixating on a visible target. Clearly, neither a wholly compensatory mechanism, nor a wholly disinhibitive mechanism fully accounts for the pattern of eye tracking disorder seen at a group level in schizophrenia. Recently, Levy (et al., 2000) examined which specific measures of eye tracking performance could adequately differentiate between qualitatively ‘good’ and ‘poor’ eye
tracking, with the results of a stepwise discriminant analysis clearly suggesting that “eye tracking disorder is a multivariate process, involving a primary impairment in the smooth pursuit system characterised by increased CUS and reduced gain, and secondarily, disinhibition of intrusive saccades” (p. 171: with only the frequency of AS intrusions, not CUS differing between good and poor trackers). As such, careful consideration of specific measures of eye tracking performance continues to be required in research examining this disorder (or disorders) among individuals with schizophrenia.

Neurology of pursuit

The neural pathways involved in visual pursuit among primates have been relatively well characterised, although the exact circuitry involved in humans is less clear (Hutton & Kennard, 1998). As displayed in Figure 27 and 28, control of pursuit is distributed across a number of cortical and subcortical regions (Hong, Avila & Thaker, 2003). While it is beyond the scope of the current discussion to examine the neurology of this system in depth (the reader is directed to the excellent reviews of Eckmiller, 1987 and Macavoy & Bruce, 1995 for more detailed information), the primary areas involved in the system can be summarised as follows: the motion characteristics of a moving target perceived in the retina are processed in the primary visual cortex, and this information is subsequently transmitted to the medial temporal (MT in monkeys, area V5 in humans) and medial superior temporal (MST or area V5a) areas in the temporo-occipito-parietal junction. Information is subsequently projected through the pons and cerebellum to the vestibular nuclei in the medulla and then transmitted to the oculomotor nuclei to drive the eye movement. Additionally, areas MT and MST also have projections to the posterior parietal cortex (PPC) and frontal eye fields (FEF) which themselves also project to pontine nuclei (Hutton & Kennard, 1998; Macavoy & Bruce, 1995). Two of these regions
have received particular attention in terms of schizophrenia research (see, for example: Pack, Grossberg & Mingolla, 2001; Sweeney et al., 1998). Area MT contains cells which are tuned to the direction and speed of a moving target. Chemical lesions of this area in primates produces problems with the maintenance of smooth pursuit, with performance characterised by low gain and increased CUS, with greater disruption as target speed increases (Macavoy & Bruce, 1995; Dursteler, Wurtz & Newsome, 1987). These lesion studies (Newsome, Wurtz, Dursteler & Mikami, 1985) displayed particular patterns of tracking that suggested that the observer was underestimating target velocity. Recently, studies among schizophrenia patients have identified deficiencies in motion perception thresholds in these participants, and that motion perception thresholds were strongly and significantly correlated to smooth pursuit gain amongst patients with schizophrenia but not for control participants (Chen et al., 1999; Stuve et al., 1997). Secondly, there is evidence to suggest that the FEF may be particularly involved in the smooth pursuit deficit seen in schizophrenia. Neurons in the FEF respond to the constant velocity and sinusoidal target stimuli used in eye tracking studies, and also to smooth pursuit tracking movements themselves (MacAvoy, Gottlieb & Bruce, 1991; Gottlieb, MacAvoy & Bruce, 1994). Mictostimulation of this area elicits smooth pursuit, and lesions produce eye tracking performance characterised by reduced gain, increased CUS and increases in intrusive saccades (MacAvoy & Bruce, 1995). In participants with schizophrenia, both PET and fMRI studies have shown that reduced activity in the FEF is associated with abnormal pursuit performance (Abel, Levin & Holzman, 1992; Ross et al., 2004; Sweeney et al., 1999).
Figure 27: Schematic summary diagram of the neural circuitry involved in human and primate smooth pursuit eye movement control (From: Hong, Avila & Thaker, 2003, p. 1929). Key: ACC: anterior cingulate cortex; DLPFC: dorsolateral prefrontal cortex; DLPN: dorsolateral pontine nucleus; FEF: frontal eye field; MST: medial superior temporal lobe; MT: middle temporal lobe; NRTP: nucleus reticularis tegmanti pontis; PPC: posterior parietal cortex; SEF: supplementary eye field. Retinal guided motion: the use of immediate motion information of the image on the retina to change eye movements; Extraretinal guided motion: the use of previous target and eye motion information to change subsequent eye motion.

Figure 28: Locations of cortical areas involved in the control of eye movements (from Kandel, Schwartz & Jessell, 1991, p. 673).
Other influences on eye tracking performance

There are a number of factors other than the presence of a clinical diagnosis of schizophrenia that may contribute to the presence of an eye tracking disorder. In order to more clearly understand the nature of eye tracking performance amongst individuals with clinical diagnoses, the role of medication, medication-induced movement disorders, smoking, attention, general neuropsychological function, clinical state and age in particular all require examination. The role of each of these concerns in eye tracking will be reviewed briefly below.

Medication Effects

There is clear evidence that several psychoactive medications influence eye tracking function among neurologically-intact individuals. The N-methyl-D-aspartate (NMDA) antagonist, ketamine, produces dose-dependent decreases in gain and increases in CUS (Radant, Bowdle, Cowley, Kharasch & Roy-Byene, 1998; Weiler, Thaker, Lahti & Tamminga, 2000). Methadone, an opiate receptor agonist, reduces eye tracking gain (Rothenberg, Schottenfeld, Selkoe & Gross, 1980). Diazepam, and Lorazepam, both benzodiazepines, produce dose-dependent reduction in gain with associated increases in CUS, with this effect generally consistent across low to moderate target velocities, and similar to the patterns seen following administration of alcohol (Abel & Hertle, 1988; Masson et al., 2000; Rothenberg & Sekloe, 1981). Among patients with diagnoses of affective psychosis, lithium carbonate has been shown to induce qualitatively-abnormal pursuit tracking despite improvements in clinical state (Levy et al., 1985). However, studies using quantitative measures of overall pursuit quality and saccadic intrusions failed to identify any difference between lithium-treated patients with affective psychoses and neurologically-intact participants, nor was any change apparent when previously
medicated participants were withdrawn from lithium therapy (Gooding, Iacono, Katsanis, Beiser & Grove, 1993).

There are clear reasons to expect an effect of antipsychotic medication on eye tracking performance. Firstly, these medications exert much of their effect through dopamine receptor antagonism (in the case of typical antipsychotics: Seeman & Lee, 1975) or mixed dopamine-serotonin receptor antagonism (Stahl, 1999), and there is rich dopaminergic innervation in cortical regions involved in the oculomotor systems driving eye tracking (Eckmiller, 1987; Kandel, Schwartz & Jessell, 1991). Secondly, abnormalities of pursuit eye tracking are seen in Parkinson’s disease, a disease characterised by a reduction of dopamine at both subcortical and cortical levels, which are reversible with levodopa (dopamine: Waterson, Barnes, Graely & Collins, 1996; White, Saint-Cyr, Tomlinson & Sharpe, 1983). Finally, administration of antipsychotics to neurologically-intact individuals induces eye tracking deficits (King, 1994; Malaspina et al., 1994). However, there are numerous lines of evidence that clearly suggest that the eye tracking disorder seen amongst observers with schizophrenia cannot be solely attributed to an artefact arising from pharmacological effects. Persuasively, the initial finding of dysfunctional tracking by Diefendorf and Dodge (1908) predates the neuroleptic age by nearly half a century (chlorpromazine was first synthesised late in 1950 and the first report of its use in psychiatry did not emerge until 1952: Delay, Deniker & Harl, 1952; Lehmann & Ban, 1997). Moreover, a proportion of medicated participants with schizophrenia have been shown to display eye tracking performance indistinguishable from neurologically intact participants on any specific measure of performance (including gain, CUS, BUS, SWJ, and AS, in an experiment with clearly sufficient experimental power to identify between-groups differences: Levy et al., 2000). Finally, reduced gain in comparison to neurologically-intact observers when tracking a target across a broad target velocity range.
(10°/sec to 36°/sec) has been shown in neuroleptic-naïve, first-episode schizophrenia patients (Hutton et al., 1998; 2001). These findings, supported by evidence suggesting no change in global eye tracking performance and/or gain in the weeks following instigation of neuroleptic treatment in patients (Campion et al., 1992; Kuffererle et al., 1990) or following short-term periods of medication withdrawal (Thaker, Ross, Buchanan, Adami & Medoff, 1999), clearly do not support the suggestion that the eye tracking disorder seen amongst individuals with schizophrenia is wholly caused by neuroleptic medications. However, it remains unclear as to whether the specifics of the tracking deficits seen amongst neuroleptic-naïve individuals are the same as those observed in those chronically treated with antipsychotics. For example, Hutton (et al., 2001) showed that gain was reduced (over target velocities of 10°/sec to 36°/sec) among medicated and medication-naïve first-episode psychosis patients, and among medication-free chronic (non-attenders for depot medications for at least 6 months) schizophrenia participants when compared with neurologically-intact participants, however, gain was significantly further reduced amongst individuals chronically treated with antipsychotics, even when age and symptom severity were statistically controlled. The frequency of CUS, in contrast, appeared unaffected by duration of medication in the Hutton (et al., 2001) study. Further, some studies have identified specific changes in saccadic involvement during pursuit following antipsychotic administration, with Rea, Sweeney, Solomon, Walsh and Frances (1989) showing an increase in the number of small-amplitude saccades, and a concomitant decrease in frequency of large amplitude saccades, correlating with increase in neuroleptic dosage. In support of this effect, Spohn, Coyne and Spray (1988), found an increase in the frequency of large-amplitude saccades when antipsychotic medication was discontinued, independent of changes in clinical state. While there appear to be certain specific exacerbations of existing deficits following administration of typical antipsychotic medication (simple dopaminergic agonists), there
is some suggestion that these may be further affected through administration of the atypical antipsychotic, clozapine: reducing gain, and increasing both CUS frequency and amplitude when compared with placebo or the typical antipsychotic, fluphenazine (Litman, Hommer, Radant, Clem & Pickar, 1994; Friedman, Jesberger & Meltzer, 1992). However, as has been noted by Hutton (et al., 2001), this effect may be a function of the sedative effects of this drug, mirroring the effect of other sedatives such as benzodiazepines on eye tracking, which may be particularly relevant in short-term crossover studies such as the Litman (et al., 1994) investigation. No investigation of the specific effects of other atypical antipsychotic medications on eye tracking in schizophrenia has yet been published.

In summary, the weight of evidence to date clearly suggests that antipsychotic medications are not responsible for the presence of eye tracking disruptions among participants with schizophrenia. However, there are indications that these medications have the potential to further exacerbate the existing deficit, or to influence specific aspects of the eye tracking system. As such, medication status remains an important consideration in studies of eye tracking in schizophrenia.

Medication-induced movement disorders

Antipsychotic medications have the potential to induce a number of different types of movement disorders as secondary consequences of their actions (Cunningham-Owens, 1999). There have been surprisingly few studies of such effects, which would appear particularly relevant given the potential for neuroleptic-induced Parkinsonian-like extrapyramidal effects, and the existing literature showing eye-tracking deficits in this
disorder (Waterson, Barnes, Graely & Collins, 1996; White, Saint-Cyr, Tomlinson & Sharpe, 1983). King, Mills, Mannion and Green (1999) showed that extrapyramidal movement symptoms in observers with schizophrenia correlated with the frequency of saccades during pursuit at high target speeds (40°/sec) but not at low to moderate velocities (16°/sec-27°/sec). Tardive dyskinesia is another possible neuroleptic-induced movement disorder, and characterised by abnormal, involuntary movements (Cunningham-Owens, 1999). Several studies have suggested an association between tardive dyskinesia and abnormalities of pursuit eye tracking in schizophrenia (Oepen, Thoden & Warmke, 1990; Spohn, Coyne, Lacoursiere, Mazur & Hayes, 1985; Spohn et al., 1988), however, these only identified very small relationships (tardive dyskinesia accounting for approximately 10% of the variance in eye tracking), and all employed EOG methods for recording eye tracking, a method which is highly sensitive to muscle artefact, which is the exact effect that would be expected to be increased in participants with tardive dyskinesia (Ross et al., 1998). Studies employing IR methods for eye tracking recording (a technique less sensitive to muscle movements), have found no relationship of tardive dyskinesia with either global qualitative measures or specific components of eye tracking (gain, CUS frequency and amplitude, BUS, or intrusive saccades: Thaker, Nguyen & Tamminga, 1989; Ross et al., 1998). Taking these findings together, there appears to be no substantial impact of neuroleptic-induced extrapyramidal movement disorder or tardive dyskinesia on eye tracking performance in schizophrenia, at least at the low to moderate target velocities commonly employed among studies in this area.

**Smoking**

Tobacco smoking is substantially more prevalent amongst individuals with schizophrenia in comparison to the general population (74-92% in various studies, compared with 35-
54% amongst psychiatric patients generally, and 30-35% of the general population), with some investigations suggesting that this may reflect mood-, cognitive- or medication-regulating functions (Goff, Henderson & Amico, 1992; Lohr & Flynn, 1992; Le Houezec, 1998). A provocative study by Sibony, Evinger and Manning (1988), showed a decrease in gain, and increase in saccadic involvement during pursuit following smoking of a single cigarette in neurologically intact individuals. However, this study involved just three participants, and a careful replication study (Thaker, Ellsberry, Moran, Lahti & Tamminga, 1991) showed no effect of smoking on qualitative quality of pursuit but a significant increase in SWJ frequency. However, this increased SWJ frequency, while not due to chance (statistically significant) was trivial in magnitude, with the occurrence remaining extremely infrequent (less than one per cycle). A recent study among observers with schizophrenia showed that smoking had a positive effect on pursuit gain (although this remained significantly lower than neurologically-intact control participants) as well as frequency of LS (reducing this to a similar frequency to control participants), but no effect on SWJ or AD frequency (Olincy, Johnson & Ross, 2003). Taken together, studies to date have shown that smoking exerts no substantial effect on either global or specific measures of eye tracking.

Temporal Stability and Age Effects

When considering the question of the stability of eye movement measures over time, the effect of changes due to normal ageing, acute- and chronic- medication effects, and of clinical state are all closely intertwined, and difficult to disentangle. Clearly, the identification of defects in eye tracking in medication-naïve and medicated first-episode patients (Hutton et al., 1998; 2001), remitted (Arolt, Teichert, Steege, Lencer & Heide, 1998), and chronic (King, Mills, Mannion & Green, 1999) observers with schizophrenia
all argue for the presence of a stable eye tracking deficit at a group level in schizophrenia, at least across the most commonly studied age range (late teens to late middle age). However, very few prospective studies have been carried out on this issue.

In terms of the stability or reliability of eye movement measures, global measures of eye tracking accuracy among participants with schizophrenia remain stable over the short-term course of acute treatment (4 weeks: Rea et al., 1989), medium term (9 months: Gooding, Iacono & Beiser, 1994), and longer durations (over two years: Sweeney et al., 1998), despite intervening changes in medication status and clinical state. Using more specific measures, Ettinger (et al., 2003), among neurologically-intact participants, demonstrated acceptable reliability of gain over a two month test-retest period, but only at moderate to high velocities (36°/sec to 48°/sec) and not at lower target speeds (12°/sec to 24°/sec). CUS frequency was reliable over a range of velocities (24°/sec to 48°/sec, but not 12°/sec), and AS frequency appeared reliable over all target velocities assessed (12°/sec to 48°/sec). Ettinger (et al., 2003) also showed that, while some of these measures did not reach commonly accepted levels of reliability, the differences in recordings over time did not reach statistical significance. Similarly, Rea (et al., 1989) provided indications that, while global measures of eye tracking may remain stable over a short-term period among observers with schizophrenia, identifiable changes may occur in the fine mechanics of the tracking process, such as changes in saccadic amplitude.

Considering eye movement measures over the long-term, amongst neurologically-intact participants, ageing causes a deterioration of smooth pursuit. Kuechenmeister, Linton, Mueller and White (1977) showed that qualitative global measures of pursuit performance were superior in younger (20-30 year) observers than older participants (aged 50 and above), although such differences did not reach statistical significant in their
study. Studies similarly examining differences between young and elderly, neurologically-intact, observers using more specific measures of tracking performance show that gain is reduced by ageing, with effects small at low target velocities (10°/sec) but progressively more affected with increasing target speed. In concert with this, saccadic frequency, largely relating to the presence of CUS, but also of intrusive SWJ, is increased among elderly participants, with such an effect largely independent of target velocity (Ciuffreda & Tannen, 1995). A recent careful study (Ross et al., 1999) with a moderately large sample size of neurologically-intact (n=64, age range 18-79 years) and schizophrenia (n=58, age range 18-70) observers, showed that, across both groups, gain reduced with age, particularly after 55 years, with a regression model suggesting that age accounted for approximately 19% of the variance in gain (assessed at the moderate target velocity of 17°/sec) in this sample. Consistent with this, CUS frequency was shown to increase with age, with age estimated as accounting for approximately 16% of the variance in this measure. Regression models also suggested that age accounted for approximately 19% of the variance in large amplitude (>4°) AS and small amplitude LS (1°-4°), the frequency of both of which increased with age.

In conclusion, there is evidence for a relative stability of global measures of pursuit performance over time, particularly across the age groups commonly examined in schizophrenia research (20s-50s). However, while age is clearly not a major contributor to eye tracking performance, it does exert a moderate influence on the specific components of eye tracking (gain, compensatory and intrusive saccades), and as such, merits consideration during studies of eye tracking performance.
While performance between individuals is highly variable, at a group level schizophrenia has been associated with a generalised reduction in neurocognitive function (Green, 1998). Moreover, again at a group level, particular deficits in sustained visual attention, as assessed by measures such as the Continuous Performance Task (CPT), occur amongst those with a diagnosis of schizophrenia (Nuechterlein, 1991), and there appears to be some overlap between the neural structures involved in visual attention to those involved in the control of eye movement (Buchel, Josephs, Rees, Turner, Frith & Friston, 1998). If the eye tracking deficit in schizophrenia is to be investigated, particularly as a measure of genetic liability for the diagnosis (Levy, Holzman, Mattysse & Mendell, 1993), then it is important to establish that the deficit is not simply a secondary consequence of generalised cognitive deficit or of a specific deficit in visual sustained attention.

Several studies have shown that the presence of increased distraction, through means of a simultaneous cognitive task (such as serial subtractions) can have deleterious effects on eye tracking performance, both among neurologically intact participants and patients with schizophrenia diagnoses (Brezinova & Kendell, 1977; Tomer, Mintz, Levy & Myslobodsky, 1981). Similarly, amongst both groups, the presence of visual distractors reduces gain, and increases AS frequency during eye tracking (Kaufman & Abel, 1986; Nolte, Moser, Arolt & Kompf, 1999). Likewise, methodological manipulations to enhance attention to the moving target (such as manipulating the colour or form of the stimuli and requesting that the observer monitors and reports each change) improves eye tracking performance both amongst those with chronic schizophrenia and neurologically-intact observers, increasing global pursuit quality, reducing AS frequency and CUS amplitude (but not CUS or SWJ frequency: Sweeney et al., 1994). Both qualitative and quantitative measures of global tracking performance among first-episode psychosis
patients are enhanced by such manipulations, to the extent where their performance is no longer distinguishable from control participants (Yee, Nuchterlein & Dawson, 1998).

In terms of sustained visual attention, while some studies have shown that global measures of eye tracking correlate with performance on the CPT, this relationship appears to be relatively small and to maximise with increasing difficulty of the attention task (explaining 20% or less of variance in eye tracking measures: Grawe & Levander, 1995; van den Bosch, 1984). Moreover, studies that have included CPT performance as a covariate have either shown that patients with schizophrenia displayed eye tracking disorder but did not differ from the comparison group on CPT performance (Nolte et al., 1999) or that dysfunctional pursuit remained apparent in patients even when CPT differences were statistically controlled (Stuve et al., 1997).

Addressing the influence of general cognitive function on eye tracking performance, Hutton (et al., 2004) have shown that eye tracking gain is uncorrelated with either Weschler Adult Intelligence Scale (Revised: WAIS-R) or National Adult Reading Test IQ scores among neurologically-intact or first-episode psychosis observers. Grawe and Levander (1995) similarly failed to identify any relationship between qualitative or quantitative measures of eye tracking quality and WAIS-R Similarities and Block Design subtests (measures closely related to the WAIS-R general intelligence factor). Similarly, no relationships were identified between global measures of eye tracking and measures of spatial working memory, planning, set-shifting or divided attention (Grawe & Levander, 1995; Hutton et al., 2004). Examining relationships with more specific measures of eye tracking performance, Friedman, Kenny, Jesberger, Choy and Meltzer (1995) identified no relationships between performance on neuropsychological measures (Wisconsin Card Sort: WCST; Controlled Oral Word Association: COWAT; and Digit Symbol) with
frequency of intrusive saccades (SWJ and AS). However, relationships between the adaptive components of tracking (gain and CUS) were identified with the COWAT and Digit Symbol (but not perseverations on the WCST), although these were moderate, accounting for 25 percent of shared variance or less.

In sum, these findings clearly suggest that the presence of eye tracking dysfunction among individuals with schizophrenia is not simply a secondary effect of generalised cognitive dysfunction. Moreover, deficits in attention are not responsible for the eye tracking deficit, as pursuit dysfunction occur, independent of CPT performance, and while attentional manipulation may improve eye tracking performance, this effect occurs among both those with diagnoses of schizophrenia and neurologically-intact controls. Finally, while there have been some interesting relationships identified between speeded neuropsychological variables (COWAT and Digit Symbol) and the adaptive components of the eye tracking system amongst observers diagnosed with schizophrenia, no such relationships have been identified with the disinhibitive aspects of the system (intrusive saccades) in such participants.

Open questions in regard to eye tracking deficits and schizophrenia

To this point in this brief overview, the discussion of the eye tracking performance in schizophrenia has been restricted to examination of particular deficits identifiable at a group level. There is certainly abundant evidence to suggest that among individuals receiving a diagnosis of schizophrenia as a group, dysfunctions in eye tracking are a robust and reliable effect: eye tracking disorders can be identified among those at genetic risk for the diagnosis (Ross, Hommer, Radant, Roath & Freedman, 1996; Iacono,
Morreau, Beiser, Fleming & Lin, 1992), within medication-naïve individuals upon their first admission for the experience of symptoms diagnosable as schizophrenia (Hutton et al., 2001), and remain present despite fluctuations in clinical state (Gooding, Iacono & Beiser, 1994; Schlenker & Cohen, 1995; Yee et al., 1998): through periods of acute psychosis (Iacono et al., 1992), to relative remission (Arolt, Teichert, Steege, Lencer & Heide, 1998), and over a chronic illness course (King et al., 1999). However, as was discussed in the early stages of this manuscript, it is very clear that a diagnosis of ‘schizophrenia’ is certainly not a homogeneous grouping: there are only moderate levels of concordance between the DSM and ICD definitions of the disorder (Daradekeh et al., 1997; McGorry et al., 1995); these classification schedules comprise residual elements of classical conceptions of the diagnosis, without fully endorsing any (Maj, 1998) and without any existing pathological marker to validate them (McGorry, et al 1992; Monti & Stranghellini, 1996); and the polythetic nature of the current DSM and ICD schedules allow individuals without a single common symptom to receive the same diagnostic categorisation (Jablensky 1999; Rosenman et al., 2000). The DSM itself notes that the current classification schedules are a pragmatic consensus response to imperfect knowledge in regard to aetiology, that the diagnostic categories hence remain open to revision, and that it can not be assumed that individuals sharing a diagnosis are homogenous even in regard to the defining diagnostic criteria (APA, 1994). Given these limitations, it is inappropriate to discuss any identified deficit as if it is present in all those with a particular diagnosis, and instead important to identify the boundaries and correlates of deficits that display potential as genetic or validating markers, such as is the case for eye tracking disorder in ‘schizophrenia’.

From even the initial studies in the modern age of eye-tracking performance research in schizophrenia it was apparent that dysfunctional tracking was common, but not
ubiquitous, amongst those with the diagnosis (Holzman et al., 1973; 1974). The presence of eye tracking disorder is often defined on the basis of qualitative, global assessments of tracking quality, using arbitrary distinctions to define ‘normal’ and ‘disordered’ tracking (such as a rating above a mid-point on the five-point Benitez, 1970 or Shagass, Roemer & Amadeo, 1974 scales: Friedman et al., 1995; Lees Roitman, Keefe, Harvey, Siever & Mohs, 1997; Malaspina et al., 2002). These methods tend to identify approximately 50% of first-episode, mixed, or chronic samples of individuals with schizophrenia as experiencing ‘disordered’ eye tracking (Keefe et al., 1989; Levy et al., 2000; Malaspina et al., 2002). Other authors have attempted to define ‘disordered’ eye tracking on the basis of the (similarly arbitrary) cut-off point of two standard deviations away from the mean of control group performance on quantitative measures such as root mean square (RMS) deviation between target and eye waveforms, the natural logarithm of the signal to noise ratio (both global but quantitative measures of pursuit quality), or gain and have identified a similar (Allen, 1997; Sweeney et al., 1994) or lower (Ross et al., 2002) rate of ‘disordered’ eye tracking. Over the last decade, several research groups have applied a more statistically rigorous approach to examining the prevalence of ‘disordered’ eye tracking disorder among those with a diagnosis with schizophrenia. Applying the technique of mixture analysis, multiple independent studies have shown that the distribution of measures of global eye tracking performance (either RMS error or gain) among those with a schizophrenia diagnosis is more reflective of a population characterised by a mixture of two normal distributions, rather than of a population with a single normal distribution of performance (Iacono et al., 1992; Ross et al., 1992; 1996; 2002). Such a finding has also been shown to apply to first degree relatives of those with a diagnosis of schizophrenia (Iacono et al., 1992; Ross et al., 2002). The presence of mixture suggests that there are two fundamentally different underlying phenomena in the eye tracking performance data amongst samples of patients with schizophrenia. When
separated into groups on the basis of these distributions, depending on the performance measure used in the analysis, 21-34% of those with schizophrenia fall into an ‘eye tracking disordered’ group (Ross et al., 1996; 1997; 2000; 2002), and the remaining patients show no difference to neurologically-intact controls on any eye movement measure (gain, compensatory or intrusive saccades: Levy et al., 2000; Ross et al., 1997, although see: Ross et al., 1996).

Given the promising genetic links for eye tracking disorder (Katsanis, Taylor, Iacono & Hammer, 2000; Calkins & Iacono, 2000; Levy & Holzman, 1997; Iacono, 1998), then it would be beneficial from a methodological and statistical viewpoint for studies to reduce the ‘noise’ in their analyses by treating eye tracking performance in a manner consistent with its nature: rather than trying to understand the deficit by examining differences between individuals with schizophrenia and neurologically-intact controls, if eye tracking performance among patients is indeed reflective of two populations, only one of which has abnormal eye tracking, then more sensitive tests and more reliable results will be gained by examining the dysfunctional group alone (Ross et al., 1996). One line of research following such an approach has been to examine whether there are any variables that differentiate between those individuals with a diagnosis of schizophrenia that do, and do not, produce defective eye tracking, in order to define the symptomatological boundaries of these sub-groups.

One particularly promising point of differentiation has been the presence of the ‘deficit syndrome’ amongst those experiencing eye tracking disorder. The deficit syndrome is defined on the basis of persistent ‘negative’ symptoms that are proposed as being idiopathic to the illness rather than as a secondary consequence of medication side-effects or withdrawal due to depression or psychotic features, and there is emerging
evidence of distinct patterns of course, biological correlates and treatment response for those classified as experiencing the deficit syndrome ‘subtype’ of schizophrenia in comparison to others with a diagnosis of schizophrenia (Kirkpatrick, Buchanan, Ross & Carpenter, 2001). In a study of the effect of tardive dyskinesia on eye tracking performance, Thacker, Kirkpatrick, Buchanan, Ellsberry, Lahti and Tamminga (1989) first noted that patients with the deficit syndrome produced a greater number of saccades during pursuit than others diagnosed with schizophrenia. Some years later, Ross (et al., 1996) also identified a tracking dysfunction (deficient eye acceleration during the early stages, but not the maintenance phase, of closed-loop pursuit) that was peculiar to those patients diagnosed with the deficit syndrome. In a subsequent study (Ross et al., 1997), applying mixture analysis to RMS error values when tracking a slow velocity target, it was shown that the majority of deficit syndrome patients were also classified into the eye tracking disordered subgroup: 9 of the 12 deficit patients in comparison to 9 of the 40 non-deficit schizophrenia patients were classified in the eye tracking disordered subgroup (and hence half of those with eye tracking disorder were also classified as having the deficit syndrome). This association between eye tracking disorder classification and the deficit syndrome was replicated by an independent group (Malaspina et al., 2002, with 8 of their 11 deficit syndrome patients classified as eye tracking disordered using global qualitative ratings, compared to 6 of 20 non-deficit patients). However, two subsequent studies with slightly larger sample sizes failed to identify any differences between deficit and non-deficit schizophrenia patients in terms of gain, CUS, SWJ or AS rate across a range of target velocities (9°/sec to 24°/sec: Hong et al., 2003; Nkam et al., 2001). Given these mixed findings, the potential of an association between the deficit syndrome and eye tracking disorder appears to be a promising but open question.
While the deficit syndrome refers to a stable, trait-like, presence of negative-type symptoms, other groups of symptoms, such as thought disorder may also remain relatively stable over a longitudinal course for some individuals (Marengo & Harrow, 1997; Metsanen, Wahlberg, Hakko, Saarento & Tienari, 2005). One of the earliest studies of the modern literature in this area found that participants with schizophrenia classified as eye tracking disordered on the basis of qualitative ratings experienced higher levels of thought disorder than patients with normal tracking performance (Holzman et al., 1974). While this finding had been subsequently replicated among chronic schizophrenia patients (Keefe et al., 1989) and in mixed samples of schizophrenia, schizophrenia-spectrum, and affective-psychosis patients (Solomon, Holzman, Levin & Gale, 1987), this relationship has attracted little subsequent research attention.

An alternative approach to determining whether there are any variables that differentiate between those individuals with schizophrenia diagnoses that also experience eye tracking dysfunctions from those that do not is to apply a dimensional methodology. Some authors consider that the examination of relationships between symptoms (considered as state variables) and the enduring eye tracking dysfunction (a possible trait variable) may be undermined due to the differing rates of change of the two variables involved (Solomon et al., 1987). However, it is important to consider that syndromes, correctly defined, are groups of symptoms that ebb and flow together independently of changes in other symptom groups, with the suggestion that these syndromes thus represent the level of functioning of distinct pathological processes (Buchanan & Carpenter, 1994; Ratakonda et al., 1998). So conceptualised, if the syndrome or dimensional symptom groupings are valid, then these variables, rather than simply useful as presenting a cross-sectional portrait of an individual’s current clinical state, provide a representation of putative pathological processes (Rosenman et al., 2000). If the diagnostic entity defined
as ‘schizophrenia’ is indeed a complex of multiple underlying pathological processes, then it may be that one (or more) of these is closely related to the pathology underlying eye tracking dysfunction, which may contribute to the explanation of why only a small proportion of those diagnosed with ‘schizophrenia’ experience eye tracking dysfunction, despite the strong genetic links for this defect.

Adopting the two-factor conception of schizophrenia (Crow, 1980), early studies applying the dimensional methodology identified correlations between both the degree of ‘positive’ and ‘negative’ symptom dimensions and global measures of eye tracking performance, although the total degree of expressed symptomatology was unrelated to performance (Katsanis & Iacono, 1991). Inverse relationships of moderate magnitude (explaining around 16% shared variance) were identified between the degree of positive symptoms (defined through the SAPS sum score or PSE subscores) and global measures of eye tracking performance among both mixed and chronic patient samples (Bartfai, Levander, Ryback, Begeren & Schalling, 1985; Katsanis & Iacono, 1991; Kelly et al., 1990). However, a more recent study using a moderately large (n=78) and demographically more representative patient sample identified only a smaller magnitude (6% shared variance) and positively-related correlation between PANSS-defined ‘positive’ symptomatology and global eye tracking performance (Lee, Williams, Loughland, Badison & Gordon, 2001), and other studies have failed to identify any associations between the ‘positive’ symptom dimension and eye tracking (Lees Roitman, et al., 1997; Sweeney et al., 1992; 1994). Consistent with the finding of a relationship between eye tracking and the presence of the deficit syndrome (Ross, 2000), moderate (4-30% shared variance), positive relationships between eye tracking and the degree of ‘negative’ symptoms (variously defined by the SANS sum score, BPRS blunting subscale or PANSS negative subscale) have been identified in acute, mixed and chronic schizophrenia
cohorts (Blackwood, Clair, Muir & Duffy, 1991; Katsanis & Iacono, 1991; Lees Roitman et al., 1997; Simons & Katkin, 1985; Sweeney et al., 1992; 1994). Such relationships have been shown both for global (RMS error or qualitative ratings: Katsanis & Iacono, 1991; Lees Roitman et al., 1997; Sweeney et al., 1994) and specific assessments of eye tracking performance (gain, CUS and AS frequency: Sweeney et al., 1992; 1994). However, there have also been numerous failures to identify such relationships in first-episode (Gooding, Iacono & Beiser, 1994; Iacono et al., 1992; Sweeney et al., 1992) or mixed schizophrenia populations (Flechner et al, 1997; Gaebel & Ulrich, 1988; Kelly et al, 1990; Keefe et al, 1989; King et al., 1999; Lee et al, 2001; Lieberman et al., 1993; Sweeney et al., 1998; 1999).

While it became apparent as early as the mid-1980s (Bilder, Mukherjee, Reider & Pandurangi, 1985; Liddle, 1987) that the manifestations of schizophrenia were too complex to be described simply in terms of ‘positive’ and ‘negative’ syndromes (Lezenweger, Dworkin & Wethington, 1989), just two studies to date have examined the relationship between eye tracking performance and the more favoured three-dimensional conception of schizophrenia (dividing the two-factor ‘positive’ symptom dimension into ‘reality distortion’ and ‘disorganisation’ syndromes: APA, 1994). Both of these have included large cohorts of either first-episode (n=109, Hutton et al., 2004) or population-representative mixed in- and out- patients (n=78: Lee et al., 2001), and have both shown the degree of ‘disorganisation’, but not ‘reality distortion’ or ‘negative’ symptom dimensions were related to eye tracking performance. Hutton (et al., 2004) identified a small but significant relationship between the degree of disorganisation symptoms (defined by the sum of the SAPS ‘bizarre behaviour’ and ‘positive thought disorder’ global subscale scores: \( r=0.21, p<0.05 \)) and eye tracking gain (averaged over target velocities of 10°/sec to 36°/sec), but near zero-order relationships for both reality distortion (SAPS hallucinations and delusions: \( r=0.09, \text{ns} \)) and negative (SANS subscales:}
symptom dimensions amongst a sample of 109 first-episode schizophrenia patients. While the statistically significant relationship is of small magnitude, this is an important finding in light of the repeated failure to identify any syndrome relationships using the two-factor dimensional model among first-episode patients (Gooding et al., 1994; Iacono et al., 1992; Sweeney et al., 1992) despite the presence of eye tracking disorder amongst a proportion of participants in each of these studies. The Lee (et al., 2001) study of 78 in- and out- patients directly compared the relationships between syndromes and global eye tracking performance (RMS error) using the two- and three-factor models of the symptomatology of schizophrenia. While small relationships between eye tracking and both positive (PANSS positive subscale: $r=0.23$, $p<0.05$) and negative (PANSS negative subscale: $r=0.20$, $p=0.08$) were identified using the two-factor model, when these same symptoms were re-grouped in line with the three-factor model, relationships between eye tracking and the ‘disorganisation’ dimension were moderately strong (PANSS items ‘conceptual disorganisation’, ‘stereotyped thinking’, ‘difficulty in abstract thinking’ and ‘excitement’: $r=0.39$, $p<0.001$), and those for ‘reality distortion’ (PANSS items ‘suspiciousness’, ‘hostility’, ‘grandiosity’, and ‘delusions’: $r=-0.06$, $p=0.61$) and ‘psychomotor poverty/negative’ (PANSS items ‘blunted affect’, ‘emotional withdrawal’, ‘social withdrawal’, ‘lack of spontaneity of conversation’ and ‘poor rapport’: $r=0.06$, $p=0.62$) were reduced almost to zero-order relationships. In support of such findings, an early study by Solomon (et al., 1987) identified a significant relationship between global eye tracking performance and degree of thought disorder. While this relationship was small ($r=0.21$, $p<0.05$, 4.2% shared variance), this may have been deflated by the mixed participant sample of schizophrenia and affective psychosis patients as the latter group may have only experienced eye tracking dysfunctions as a secondary consequence of medication (Lithium: Levy et al., 1985).
In the first study of this thesis, it was shown that the symptom groupings defined as ‘syndromes’ in the two- and three- factor models of symptomatology do not hold together well when examined at a symptom item level. Beyond the Solomon (et al., 1987) study, just two other authors have investigated the relationship between eye tracking performance and symptom groupings more refined than those applied within the two- and three- factor models. Malaspina (et al., 2002) showed that only the alogia items from the Schedule for the Deficit Syndrome (Kirkpatrick, Buchanan, McKenney, Alphs & Carpenter, 1989), and not those measuring social dysfunctions (diminished social drive, sense of purpose or curbing of interested) or emotional blunting (diminished emotional range or restricted affect) were related to global eye tracking performance among a mixed schizophrenia sample (n=31). Consistent with this, Ciuffreda, Alpert, Blackstone, Fudge and Thaler (1993), identified strong relationships for SANS ‘alogia’ and ‘attentional impairment’ subscales and the frequency of saccades during eye tracking (around 25% shared variance respectively), but no such relationships for other SANS subscales (‘avolition/apathy’, ‘anhedonia/asociality’ or ‘affective flattening’) within a chronic schizophrenia sample (n=16).

This aim of this component of the current thesis is to determine whether external validation of the eleven factor symptom model can be derived through the identification of specific relationships with measures of eye tracking performance. As noted in the second study in this manuscript, if significant correlations between measures of eye tracking and symptom groupings under the proposed eleven-dimension model of symptomatology can be identified that are not apparent when the more compact three- or five- factor symptom models are applied, or if symptom relationships that are identifiable with these compact symptom models are not consistent across each of the refined subdivisions of that component in the eleven-factor model (for example, the concept of
‘disorganisation’ in the three-factor model is subdivided into ‘bizarre behaviour’, ‘conceptual disorganisation’ and ‘hostility’ in the eleven factor model, and for these symptom subgroupings to display differential relationships would be incompatible with the assumptions of the three-factor model), then this would provide some external validation for that aspect of the eleven-dimensional model.

On the basis of the findings of the very small number of studies examining correlations between symptom groupings (‘syndromes’) and measures of eye tracking, it is very difficult to hypothesise particular relationships between eye tracking measures and the symptom dimensions in the proposed eleven-factor model. From the existing studies, the most likely candidates are the groupings ‘negative signs’, ‘conceptual disorganisation’ and ‘cognitive dysfunction’. The ‘negative signs’ grouping is one of the three sub-groupings of ‘negative’-type symptoms defined in the eleven-factor model, and it is proposed as a correlate of eye tracking performance because, while there have been mixed findings in regard to the relationship between negative-type symptoms (broadly defined) and eye tracking (Katsanis & Iacono, 1991; Lee et al., 2001), two studies using tightly-defined symptom groupings identified significant relationships between alogia (a component of the ‘negative signs’ grouping in the eleven-factor model) and eye tracking, but no such relationships for symptoms of ‘social dysfunction’ (social and emotional withdrawal: Ciuffreda et al., 1993; Malaspina et al., 2002, which is treated as an independent grouping in the eleven-dimension model). The eleven-dimension model symptom grouping of ‘cognitive dysfunctions’ is hypothesised as a correlate of eye tracking as one of its component symptoms, within the SANS ‘attention’ subscale was identified as a strong correlate of tracking (Ciuffreda et al., 1993), and another of its component symptoms contributed to the ‘disorganisation’ grouping, which was identified as a strong correlate of performance in the Lee (et al., 2001) study. Similarly, the ‘conceptual disorganisation’
grouping in the eleven-factor model is hypothesised as a correlate of eye tracking performance, as these symptoms formed the core of the ‘disorganisation’ dimension which was significantly related to eye tracking performance in both the Hutton (et al., 2004) and Lee (et al., 2001) studies, and these symptoms alone were significantly correlated with eye tracking in the Solomon (et al., 1997) study.

The majority of studies examining relationships between ‘syndromes’ and eye tracking have applied global measures of performance, such as RMS error, signal to noise ratios, or qualitative assessment of tracking. Several studies have shown that these global measures of eye tracking in schizophrenia actually reflect a multivariate process (Levy, et al., 2000; Ross, Thacker, Buchanan, Lahti & Medoff, 1998), measuring both the interactive involvement of the pursuit and saccadic systems in eye tracking (reflected by gain and compensatory CUS), and also the degree of saccadic disinhibition (reflected by intrusive saccades such as SWJ, AS and LS). Given the paucity of research examining relationships between symptom groups and eye tracking performance, only tentative speculations can be made as to whether the hypothesised symptom groupings (‘negative signs’, ‘cognitive dysfunction’ and ‘conceptual disorganisation’) are related to the interactive tracking component, or to the disinhibitive aspect, of the eye tracking deficit in schizophrenia.

Ross (et al., 1997; 2000) has noted similarities in the neural correlates of abnormal smooth pursuit and of enduring negative symptoms, in terms of reduced metabolism in frontal and parietal association cortex (Ross et al., 1995; Tamminga et al., 1992) and abnormalities of the caudate nucleus (Buchanan et al., 1993; Ross et al., 1995). As to whether these may relate to the interactive tracking aspect or the disinhibitive aspect of eye tracking performance, findings have, to date, been mixed: Malaspina (et al., 2002)
suggested that alogia was related to global eye tracking performance; Ciuffreda et al., 1993) showed relationships for both SANS alogia and attention subscales with the frequencies of saccades during pursuit (however, it has been shown that 70-80% of all saccades during pursuit are compensatory CUS: Levy et al., 2000); and Sweeney et al., 1992) identified relationships between the global SANS score and gain and CUS, as well as AS frequency. Given that the latter was the only study of symptom grouping-performance relationships to date applying specific quantitative measures of eye tracking, it is proposed that if the ‘negative signs’ and ‘cognitive dysfunction’ groupings of the eleven-factor model are related to eye tracking performance, they will be related to gain, and hence, compensatory positive-direction saccade frequency (given that they are sub-groupings of ‘negative’ symptoms, broadly defined).

In contrast, there is some evidence to suggest that the other hypothesised correlate of eye tracking performance, the degree of ‘conceptual disorganisation’ (positive formal thought disorder) may be related to the disinhibitive aspect of the eye tracking disorder in schizophrenia. This has arisen from the finding of a relationship between the degree of errors on the antisaccade task and the degree of thought disorder symptoms in participants with schizophrenia (Shiraishi, Kamijo & Kojima, 2000). The antisaccade task requires the suppression of reflexive saccades for success, and it has been proposed that the failure of saccadic suppression on this task may be another manifestation of the disinhibition of saccades identified among those with schizophrenia diagnoses during eye tracking (Matsue et al., 1986) and fixation (Amador et al., 1991) tasks (Henderson, Crawford & Kennard, 1996).

In summary, while there is currently only a small amount of literature in regard to the relationship between symptom groupings and eye tracking performance in schizophrenia,
it is hypothesised that the ‘negative signs’ and ‘cognitive dysfunction’ groupings in the proposed eleven-factor model of symptomatology will be related to the interactive compensatory components of smooth pursuit eye tracking (gain and positively-directed CUS); and the ‘conceptual disorganisation’ grouping will be related to the saccadic disinhibition component of eye tracking performance (largely reflected by saccades made in the direction opposite to the target).
Method

Participants

Clinical participants were a subset of the same cohort as those hundred individuals contributing to the first study in this series, whose characteristics are described in detail in that section. Ninety-five individuals from this group participated in this study, with those five individuals from the full cohort excluded due to the fact they were currently receiving pharmacotherapy with lithium or phenelzine sulphate, as these medications may induce eye movement dysfunctions (Gooding, Iacono, Katsanis, Beiser & Grove, 1993; Levy & Holzman, 1997; Levy et al., 1985). In brief, of the 95 clinical participants contributing to this component of the study, 83 had a current DSM-IV (American Psychiatric Association, 1994) diagnosis of schizophrenia, and the remaining 12 were diagnosed as experiencing schizoaffective disorder. Participants were recruited from a range of in- and out-patient services and community treatment centres. Other than receiving treatment with the aforementioned medications, exclusion criteria included use of illicit psychostimulant drugs in the preceding month, or any neurological illness or injury within the preceding two years. The 77 male and 18 female participants had a mean age of 33.8 years (SD=9.7, range 19 to 69 years), and an average of 10.7 years of education (SD=2.0, range 6 to 16 years). The mean duration of diagnosis was 12.3 years (SD=9.8, range 0 to 46 years), and the majority of these participants could be classified as experiencing chronic schizophrenia, with 86 participants experiencing symptoms for two years or more and 45 for more than ten years. At the time of interview, 23 inpatients were either nearing the end of their stay on an acute psychiatric ward or residing in a psychiatric rehabilitation facility, with the remaining 72 participants receiving treatment from either community mental health centres or general medical practitioners. All but
four participants were receiving treatment with antipsychotic medications at the time of interview (24 receiving ‘typical’ dopamine antagonising antipsychotics, 81 ‘atypical’ mixed serotonin-dopamine antagonising medications), with the sample receiving a mean chlorpromazine equivalent of 463.9mg/day (SD=260.5, range 0-1178 mg/day). Twenty-two participants were receiving benzodiazepines as part of their daily medication or using them pro te nata, with the benzodiazepine equivalence for the total sample being 4.3 mg/day of diazepam (SD=15.9, range 0-125 mg diazepam/day; 18.4 mg/day of diazepam amongst those 24 individuals receiving such medications). Fourteen individuals were receiving anticholinergic medications such as benztropine mesylate or benzhexol hydrochloride for treatment of antipsychotic medication-induced movement disorders. A further 12 participants were receiving the mood-stabilising agents carbamazepine or sodium valproate either for the treatment of psychiatric symptoms or for the control of epilepsy. Statistical comparisons between this group of 95 participants and the five that were excluded from this phase of the study found no statistically significant differences (p<0.05) between these groups.

A group of 102 neurologically-intact individuals, largely drawn from a university population, were also examined for the provision of comparison data. This group consisted of 74 males and 28 females, with a mean age of 32.3 years (SD=9.0 years, range 18 to 53 years) and an average of 13.1 years of education (SD=1.8, range 10-19 years). Exclusion criteria were consistent with those applied to the clinical cohort. Ten of these participants had experienced a clinical mood disorder (cyclothymia, n=1; major depressive episode, n=6; post-natal depression, n=1; manic episode, n=1; panic disorder, n=1) of some description at some stage of their lives, with one other experiencing reactive acute stress disorder. Three participants were currently receiving treatment with antidepressant medications, one with benzodiazepines taken pro te nata (although they had
not taken them in the 48 hours prior to assessment) and one was receiving sodium valproate as a prophylactic for epilepsy.

There were no significant differences between the clinical and the control group in terms of sex (81% vs. 73% male respectively: $\chi^2_1=1.98$, $p=0.18$) or age (mean 33.8 vs. 32.3 respectively: $F(1,195)=1.34$, $p=0.25$), the variables most likely to impact on eye movements (Kuechenmeister et al., 1977). It should be noted, however, that the control group showed statistically superior performance on a number of variables pertaining to general intellectual functioning: a significantly greater number of years of education (13.1 vs 10.7 years respectively: $F(1, 195)=80.23$, MSE=87.3, $p<0.001$); a higher mean WAIS-III vocabulary subtest scaled score (13.7 vs. 8.6 respectively, $F(1, 194)=139.4$, MSE=9.2, $p<0.001$); and a higher National Adult Reading Test Predicted Full-Scale IQ (113.9 vs. 103.2 respectively: $F(1,192)=49.98$, MSE = 111.7, $p<0.001$).

All participants had normal or corrected to normal vision.

**Apparatus**

The target stimulus was a small circular spot with a diameter 0.19° of visual angle at a viewing distance of 1.5 metres. The target spot was generated by a uniphase neon-helium gas laser which was controlled by a General Scanning Optical Scanning Head (Model XY0507V X-Y Optical Scanning Head: General Scanning, Inc.) and Controller unit (Model DSC2005 Series Digital Scanning Controller: General Scanning, Inc.). The target stimulus was back-projected on a large opaque projection screen (38.6° x 48.5°) with a luminance of 0.8 cd/m² against a background of 0.2 cd/m². Binocular eye movements were recorded (although only data from the right eye was used for analysis) using an
infra-red limbus reflection device (IRIS, Skalar Medical, Netherlands) with a linear range of \( \pm 10^\circ \), with 2 minutes of arc optimal resolution. Eye and target position signals were sampled at 100 Hz with 12-bit resolution, and a hardware anti-aliasing filter with cut-off frequency of 100 Hz was used to filter eye position. Target stimuli were controlled by a modified REX (Real-time Experimentation platform) data acquisition and analysis system (Hain, 1995) running on a PC platform.

**Method**

For clinical participants, collection of data in relation to eye movements was made in the third of three 1.5 to 3 hour sessions during which data for all three phases of the current study were collected. During this session, eye movement data was collected first, followed by the computer-based neuropsychological tasks (reaction time, continuous performance task and finger tapping) along with any other outstanding tests as appropriate.

Control participants were assessed in a single session of approximately one hour duration. Following a discussion of demographics and relevant medical and psychiatric history, participants were administered the Vocabulary subtest of the WAIS-III as an index of general intellectual ability. Subsequently, participants were assessed on the finger-tapping, simple reaction time and continuous performance tasks using the same method and instructions applied to the control group.

The procedure for the collection of eye movement data was the same for all participants. Individuals were comfortably seated 1.5 metres away from a stimulus projection screen. Their head position was controlled by a head-rest in order to eliminate the possibility of
vestibulo-ocular movements contributing to tracking of the stimulus (Warren & Ross, 1998). All recording took place in an almost totally darkened room, as it has been shown that eye tracking performance in among those with schizophrenia may be affected by ambient light level, with performance best in dark testing conditions (Pivik, Bylsma & Cooper, 1988; Pivik, 1991). Calibration data from fixations at a central point and at ±10° of visual angle from central fixation were used to convert the digitised recording of each participant’s infra-red sensor data to excursion of eye movements. The horizontal linear pursuit task required participants to visually track the position of a laser point which was oscillating horizontally with a triangular waveform of an amplitude of 20° of visual angle (±10° of visual angle from a central fixation point). The stimulus moved at constant velocity, and data was recorded at speeds from 5 to 35 degrees of visual angle per second (deg/sec) in 5 deg/sec steps. Five tracking cycles were recorded for each velocity condition, for a total recording time of 80 seconds. Participants also completed four other eye movement paradigms (assessing reflexive saccades, antisaccades, and tracking of sinusoidal and foveofugal / foveopetal step-ramp stimuli), however, this information will be reported in studies separate to this manuscript.

Data Analysis

Raw eye movement data was analysed using the REX eye movement analysis program and exported to Matlab for further analysis. Eye blinks during saccadic pursuit were identified through manual examination of the eye position and velocity recordings, and excluded from subsequent analyses. The following parameters were calculated: dual-mode pursuit velocity, dual-mode pursuit gain, single-mode pursuit velocity, single-mode pursuit gain, number of positive saccades, number of negative saccades, and a qualitative rating of pursuit integrity. Each of these are defined as follows: ‘dual-mode’ pursuit velocity...
refers to the average velocity of the eye at each target frequency, with any periods of eye
blink removed. As such, this reflects the combined capacity of the smooth-pursuit and
saccadic systems to together keep pace with the target stimuli. *Dual-mode pursuit gain* was
the ratio of the average dual-mode pursuit velocity to that of the target. *Single-mode pursuit
velocity* was the average velocity of the eye at each target frequency, with any periods of
eye-blink and any period of saccadic system activity removed. Saccadic activity was
identified by an algorithm that identified any periods of eye movement greater than 60°/s
over a spatial distance of 0.2 degrees of arc during pursuit, and was verified through
manual examination of the eye movement recording. This variable is thought to reflect
the performance of the smooth-pursuit system on its own in tracking of the target
stimulus. *Single-mode pursuit gain* was the ratio of the average single-mode pursuit velocity
to that of the target. *Positive saccades* were identified as any periods of eye velocity greater
than 60°/sec over a spatial distance of 0.2 degrees of arc made in the same direction as
the target, during pursuit. Positive saccades will primarily reflect compensatory catch-up
saccades, which represent 70-80% of all saccadic activity during eye tracking and occur at
increased frequency among observers with schizophrenia when compared with
neurologically-intact controls (Levy et al., 2000). Intrusive saccades in a positive
direction, primarily SWJ and AS, together represent 4-8% of all saccadic activity during
pursuit but do not appear to be more common among schizophrenia patients than
controls (Levy et al., 2000; Sweeney et al., 1994). Small amplitude AS (1°-4°), classified as
LS by Ross and colleagues do occur at greater frequency among observers with
schizophrenia than control observers, but are even less common than AS, and as such
this low frequency means that they will contribute little variance to the frequency of
positively-directed saccades (Ross et al., 1999; 2001; 2002). The majority of variance in
the positive saccade variable will therefore be contributed by compensatory CUS. *Reversal
saccades* were defined on the same velocity and distance criteria as positive saccades,
although only if the saccade produced was in the opposite direction to the target. Reversal saccades will reflect a combination of compensatory back-up saccades and intrusive SWJ. Compensatory BUS comprise 12-20% of all saccadic activity during eye tracking, but, like the less frequent SWJ (representing 4-6% of saccadic activity) do not appear to occur at greater frequency among observers with schizophrenia than control observers (Fletcher et al., 1997; Levy et al., 2000). The variance in reversal saccades will, then, be a mixture of compensatory (BUS) and inhibitory (SWJ) components, however, the influence of intrusive saccades will be greater in this variable relative to that in the measure of positive saccades. Finally, qualitative assessments of the quality of overall pursuit at the target velocities of 5, 10 and 15 deg/sec were made using a scale from 1 (best) to 4 (worst) using exemplars provided by Benitez (1970). The distribution of performance on each of these variables at each of the target velocities were examined for normality and transformed where appropriate as normal distribution of these variables would facilitate the accurate calculation of regression parameters.

Stepwise linear regression analyses were used to determine whether dimensions of the three-, five- or eleven- factor symptom models examined in the current study emerged as significant predictors of performance on the eye movement tasks. The three- and five-factor models of symptoms were built from the largest or most comprehensive studies in their respective literature (Andreasen et al., 1995 and Greube, Bilder & Goldman, 1998 for the three-factor model using the SANS and SAPS; and Lindenmeyer et al., 1995 and White et al., 1997 for the five-factor model using the PANSS) and extended through a rational correlational process to include those symptoms from the SANS, SAPS, PANSS and BPRS-E used in the development of the eleven-factor model in order to generate a fair comparison between symptom models. This process is discussed in detail in the Second study of this thesis.
Prior to the regression analysis process, a series of variables that may potentially relate to performance on each of the eye movement dependent measures (as identified from the prevailing literature: e.g. Levy & Holzman, 1997; including age, years of educational experience, chlorpromazine equivalents of current antipsychotic medication, duration of illness, visual attention over 2.5 minutes as indexed by the sensitivity index of the Continuous Performance Task Identical Pairs version, and the degree of extrapyramidal symptoms experienced as indexed by the Simpson & Angus, 1970, scale) were examined for such relationships and where these were notable (p<0.1) these were forced into the regression equations prior to the stepwise inclusion of symptoms under any of the symptom models to ensure that the variance explained by symptoms would be distinct from any of these well-recognised sources. Stepping criteria was p<0.05 for entry and p>0.10 for removal from the regression equations. In each instance, the data was carefully examined to ensure that the assumptions underlying the regression technique were met: the residuals under the predicted model (the difference between the true score and the score predicted by the model) tested for normality, and residuals with absolute standardised values greater than 2.5 investigated to determine whether they had notable leverage on the regression model produced; multicollinearity issues were explicitly tested using tolerance values and the condition index; with issues of linearity between variables and homoscedasticity of residuals examined graphically. Where significant relationships between symptoms and eye movement variables were identified through regression, relationships between individual measures and the symptoms involved were examined in more detail.

To examine relationships between items, initially Spearman’s Rank correlation coefficients were calculated, as this technique does not rely on the assumption of normal
distribution of items, which is relevant given that clinical data distribution tends to be positively skewed by the nature of its measurement (items involved tend to measure only one tail of the distribution of given symptom constructs). However, results of such analyses were very similar and congruent with the results of Pearson Product Moment correlations and, as such, the latter were discussed for consistency with the prevailing literature in the area (e.g. Hutton et al., 2004; Katsanis & Iacono, 1991; Lee et al., 2001; Lees Roitman et al., 1997; Sweeney et al., 1994). Bonferroni corrections to minimise the impact of Type 1 errors on data analysis were not conducted, as the requirements of these would be too restrictive for the exploratory nature of this study and liable to instead produce Type 2 errors. To produce a balance between these issues, the alpha level of 0.01 was used to denote significance when discussing correlational analyses in the current study, with the alpha level of 0.05 discussed in reference to trends. Partial correlations, removing the effects of other influencing variables and power analyses for correlation coefficients were also examined.