

**Infant and Toddler Precursors
of Attentional Processes
in Fragile X Syndrome:
A Neurodevelopmental Perspective**

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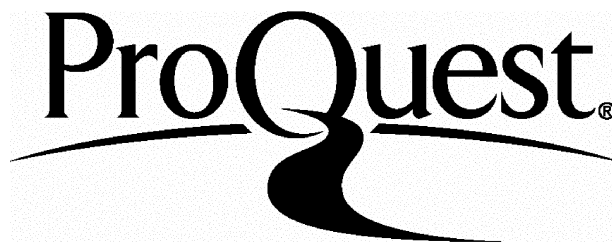
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Abstract

With the recent sequencing of the human genome, the following question has attracted much interest: can the function of single genes be linked to specific neural and cognitive processes? Within this context, developmental disorders of known genetic origins have been used as naturally-occurring models to link the function (and dysfunction) of genes with cognition. Fragile X syndrome (FXS) is a genetically inherited disorder associated with the silencing of a single gene involved in experience-dependent changes at glutamatergic synapses. In adulthood, it is associated with core attentional difficulties accompanied by seemingly proficient visuo-perception, but the profile of infants and toddlers has not been investigated. In this thesis, fragile X syndrome is used as a tool to investigate how initial changes in a *generalised* property of all cortical neurones can nonetheless result, in the adult, in *core* difficulties in the control of attention. I argue that, even in disorders associated with the silencing of a single gene like FXS, the answer requires a developmental approach.

Chapter 1 delineates a theoretical distinction between endogenous and exogenous influences on attentional control, whereas Chapter 2 defines methodological issues in assessing atypical attention, such as tools for the assessment of general developmental level and choices of control groups. Part II focuses on tasks tapping endogenous attention control. In particular, Chapters 3 and 4 examine the control of eye-movements and manual response conflict in infants and toddlers with FXS and in typically developing controls. In contrast, Part III concentrates on the exogenous effects of sudden peripheral onsets on visual orienting (Chapter 5) and of the perceptual salience of targets during visual search (Chapter 6). Finally, Part IV traces longitudinal changes in visual search performance. The findings suggest that, like adults with the syndrome, infant and toddlers with FXS display striking deficits in endogenous attention. However, unlike adults, infants are also characterised by atypical exogenous influences on attention and longitudinal changes in performance point to complex developmental relationships between early and later measures of attention.

The findings are discussed in terms of their theoretical implications for fragile X syndrome and other developmental disorders affecting attention. They challenge the notion of direct genotype-phenotype mappings that fail to take development into account.

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*For my closest developmentalists,
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General Introduction

Chapter 1

Theoretical Issues

With the recent sequencing of the human genome, the field of functional genomics has attracted much interest from cognitive neuroscientists concerned with the following question: can the function of single genes be linked to specific neural and cognitive processes? Within this context, developmental disorders of known genetic origins have been used as naturally-occurring models to link the function (and dysfunction) of genes with cognition.

Decreased or absent expression of a particular gene product, accompanied by a particular cognitive dysfunction, is taken as evidence for the necessity of that gene for implementing that function. However, if used carelessly, this approach carries three implicit assumptions. Firstly, it postulates (rather than tests empirically) that the cognitive correlates of the genetic dysfunction with a domain or process are “static”. Often, areas of cognitive impairment and proficiency are only tested in adulthood and impaired performance is directly correlated to gene expression. Thus, a particular cognitive function is taken to be equally affected (or unaffected) across developmental time, with a dysfunctional domain or process in adulthood characterised by early inefficient functioning. Theoretical objections and empirical evidence have challenged these assumptions in the study of developmental disorders (Bishop, 1997; Karmiloff-Smith, 1998; Paterson et al., 1999) because they ignore the role of development itself in determining phenotypic outcomes across domains. Secondly, it is assumed that, if

an individual with a given syndrome displays a cognitive deficit that is normally associated with the functioning of a particular neural circuit, the effects of the syndrome are circumscribed to that particular neural circuit, without affecting, even subtly, other functions. Finally, developmental relationships between areas of cognitive impairment and proficiency are not investigated, thus implicitly accepting not only simple mappings between genetic mutation and impairments, but also the independence of efficient and inefficient processes, both at the cognitive and neural level.

The overall aim of the present thesis is to challenge further the notion of direct genotype-phenotype mappings that do not take development into account. My focus will be on the set of processes contributing to visual selection, because these basic mechanisms gate the specialisation of visual processing through development. Selective attention impairments have been studied extensively in adults who suffered localised brain damage, in an attempt to understand the contributions of distinct areas to visual selection. In comparison, little is known about the relative contribution of cellular properties of neurones to different attentional processes or about how initial genetically-specified changes affect visual selection at different developmental time-points. Here, fragile X syndrome is used as a tool to investigate how initial changes in a generalised property of all cortical neurones can nonetheless result, in the adult, in core attentional difficulties. I shall argue that, even in disorders associated with the silencing of a single gene like fragile X syndrome, our answer requires a developmental approach.

In a selective review of the literature, I will highlight how tracing developmental trajectories enriches our understanding of both visual selection itself and fragile X in particular and how such an approach produces the novel, testable hypotheses addressed in this thesis. First, I shall investigate whether endogenous control is affected early in the development of individuals with fragile X syndrome, as well as in adulthood. Secondly, I shall evaluate whether other seemingly unaffected processes in adults with the syndrome display early, subtle impairments. Finally, I shall investigate developmental changes within and across these processes, comparing and contrasting predictions from two distinct views of functional brain development (detailed in Johnson, 2001).

1.1. An integrated framework for studying visual selection

“Every one knows what attention is. It is the taking possession by the mind, in clear and vivid form, of one out of what seem several simultaneously possible objects or trains of thought. [...] It implies withdrawal from some things in order to deal effectively with others.”
(James, 1890/1950, pp. 404-5)

As illustrated by the quotation above, more than a century ago William James argued that the nature of attention is apparent in our everyday phenomenology. In fact, the understanding of selective attention remains an exciting challenge, as demonstrated by the many discrepant theories of the processes leading to efficient selection (e.g., Bundesen, 1990; Duncan & Humphreys, 1989; Treisman & Gelade, 1980; Treisman, 1982; Wolfe, 1998). Different theorists accept attentional processes as a set of basic mechanisms influencing perception and gating learning, crucial for attending to information that is relevant to our current goals and, for example, for ignoring irrelevant stimuli within our cluttered visual environment (e.g., Pashler, 1998). However, the mechanisms through which this selection operates remain hotly debated. Reconciling such divergences is beyond the scope of the present thesis, but a clear operational definition of the processes involved is vital for generating hypotheses in the case of developmental disorders. Furthermore, an understanding of the neural properties that are necessary to implement selective attention at the cellular and systems level is crucial when attempting to understand the effects of genetic modifications, as these indeed affect low-level neural properties. The following section will therefore focus on providing an integrated theoretical framework for understanding visual selective attention at the cognitive level and on discussing what is known about the requirements for its neural implementation. Throughout this review, I shall distinguish between the literature focused on the adult cognitive system and what is known about the neurodevelopmental trajectories leading to the adult outcome, as this is of utmost importance when investigating attentional processes in genetic disorders.

1.1.1. Attentional processes: The cognitive level of description

Adult models of selective attention

“Attention may be either passive, reflex, non-voluntary, effortless; or active and voluntary.” (James, 1890/1950, p. 416)

As psychology emerged as an independent discipline, it was William James who first argued for the existence of many varieties of attention and pinpointed a distinction between endogenous and exogenous “types” of attention, following an ancient line of thought in the philosophical literature (for a review, see Hatfield, 1998). For William James, “in *passive immediate sensorial attention* the stimulus is a sense impression, either very intense, voluminous, or sudden, [...] or else it is an *instinctive* stimulus, a perception which, by reason of its nature rather than its mere force, appeals to some one of our normal congenital impulses and has a direct exciting quality” (James, 1890/1950, pp. 416-7). In contrast, James’ voluntary attention is goal-driven: “we never make an *effort* to attend to an object except for the sake of some *remote* interest which the effort will serve” (p. 416). In modified form, this basic distinction recurs within current models of visual selection and therefore will be the organising theme of the present thesis.

Attention researchers today focus on the interaction of, rather than a neat separation between, “types” of attention (Yantis, , 1998, 2000). However, they converge on the idea that efficient selection depends on both endogenously-driven goal-related attentional biases and exogenously-driven processing of stimulus characteristics such as, for example, target perceptual salience (Desimone & Duncan, 1995; Duncan & Humphreys, 1989; Treisman & Sato, 1990; Wolfe, 1994). Amongst these models, the interaction between these influences on selection is central to a framework in which attention is the emergent property of competitive interactions working in parallel across the visual field, the “biased-competition model” (Desimone & Duncan, 1995). As will be discussed below, evidence from single-cell recording (e.g., Luck et al., 1993) and functional imaging (e.g., Kastner & Ungerleider, 2000, 2001) suggests its neural plausibility and makes it a leading current model of the

attentional processes involved in selection. At the behavioural level, the model suggests that selectivity (the screening of irrelevant stimuli or irrelevant responses) is biased towards information that is currently relevant to behaviour, i.e., dependent on an endogenous representation of the goal. Stimulus-driven biases on competition are equally important, as exemplified by the mechanisms for figure-ground segregation. Similarly, other researchers have investigated how, in the temporal domain, peripheral stimuli with an abrupt onset exogenously drive attention orienting with limited influences of endogenous control (Jonides, 1980, Jonides & Yantis, 1988).

What is meant by this distinction? What are the theoretical implications of adopting particular terms to describe it rather than others? Table 1.1 lists a series of terms that have been used interchangeably by researchers, both within the field of attention and in related disciplines to juxtapose passive and active aspects of processing. I provide a simple definition of these dichotomies and trace their field of origin, as well as discussing some of the major criticisms levelled against them. For example, the distinction between “automatic” and “voluntary” processes has been employed in the literature to account for conflict effects, such as the classical Stroop effect, or the Simon effect (the focus of Chapter 4). However, recent empirical evidence has challenged the usefulness of the word “automaticity” (discussed by multiple authors in Prinz & Hommel, 2002). As is apparent, all terms can be criticised on some grounds, but different dichotomies carry more or fewer assumptions about the properties of the cognitive system. For instance, drawing again on “automatic” and “voluntary” processes, adopting such a dichotomy necessitates a definition of wilful action. Similarly, differentiating between “subconscious” and “conscious” requires an elaboration of what is meant by consciousness itself, leading to difficulties in operationalising terms for empirical investigations. The terms “exogenous” and “endogenous” are adopted here as both are less theoretically laden than the other terms described in Table 1.1. Indeed, they simply qualify the major direction of the flow of information contributing to perceptual experience; on the one hand, external, with processing driven by the perceptual properties of stimuli; on the other, internally generated information (from memory, expectations).

Table 1.1. Synopsis of dichotomous terms used to juxtapose endogenous and exogenous aspects of control. [Next page]

Term	Definition	Term	Definition	Field of Origin	Criticism
Within the attentional literature:					
<u>Exogenous</u>	Externally generated information, driven by the properties of the environment and of incoming stimuli	<u>Endogenous</u>	Internally generated information, driven by representations of current goals, task demands, memory and expectations	Used both in the adult attentional literature (e.g., Driver & Spence, 1998; Yantis, 2000) and in the developmental literature (e.g., Hood et al., 1998)	Grouping heterogeneous sets of processes. Most tasks require an interaction between the two, rather than one or the other
<u>Bottom-Up</u>	From lower levels of a processing hierarchy. It implies automaticity of processes	<u>Top-Down</u>	From higher levels of a processing hierarchy	Grounded in literature on neuroanatomical circuits and neurophysiology (e.g., Felleman & van Essen, 1991; Desimone & Duncan, 1995)	Implies a hierarchy of processes. This is not always plausible and ignores more dynamic interactions
<u>Automatic</u>	Reflexively driven, depending on the activation of overlearned or prepotent responses	<u>Voluntary</u>	Driven by willful control	Often used in the literature on response conflict, for example treating classical effects such as the Stroop effect (reviewed in MacLeod, 1991)	Experimental manipulations have shown that processes thought to be automatic can be modified adaptively by task demands (Prinz & Hommel, 2002)
In related fields:					
<u>Implicit</u>	Often implies that it is not represented through meta-cognitive knowledge	<u>Explicit</u>	Involving meta-cognitive knowledge. Can be either verbalised, generalised or transferred	From a number of fields. Notably used in memory and learning (e.g., Tulving & Schacter, 1990)	Like the distinction below, requires operationalising the constructs of “consciousness and awareness”
<u>Subconscious</u>	Inaccessible to awareness	<u>Conscious</u>	Accessible to awareness	From the psychology of mind (e.g., Kim, 1996)	Difficult to operationalise for empirical testing

Table 1.1. Synopsis of dichotomous terms used to juxtapose endogenous and exogenous aspects of control.

The usefulness of the distinction is demonstrated by a hybrid theory with the potential of solving a long-standing controversy in attention, which focuses precisely on measuring influences of perceptual (stimulus-driven) and attentional (goal-directed, task-relevant) manipulations of load (Lavie, 1995, 2001). Much of the debate on attention in the latter half of the last century focused on the locus at which attention filters perceptual information for processing, in the cascade of events from sensory input to motor output. Models can be broadly divided into those conceiving of attention as a serial process, binding features of the visual environment on the basis of their spatial location (Eriksen & Eriksen, 1974; Posner, 1980; Treisman, 1969, 1982), and models viewing attention as the emergent property of parallel processing across the visual field (Bundesen, 1990; Duncan & Humphreys, 1989, 1992; Desimone & Duncan, 1995). Although many differences between these theoretical positions remain unresolved, there have been some very fruitful attempts to reconcile them. Lavie (1995) noted that while experimenters supporting an early locus of selection characteristically employed displays that were high in perceptual load, those arguing for a late locus of attentional selection employed paradigms characterised by low load. Using multiple operational definitions of perceptual load, she gathered converging evidence suggesting that this factor determines the locus of selection. More recently, Lavie (2000, 2001) has discussed how the effects of increasing goal-related demands are not equivalent to those of manipulating perceptual load. These conclusions suggest that goal-related and sensory-driven influences on selection can be fruitfully manipulated across tasks investigating visual selection mechanisms.

In sum, distinguishing between exogenous and endogenous influences has been and still is a promising avenue for attention researchers. However, it is now crucial to consider a caveat. Yantis (1998, 2000) discusses how disentangling exogenous and endogenous influences is extremely difficult in practical terms and how attempts to do so may be too artefactual to represent what occurs during selection in naturalistic conditions. He proposes that visual selection results not solely from one factor or the other, but from the interaction between the current behavioural goals and the properties of the stimuli to be processed, acting to mutually constrain each other. All attentionally demanding tasks, therefore, would load on both exogenous and endogenous factors. Nevertheless, tasks can be designed for performance to load differentially on either stimulus-driven or goal-related factors. This will

be the strategy employed in this thesis. In order to use this distinction within a developmental framework, it is essential to review what is known about the developmental trajectories of both sets of processes. Indeed, using this distinction in terms of real-time processing does not provide any clues as to whether there are developmental differences and interactions between exogenous and endogenous factors.

Aspects of developmental change

As in the adult literature (James, 1890/1950, p. 416, Parasuraman, 1998), multiple “varieties of attention” have also been distinguished across development in infancy and early childhood (e.g., Hood, Atkinson, & Braddick, 1998; Colombo, 2001). For example, Colombo (2001) distinguishes between endogenous attention and a variety of stimulus-driven processes, including spatial orienting to peripheral stimuli, and attending to object features in the environment. Unfortunately, the ease with which we can compare information on the early development of selection with adult data is limited by the use of different experimental techniques. Often, the methodologies employed with infants and young children are so discrepant from those used with adults that paradigms appear incommensurable. For example, while many adult attentional paradigms require manual responses (investigated in Chapters 4 and 6), paradigms employed with infants and young children test visual orienting as measured by saccades (Chapters 3 and 5).

Researchers using identical methodologies across the life-span partially fill this gap. Evaluating performance on classical adult tasks of selective attention, Enns, Brodeur and Trick (1998) examine life-long developmental changes in performance. Evidence from paradigms testing orienting, filtering, search and priming highlights that certain components (covert exogenously-driven orienting and visual search for very salient features) show relatively little developmental change compared to others which do (such as the filtering of distractors or the visual search for conjunctions). For instance, comparing orienting to peripheral cues at variable cue-target intervals, Brodeur and Enns (1997) showed that stimulus-driven covert orienting undergoes relatively minor developmental change over the life-span. In contrast, the ability to use the predictive value of a cue to direct orienting (i.e., endogenous orienting) improved dramatically from childhood to adulthood and decreased in elderly participants. Similar developmental differences emerged in the voluntary control of

attention in visual search displays, but not in identifying targets distinguished from distractors on the basis of single salient features (Trick & Enns, 1998). Thus, it is crucial to note that, first, when investigating cognitive factors affecting selection in both typically and atypically developing individuals endogenous and exogenous influences on selection may not develop along the same trajectory. Therefore, the processes of developmental change for each of stimulus-driven and goal-related influences on selection will need to be examined both and given equal emphasis. Secondly, it remains unclear whether, and if so how, these sets of influences interact with each other throughout development.

Studies aimed at adapting adult tasks to tap endogenous control in young children and toddlers show the emergence of increasing endogenous control throughout toddlerhood and early childhood (Gerardi-Caulton, 2000; Diamond, 2001; Diamond et al., 2003). Such a finding is certainly not new; tasks that were especially designed for infants had repeatedly shown this, but methodologies and results were not directly comparable to adult performance and therefore precise developmental trajectories could only be inferred. On the other hand, the influences of exogenous manipulations on selective attention have been examined less extensively from a developmental perspective. Maylor and Lavie (1998) tested elderly and younger adults and examined the effects of perceptual load on age differences in visual selective attention. The perceptual load of relevant processing was manipulated by varying the central set size. When the relevant set size was small, the adverse effect of an incompatible distractor was much greater for the older participants than for the younger ones. However, with larger relevant set sizes, this was no longer the case, with the distractor effect decreasing for older participants at lower levels of perceptual load than for younger ones. More recently, Huang-Pollock, Carr and Nigg (2002) compared performance by young children and adults on a series of similar interference tasks. Children and adults searched displays of varying set size flanked by irrelevant distractors. Children's performance was as efficient as adults' under conditions of high but not low load. The authors suggested that early selection, involved in search at high load, engages rapidly maturing neural systems that are already functional in the young children tested. In contrast, late selection, inhibiting the interference of irrelevant distractors even at low load, engages slowly maturing systems.

These findings and their implications drive the investigations of typical developmental trajectories of response conflict and visual search in Chapters 4 and 6 of the thesis and will therefore be examined in more detail there. At a more general level, a distinction between the development of exogenous and endogenous influences on attention has been drawn much most clearly at the level of the neural systems involved in saccade planning and execution (Bronson, 1974, 1982; Atkinson, 1984, 2000; Johnson, 1990, 1998). Thus, grounding these issues in what is known about the neural implementation of the processes of interest is vital, especially when investigating developmental outcome in conditions of known genetic origins affecting neural development in particular ways. The following section therefore focuses on the neural systems implementing attention in the adult as well as on their developmental trajectories.

1.1.2. Attentional processes: Neural systems requirements

Adult neural systems and attention

How is visual attentional control achieved at the neural level? Prominent classical models on the neural level of implementation proposed attention to be the remit of segregated neural systems. For example, Posner and Petersen argued for the existence of an anterior attentional system, based on the functioning of the prefrontal cortex, as well as a posterior one, based on parietal functioning (Posner & Petersen, 1990; Posner & DiGirolamo, 1998).

However, growing behavioural evidence suggests that attention is not “localised” in particular neural areas, but it is rather the emergent property of competitive interactions across multiple neural systems (Desimone & Duncan, 1995; Frith, 2001). The biased-competition model proposes that, in many brain systems activated by visual input, processing is competitive, so that responses to different objects may be mutually inhibitory in a “winner-takes-all” process across areas processing different features of the input (Desimone & Duncan, 1995). Like the outcome of selection described at the cognitive level in the above section, neural competition amongst stimuli can be biased by both top-down, endogenously driven influences and exogenously-driven mechanisms. In the model’s original formulation, exogenous mechanisms were concerned with the intrinsic or learned

biases of the perceptual system within a spatial and temporal domain. They were not dependent on task demands (although they may involve neural feedback from higher areas). Endogenously-driven mechanisms are based upon the formation of an attentional template, specifying task requirements at hand. The biased-competition model suggests that, for visual selection, competition is ultimately resolved in the visual cortex, but the sources of endogenous biasing signals derive from a distributed network of areas in the frontal and parietal cortices (Kastner & Ungerleider, 2000, 2001).

What is the neural evidence for the biased-competition model? Single-cell recording data in lower visual areas support strong modulatory effects of these large-scale attentional systems. This is indicated by sustained elevation of pre-stimulus firing rates when an animal's attention is directed inside the receptive field (Luck et al., 1993) and an enhancement in activity of cells coding the stimulus features (Chelazzi, Miller, Duncan, & Desimone, 1993). Indeed, a stimulus optimal for driving maximal activity from a visual neurone in temporal cortex will produce greatly attenuated firing if a behaving monkey is instructed to attend elsewhere (Chelazzi, Duncan, Miller, & Desimone, 1998). The model is further supported by human functional neuroimaging evidence. In accordance with the predictions of biased competition, Kastner and Ungerleider (2000) found that activity in a large fronto-parietal network enhances responses to an attended stimulus in visual processing areas. Moreover, this activity biases the signal by increasing baseline activity associated with the expectation of a stimulus and it increases stimulus salience by enhancing neural sensitivity to stimulus contrast.

How does this leading model of attention relate to pre-existing proposals? Although it was originally placed in antithesis to earlier models of attention, there are many similarities between the processes that would implement biased competition in the brain and those proposed by other models, both in the adult (e.g., Posner & Petersen, 1990) and in the infant case (Colombo, 2001). The latter models suggest the segregation of function across particular brain areas, with executive attention being implemented by an anterior network and spatial orienting by a posterior one. With their extensive subcortical connections, the large-scale fronto-parietal networks described by Kastner and Ungerleider (2000, 2001) correspond to areas active during imaging tasks that require attention and regions which,

when damaged in the adult, produce the attentional deficits that were originally reported as evidence for segregated “attentional substrates” (e.g., Posner, Cohen, & Rafal, 1982; Posner & Petersen, 1990). So, although the original theoretical frameworks differed radically, current evidence could be interpreted in favour of both. Posner and Petersen (1990) proposed the existence of dedicated neuronal networks influencing the activity of other, modality-specific regions. Desimone and Duncan (1995), on the other hand, described attention as an emergent property of competitive interactions within task-relevant neural populations. Evidence supports both dedicated neural networks (if not as segregated as initially proposed by Posner and Petersen) and integrated competition at the single-cell level (as proposed by Desimone and Duncan, but to a greater extent in certain areas). This suggests that the two proposals are not actually incompatible; one better describes processing at a mechanistic level, and the other better describes a partial division of labour that is dependent on the functional connectivity of each area.

In summary, more classical as well as currently dominant conceptualisations of the neural bases of attention converge on a similar conclusion. For the adult system there appears to be a distinction between frontoparietal neural circuits modulating competitive activity in visual cortices, and these sensory cortices themselves. This modulation depends on feedback activity based on goal-relevant representations. However, attention is not simply the remit of these fronto-parietal networks. Rather, at the neural as well as at the cognitive level (discussed in section 1.1.1), attention emerges from both endogenous biases and exogenously-driven competitive processing.

Neurodevelopmental perspectives

As in the adult literature, the distinction between stimulus- and goal-driven factors affecting selection has been adopted in studies of attentional development, especially in investigations of visual orienting, saccadic planning and execution. Although the similarities and differences between eye-movement control and orienting of attention remain highly debated and the two systems can be dissociated, there is a broad correspondence between the factors guiding overt eye-movements and covert orienting of attention (e.g., Nobre et al., 2000). These processes will be examined in greater detail in Chapters 3 and 5, but suffice it to say

here that developmental models of attention have relied greatly on saccade onset as a measure of various attentional manipulations.

Bronson (1974, 1982) provided the first systematic account of developmental changes of visually guided behaviour. He construed developmental changes in terms of a shift from subcortical processing, based on retinocollicular pathways that are active at birth and conceptualised as reflexive and automatic, to voluntary and goal-driven control, based upon cortical pathways coming on-line after the first three months of postnatal life. However, this simple dichotomy captured inaccurately the complexity of the systems involved (Atkinson, 1984; Johnson, 1990, further discussed in Chapters 3 and 5). Johnson (1990) proposed that the characteristics of visually guided behaviour at each age should depend on which pathways are functional within a hierarchy of circuits involved in visual orienting. The functional status of each pathway would be dependent on the developmental status of the primary visual cortex, as suggested by information on the neurophysiology of the cortical pathways involved in oculomotor control (Schiller, 1985, 1998). Atkinson (1984) proposed a similar account. Using this framework, Johnson (1990) accounted for multiple phenomena associated with visual orienting in newborns and young infants, such as the externality effect and saccadic pursuit tracking in newborns, “obligatory fixation” in 1 month olds, the development of smooth pursuit tracking at two months of age, and the emergence of anticipatory saccades by four months.

However, these theories were based upon a strictly maturational account of the development of pathways influencing oculomotor control. Pathways were assumed to develop hierarchically and independently, from the retinocollicular to the cortical. By contrast, Johnson and colleagues have recently highlighted several limitations of their original model (Johnson et al., 1998). For example, it did not account for the findings that, in mature animals, eye-movement related responses from the superior colliculus depend upon cortical input (Schiller, 1998), suggesting a degree of interaction between systems that were originally supposed to develop independently of each other. How and when do these interactions begin? Their very existence suggests that maturational accounts of the development of oculomotor control should, at least in part, be carefully re-evaluated. Gradual maturation perhaps accurately describes the emergence of early functions in the

infant, but it cannot account completely for later performance, as the latter is characterised by interactions across circuits. More generally, Johnson (2001) highlighted the need to contrast predictions of maturational accounts of functional brain development with predictions from an interactive view of functional development (the “interactive specialisation” hypothesis). By this account, the emergence of function may involve the concurrent and interactive development of multiple areas, rather than the hierarchical onset of functioning across discrete and independent subcortical and cortical modules.

This approach has implications for the study of circuits involved in attentional control. On the one hand, a maturational view predicts that endogenous and exogenously-driven processes will develop independently of each other. By contrast, an interactive view of functional brain development predicts developmental interactions across them. In Part IV, I shall examine contrasting predictions from these two conceptions of the functional development of attention. First, however, follows a review of what is known about the low-level cellular bases of exogenous and endogenous influences on selection. Indeed, these need to be examined when generating hypotheses about the developmental effects of genetic modifications, as it is at this low-level of description that disorders of known genetic origins are likely to affect the starting state of the developmental system.

1.1.3. Attentional processes: Cellular requirements?

Cellular mechanisms supporting attention in the adult

What are the low-level cellular requirements for the implementation of both stimulus-driven competitive mechanisms and of the endogenous sources modulating this competition? In real time adult processing, Desimone and Duncan (1995) argued that competitive mechanisms operate equally across initially separate modules, to then be integrated to provide an overall winner. While agreeing with common winner-take-all mechanisms across areas involved in attentional selection, Driver and Vuilleumier (2001) speculated that certain brain areas may rely more strongly on such processes because of cytoarchitectonics, functional connections, or computational powers of the different types of neurones and the networks of which they are constituted. Competitive mechanisms may occur on a more local scale in lower visual areas (e.g., amongst neighbouring cells, Polat & Sagi, 1994) but on a

very high scale in other regions like parietal cortex (Pouget & Sejnowski, 1997) or prefrontal cortex (Miller & Cohen, 2001). Indeed, the higher reliance of these areas on a winner-takes-all process may explain, for example, extinction in patients with inferior parietal lobe lesions, but not lesions in other areas involved in the processing of visual input (Driver & Vuilleumier, 2001). Recently, Spratling and Johnson (2001) proposed that both computational and physiological evidence suggests that exogenously-driven competitive mechanisms across areas may be implemented by inputs from inhibitory interneurons (both at the level of local and long-range connections).

In contrast, the functions of the large-scale networks thought to be responsible for biasing selection endogenously have been proposed to depend strongly on the integration of a large number of inputs from very diverse lower-level areas. For example, the integration and reception of multiple inputs in the prefrontal cortex could provide a means to maintain behavioural goals (Miller, 2000; Miller & Cohen, 2001). Networks of prefrontal neurones fulfil the minimal requirements for this function; they maintain activity robustly against distractions as well as exhibit the flexibility necessary to update task-relevant representations when needed. What are the neural properties that support such functions? Firstly, these networks are characterised by a high capacity for integration and multimodality, provided by the convergence of diverse information through extensive connections with other cortical areas (Barbas & Pandya, 1989). Secondly, these networks rely on recurrent excitatory connections more than areas involved in unimodal sensory processing (discussed by Miller & Cohen, 2001). Numerous cytoarchitectonic and functional characteristics differentiate single neurones and networks in the fronto-parietal areas discussed above from neurones that are more directly involved in exogenously-driven processing of stimuli, ranging from differences in neurotransmitter modulation to distinct targets of extrinsic and intrinsic connections (e.g., Mountcastle, 1998). I shall concentrate on two intertwined properties, the variable complexity of dendritic trees and the role of this in recurrent connections, as I shall argue that they are relevant to an understanding of fragile X syndrome.

First, integrative functions of fronto-parietal networks are correlated with larger dendritic trees, with their increasing complexity and higher density of dendritic spines. Dendritic

spines are the regions at which dendrites make synaptic contact with glutamatergic neurones (Ramon y Cajal, 1960; Nimchinsky, Sabatini, & Svoboda 2002). As glutamate is the major excitatory neurotransmitter intrinsic to cortex (Kandel, Schwartz, & Jessell, 2000), spine density is a good marker of the number of excitatory inputs received (and integrated) by pyramidal neurones. Changes in dendritic complexity are not random, but systematic across cortical areas; dendritic spine density increases dramatically from V1 to parietal cortices (Elston & Rosa, 1997), and similarly from premotor to prefrontal cortex for both human and non-human primates (Elston & Rockland, 2002). Indeed, spine density in several cortical areas of the frontal pole and orbitofrontal cortex (Brodmann areas 10, 11 and 12) in the macaque monkey is generally threefold greater than in neurones of primary visual cortex (area 17) and twofold greater than in neurones in parietal cortex area 7a (Elston, 2000).

What are the functional implications of these structural differences across areas? Elston and colleagues proposed that dendritic complexity relates to the higher degree of convergent processing required of higher association areas. Indeed, Melchitzky et al. (1998) found that supragranular pyramidal neurones in monkey prefrontal cortex project predominantly large numbers of excitatory inputs on similar neurones. Thus, inputs on dendritic spines would create excitatory networks capable of co-ordinating the activity of neural populations sharing responses properties and could therefore provide a neural substrate for sustained activity that is crucial for goal maintenance in delayed-response tasks (Bressler, 1995; Goldman-Rakic, 1995; Miller & Cohen, 2001). These networks of pyramidal neurones would provide analogous functions to horizontal connections in sensory cortices such as V1, but would do so through excitatory, glutamatergic inputs on dendritic spines rather than through inhibitory GABA-ergic lateral connections. Therefore, the recurrent activity proposed to be crucial for goal maintenance and attentional control (e.g., Miller & Cohen, 2001) are at least in part, dependent on excitatory glutamatergic networks that, in turn, may depend on the differentially more complex structure of dendritic trees in fronto-parietal areas.

In sum, evidence on both exogenously-driven processes and endogenously-driven biases suggests that these two subsets of processes may rely on differential low-level properties of cortical networks. For example, dendritic inhibition processes seem more heavily involved

in competitive mechanisms, whereas integration of excitatory inputs may be more relevant to the functioning of frontoparietal circuits involved in endogenous biases on selection. It is crucial to note, however, that both mechanisms play some role across cortical areas, ruling out a neat separation between them. Furthermore, little is known about how early changes in the low-level cellular characteristics of the neurones implementing such processes would affect selection developmentally. Below, I examine what is known about typical developmental trajectories in the cellular mechanisms that are involved in selection, and how developmental disorders of known genetic origin provide models through which we can investigate them further.

Neurodevelopmental data

Converging evidence on both exogenously-driven processes and endogenously-driven top-down biases has been gathered through neuroimaging of the human adult brain and single-cell recording of behaving primates. However, little is known about how developmental changes in the low-level cellular characteristics of the neurones implementing such processes affect selection. An exhaustive examination of the developmental changes in the cellular properties of cortical neurones is beyond the scope of this thesis (for excellent recent reviews, see Huttenlocher, 2002; Mountcastle, 1998). I shall, however, review those that appear to be differentially involved in the mechanisms underpinning attention at the systems level, as discussed (section 1.1.2), and those that are particularly affected in fragile X syndrome (section 1.2.2).

I outlined how integration of excitatory inputs on dendritic arbors of pyramidal cells may be differentially more important for the functions of circuits involved in the endogenous control of attention than for exogenous influences. Studies of dendritic spines show remarkable reshaping of connections throughout development (Huttenlocher, 2002). They are common on the cell body of pyramidal cells early during development, but disappear during maturation (Larramendi, 1969); their overall number and density decreases, a process termed “synaptic pruning” (Huttenlocher, 1979). Importantly, Conel (1939-1963) first identified qualitative regional variation across the circuits that I suggested earlier may be differentially involved in influencing selection: dendritic development appears less advanced in lower visual areas than in prefrontal areas at various postconceptional and postnatal times.

Quantitative data confirmed these observations (Schade & van Groenigen, 1961; Becker et al., 1984). Results suggested, first, that different cortical areas show heterochronous dendritic growth; this is faster in lower visual cortices like V1, where the level of adult maturity is achieved by 24 months, and slowest in prefrontal cortex, where growth continues throughout adolescence. Secondly, the dendritic complexity attained by neurones in prefrontal cortex is much larger than that of lower visual areas. Thus, the integrative functions of which dendritic spines are markers develop differently in the areas involved in exogenous and endogenous influences on attention. Furthermore, they may play a more prominent role in areas involved in endogenous control of attention.

Investigating developmental disorders of known genetic origin allows us to ask how specific changes in low-level neural mechanisms can affect exogenously-driven and endogenously-driven influences on attentional control. Much of the existing work on developmental disorders of endogenous attentional control has focused on localised brain areas known to be crucial for control in the adult, like prefrontal cortex. In the case of developmental disorders whose genetic underpinnings are known, researchers interested in attentional control have focused so far primarily on genetic disorders affecting transmitter systems modulating the functioning of prefrontal cortex, as is the case in phenylketonuria (Diamond et al., 1997; 2003). Similarly, when screening for genetic factors contributing to disorders of attentional control whose (multiple) genetic origins have not been isolated, candidate genes tend to be selected preferentially if they are involved in the functioning of receptor systems crucial for the extrinsic modulation of prefrontal activity (e.g., Casey, Tottenham, & Fossella, 2002). However, little is known about the mechanisms through which more generalised genetic effects on cortical neural structure result in selective attentional difficulties over and above what expected given the overall developmental level. For example, Down syndrome (DS) is characterised by generalised cortical effects on dendritic spine morphology and density (Nimchinsky, Sabatini, & Svoboda, 2002) and it is known that attentional processes develop along atypical trajectories in this syndrome (e.g., Moore et al., 2002). However, interpreting the developmental effects of genetic dysfunction on attention in DS is a difficult enterprise, because the syndrome is due to trisomy of fragments or entire chromosomes. Therefore, a large number of genes are over-expressed (although a more limited number of genes appear critical in contributing to the phenotype). The task is relatively easier in genetic disorders

associated with known dysfunction of single genes. One such condition is fragile X syndrome.

1.2. Selective attention in genetic disorders: The case of fragile X syndrome

Fragile X syndrome (FXS) is the most common form of inherited mental retardation, with a prevalence of 1 in 4,000 male and 1 in 6,000 female births (de Vries et al., 1997), although these estimates vary. The vast majority of cases are due to an expansion of the CGG repeat in the untranslated '5' region of the Fragile X Mental retardation-1 (FMR1) gene which results in its promoter hypermethylation and transcriptional silencing (Jin & Warren, 2000, O'Donnell & Warren). The absence of FMR1 gene product (the Fragile X Mental Retardation protein, FMRP) is the sole genetic contribution to the fragile X phenotype (Verkerk et al., 1991, Pieretti et al., 1991). This has recently been the focus of much interest because of the possibility of relating this single gene product directly to brain structure, function and cognition in individuals with the syndrome. I shall first describe the cognitive profile characterising people with fragile X syndrome as well as its neural underpinnings. Secondly, I shall argue that the cellular and system pathophysiology of the syndrome suggests that an understanding of its attentional profile requires a dynamic developmental perspective, rather than a static description of impaired and intact processes.

1.2.1. The general cognitive and attentional phenotypes

Late childhood and adulthood: The concept of a "core" attentional deficit

Clinically the syndrome presents with mild to severe mental retardation (Hagerman & Cronister, 1996), abnormal facial features (prominent jaw and large ears) that become more prominent in adults and subtle connective tissue abnormalities (Hagerman et al., 1984). The physical morphology is a less reliable identifier of the syndrome than patients' cognitive profile (Turk, 1998). The adult cognitive profile is characterised by uneven abilities within and across domains: relative strengths in vocabulary, long-term memory and holistic information processing (Freund & Reiss, 1991) accompanied by relative weaknesses in

attention (Cornish, Munir, & Cross, 2001), visuospatial cognition (Cornish, Munir & Cross, 1999), short-term memory and sequential information processing (Freund & Reiss, 1991). Furthermore, spatial deficits appear particularly to affect skills requiring visuo-spatial and visuo-constructional abilities, with visuo-perceptual skills functioning relatively better (Freund & Reiss, 1991; Cornish, Munir & Cross, 1999). Similarly, tasks requiring short-term memory for complex sequential information are problematic for adults with FXS, whereas relative strengths for tasks requiring short-term memory for simple, meaningful information (Schapiro et al., 1995). Like adults, older children with FXS seem to have particular difficulties with tasks involving sequential processing, short-term memory recall, or reproduction of items in serial or temporal order (series of digits, objects words, motor movements, Dykens et al., 1987). Performance is relatively good in tasks requiring simultaneous rather than sequential information processing, and, while performance on the latter does not improve with age, the former does (Hodapp et al., 1991; 1992).

In conjunction with this complex constellation of strengths and weaknesses across cognitive domains, problems with attention and hyperactivity are reported as most debilitating in children and adults with FXS both by parents and clinicians. For example, Turk (1998) tested a group of boys with FXS in structured clinical interviews and found higher scores on items relating to attentional deficits, motor restlessness and anxiety. Hagerman (1987) described 73% of a sample of 37 prepubertal boys as fulfilling DSM-III criteria for attention deficit disorder and having a score in the hyperactive range. Munir, Cornish and Wilding (2000) compared the performance of boys with FXS and Down's syndrome as well as typically developing children matched for Mental Age on a wide range of tasks testing attention. The researchers concluded that the FXS group differed from the other groups in their ability to plan and organise visual search, shift attention from one target type to the other, from one concept to another, delay in responding and the failure to inhibit task-irrelevant responses. These differences were more pronounced in tasks posing higher executive demands. Similarly, a wide range of tasks were used to demonstrate deficits in selective attention, sustained attention and attentional switching as well as aspects of working memory in adult men with FXS (Cornish, Munir, & Cross, 2001). Thus, processes crucial for efficient selection have demonstrated to be atypical in childhood and adulthood, predominantly in tasks manipulating endogenous attentional control. Indeed, recently,

experts in the field have suggested that these difficulties could be subsumed by a “core” deficit in (endogenous) attentional control processes (Cornish et al., in press).

However, a number of issues are not addressed by the current literature. Firstly, what are the early origins of these prominent difficulties later in childhood and adulthood? As discussed earlier, one should never assume the early cognitive profile of strengths and weaknesses to be the same as the adult endstate. Secondly, the notion of a “core” attentional deficit needs to be clarified further in terms of what it does and does not imply. On the one hand, it is a descriptive term: it highlights the fact that attentional processes present great difficulties for individuals with fragile X syndrome, even when compared to younger typically developing individuals or individuals with developmental disorders other than fragile X syndrome. On the other hand, a “core deficit” in a developmental disorder does not equate to a “selective” deficit, i.e., impairing a single area of processing, leaving others intact. The latter construct may well apply to adults who have developed typically and later sustained selective brain damage, but it is not suitable for developmental disorders (Bishop, 1997; Karmiloff-Smith, 1998). So, while using the expression “core deficit” implies that executive control is an “area of extensive difficulties specific to the syndrome”, it need not imply that it is the sole processing difficulty characterising attention in the syndrome. Both the early attentional phenotype and the selectivity of executive deficits are matters for empirical investigation in the present thesis.

Early cognition, attention and developmental trajectories

Very few studies have addressed issues of cognitive development in young toddlers and infants with FXS (Scerif & Cornish, 2003) and, where they have existed, they have been based mainly on parental report questionnaires and structured interviews (e.g., Bailey et al., 2000, 2001; Heissl et al., 2001). Such studies have generally provided valuable insights the effects of the syndrome on language, social cognition and attention, but need to be complemented by in-depth experimental investigations of the cognitive underpinnings of areas of difficulty and proficiency in the initial states of the syndrome.

Receptive language was found to proceed at approximately half the expected rate in a large group of children aged between 20 and 89 months, while their expressive language

proceeded at approximately a third of the standard rate (Roberts, Mirrett, & Burchinal, 2001a). This indicates a steady improvement particularly in receptive vocabulary, although at a slower rate than in typically developing children, resulting in an increasing discrepancy between communication skills and chronological age. Furthermore, young children's language development seems to slow down from approximately 48 months onwards (Fisch et al., 1996; Fisch et al., 1999), although the latter findings should be taken with caution, because they derive from pooling children and adolescents across age groups. Studies following language development longitudinally in individual children and adolescents have also suggested a slowing in the improvement of linguistic skills over time plateauing at different ages (Dykens et al., 1989, 1996; Bailey et al., 1998). Overall delay is accompanied by large individual differences in both expressive and receptive language (Roberts et al., 2001a). While the level of FMR1 protein seems correlated to the level of communication skills, it is not related to the rate of development (Bailey, Hatton, et al., 2001), suggesting that other factors impact on the speed at which language improves over time in young children with the syndrome. A number of social difficulties have also been well documented in adults and children with fragile X syndrome. These include social anxiety, shyness, hyper arousal, avoidance behaviour towards unfamiliar people and gaze aversion linked to extreme social anxiety. However, social development has not been studied in young children and toddlers with the syndrome. Studies comparing gaze aversion in younger and older children found a higher incidence of this behaviour in the older children. In general, young boys with fragile X syndrome, but no concurrent diagnosis of autism, have higher social adaptive skills than matched children with autism and children with both autism and fragile X syndrome. A concurrent diagnosis of autism seems related not only to social adaptive skills, but also to the severity of cognitive delays in boys with the syndrome (Bailey et al., 2000).

As in adults, the most striking and consistent behavioural problems identified in children with fragile X are inattention and hyperactivity. Such problems have caused many children, especially boys, to be clinically diagnosed with Attention Deficit/Hyperactivity Disorder (ADHD). Using a teacher questionnaire to measure the scale of inattentiveness and hyperactivity in boys with fragile X, Cornish, Wilding and Munir (2001) found that teachers reported hyperactivity as a greater problem than inattentiveness. At the cognitive level, research indicates core problems with the ability to switch visual attention and to inhibit

repetitive behaviour in late childhood (Wilding, Cornish, & Munir, 2002). Hooper and collaborators (2000) provide suggestive evidence that these difficulties are present even earlier in childhood. Using the Leiter-R, a standardised assessment tool of non-verbal IQ, they investigated attention and memory abilities in a sample of 25 boys with fragile X syndrome between the ages of 4 and 13 years. As a group, the children showed great difficulties on subscales tapping selective attention and working memory.

There are no published studies investigating selective attention in younger children with fragile X. One key question is the extent to which difficulties with endogenous control, which are so prominent in late childhood and early adolescence, are already present during infancy and toddlerhood in fragile X. I shall address this question in Part II of the thesis. Do more subtle influences of exogenous factors impact on attentional difficulties? This will be the focus of Part III. In order to generate hypotheses about the early attentional profile in fragile X, it is vital to understand the causative molecular mechanism for the syndrome and its effects on brain structure and function.

1.2.2. Cellular and systems phenotype

The adult phenotype

The absence of FMR1 gene product (the Fragile X Mental Retardation protein, FMRP) is, as mentioned above, the sole genetic contribution to the fragile X phenotype (Verkerk et al., 1991, Pieretti et al., 1991). Greenough and collaborators (e.g., Greenough, Klintsova, Irwin, Bates & Weiler, 2001; Churchill, Grossman, Irwin, Galvez, Klintsova, Weiler, & Greenough, 2002) present robust evidence for a role of FMRP in processes underlying morphological synaptic changes in response to glutamatergic stimulation. This process is one of many “experience-dependent” synaptic processes, in which experience drives synaptogenesis. FMRP does not seem necessary for initial neuronal outgrowth, but is crucial for the refinement of dendritic spine morphology, a neural correlate of changes linked to both development and learning (Churchill et al., 2002). FMRP is an RNA-binding protein (Ashley et al., 1993, Siomi et al., 1993) that modulates the translation of a number of messenger RNAs, many of which are necessary for synaptic development and function (Brown et al., 2001). Indeed, the involvement of FMRP in increased protein translation

depends on synaptic stimulation of metabotropic glutamate receptors type I (Weiler & Greenough, 1993), both *in vitro* (Weiler et al., 1997) and *in vivo*, following rearing in a rich environment, learning of new motor skills (Irwin et al., 2000) and even unilateral whisker stimulation (Todd & Mack, 2000).

What are the structural and functional effects of FMR1 silencing? Loss of FMRP is associated with altered synaptic plasticity, as shown by knock-out mice models of FMR-1 silencing. The morphology of dendrites in FMR-1 knock-out mice is also atypical. Moreover, post-mortem studies of a small number of humans with fragile X syndrome also show this atypical dendritic morphology in parieto-occipital, temporal and visual cortex (Rudelli et al., 1985; Hinton et al., 1991; Wisniewski et al., 1991; Irwin et al., 2001). Dendrites in FMR1 knockout mice resemble immature cortex or the effects of sensory deprivation, characterised by a large number of long and thin spines¹ (as opposed to thicker and shorter ones that are characteristic of adulthood and rearing in rich environments, Turner & Greenough, 1985; Comery et al., 1997; Irwin et al. 2001). Functional effects of FMR-1 silencing have also been tested. Long-term depression (LTD) is enhanced in hippocampus, suggesting that FMRP plays a role in regulating activity-dependent synaptic plasticity (Huber et al. 2002). In contrast, long-term potentiation (LTP) is reduced at the terminal fields of hippocampal mossy fibers (Ivanco & Greenough, 2002) and this correlates with spatial deficits and sensory hyperreactivity in the mouse (Chen & Toth, 2001; Mineur et al., 2002).

Although studies of the functional effects FMR1 silencing have focused specifically on processes like LTP and LTD, the deficit has widespread effects on brain development. This is not surprising, given that FMRP is normally expressed throughout the brain (Feng et al., 1997). Structural abnormalities have also been reported in volumetric studies of whole human cerebral volumes (Reiss et al., 1995, but cf. Eliez et al., 2001) and in the volumes of specific brain areas (Reiss et al., 1991, 1994, 1995; Mostovsky et al., 1998; Eliez et al., 2001). The posterior vermis of the cerebellum is decreased (Reiss et al., 1991, Mostovski et

¹ Spines are the post-synaptic protrusions from dendrites (Ramon y Cajal, 1960) at which excitatory synapses occur (Harris & Kater, 1994; Nimchinsky, Sabatini, & Svoboda, 2002). Spine abnormalities have long been associated with mental retardation of unknown aetiology (Purpura,

al., 1998), whereas lateral ventricular volumes and caudate nucleus are increased (Reiss et al., 1991; Eliez et al., 2001). An increase in hippocampal and STG volumes has also been reported (Reiss et al., 1994), but these findings have not always been replicated (Jakala et al., 1997).

Researchers have attempted to explain both the generalised cortical effects and the more local volumetric differences in terms of FMRP expression levels in the typically developing brain. Hippocampus expresses relatively higher levels of FMRP and its lack in fragile X syndrome may explain relative volumetric differences (Reiss et al., 1994). However, such direct relationships are not warranted. For example, both hippocampus and cerebellum express particularly high levels of FMRP in typically developing brains (Devis et al., 1993; Hinds et al., 1993), but while hippocampal volumes are higher in people with Fragile X Syndrome, cerebellar volumes are lower. This outcome would not be predicted from FMRP expression levels alone (Greenough, October 2001, personal communication). Mostovsky et al. (1998) suggest that differences in expression over developmental time across cortical and subcortical areas may account for these effects. This highlights the importance of timing and development at the systems level, as well as at all other levels of description, rather than simplistic explanations in terms of FMRP expression.

Aspects of developmental change

FMRP is highly expressed in both adult and foetal brain tissues (Devys et al., 1993), but it does not act in isolation; it interacts with at least two proteins that are very similar to it in structure (Zhang et al., 1995; Hoogeveen et al., 2002). In human adult cerebellum and cerebral cortex, FMRP and these proteins are co-localised. However, in the foetal brain they are not. FMRP is located in the cytoplasm as in the adult, whereas one of the two collaborating proteins is also strongly expressed in the foetal nuclei (Tamanini et al., 1997). This suggests that the collaborative functions of FMRP may vary in undifferentiated foetal neurones compared to differentiated adults neurones. Moreover, the spine phenotype characteristic of knockout mice seems to be transient in developing knockout mice (Nimchinsky et al., 2001), suggesting that FMRP may be involved in plasticity early in development, but that even a transient delay may indeed affect neural circuitry to result in

1974), as well as Down's and Rett syndromes (Kaufmann & Moser, 2000). In the case of fragile X

long-lasting cognitive effects. Finally, excitatory synapses, whose changes in morphology are implicated in FXS, interact with different modulatory systems, including GABAergic and dopaminergic symmetric synapses (Goldman-Rakic et al., 1989; Nimchinski et al., 2002). This modulation of excitatory glutamatergic synapses by extrinsic neurotransmitters that are known to be crucial to endogenous attentional control (e.g., dopamine) depend not only on the functioning of such extrinsic neurotransmitters, but also on the adequate responses of glutamatergic synapses (Nimchinsky et al., 2002). Developmental cascading effects of defective glutamatergic function on the neuromodulatory functions of, for example, dopamine and acetylcholine, are thus to be expected.

Information on volumetry of the fragile X brain in early childhood lacked until very recently. Kates et al. (2002) gathered data for young children with FXS between the ages of 2 and 7. These reveal that overall cerebral volumes showed no difference compared to controls, whereas temporal lobe volumes were decreased (as in adults and older children with the syndrome). In contrast, parietal lobe white matter volumes showed a trend towards an increase, an abnormality that the authors linked with what is known about parietal dysfunction in adults with the syndrome, although the latter have not been investigated concurrently with structural and functional brain data.

Implications

The complex interaction of FMRP with other proteins across development suggests that the silencing of the FMR1 gene alone initiates a series of imbalances that have cascading effects on other elements of the developmental pathway at differing times through ontogeny. Similarly, changes in dendritic structure and overall structural brain changes are best considered as the endpoint of cascading effects on the structural and functional constraints of different brain areas at different developmental times, rather than the localised impairment of certain regions compared to others. Clearly the importance of considering *the developmental dimension* at the neurobiological level has implications for understanding the syndrome at the cognitive level.

syndrome, however, the causative mechanisms for this abnormality are intriguingly well understood.

Firstly, as discussed earlier, FMRP is involved in experience-dependent plasticity, a core process in development and learning. Therefore, focusing solely on the adult cognitive system would miss the emergent processes by which these restrictions in low-level synaptic plasticity result in the pattern of deficits seen in the adult. Instead, “we must consider the way in which the normal developmental process would be warped if cognitive development were attempted with a system whose plasticity is restricted” (Karmiloff-Smith, Scerif, & Thomas, 2002).

Second, given the role of activity-dependent synaptogenesis linked to glutamatergic stimulation in establishing neural networks across the developing cortex, it is likely that most, if not all, circuits in which this is involved will develop atypically to some extent. However, some cognitive domains and processes within each domain may rely less crucially on this particular low-level property, and thus they will develop to display less overt impairment. Recall that the complexity of dendritic trees and the functioning of glutamatergic connections may be crucial for the maintenance of sustained activity in recurrent circuits involved in endogenous attention. For example, endogenous influences on attentional control may rely more heavily than other functions on the integrative functions of dendritic arbors and dendrites and recurrent activity in fronto-parietal attentional networks. Therefore, they may be differentially more affected by dendritic abnormalities in fragile X syndrome than other functions, like exogenously-driven processes. However, the latter need not be immune of effects.

Recent findings provide support for the limited predictive power of protein expression alone on developmental outcome. Menon et al. (2001) found a correlation between FMRP levels and activation in frontal and parietal networks during a working memory task in young women with FXS. Moreover, when Bailey et al. (2001) examined the cognitive, motor and social development of young children with the syndrome, they found that FMRP expression accounted for a small but significant variance in the level, but not the rate of development. However, Hessel et al. (2001) showed that for boys with the syndrome, environmental factors (e.g., rated effectiveness of educational and therapeutic intervention) predicted composite behavioural scores and scores on the most problematic subscales (including inattention) in structured interviews and parental questionnaires, whereas FMRP expression levels were not

correlated with these problems. Correlations between FMRP expression and cognition have thus received support (e.g., Kaufman et al., 1999), but crucially point to the involvement of early experience in understanding FXS outcome. In other words, as with other syndromes, “development itself will be a crucial factor in governing atypical phenotypic outcomes across and within domains of both relative strength and weakness” (Karmiloff-Smith, 1998).

1.3. The development of selective attention in fragile X syndrome: A neurodevelopmental framework

As discussed in section 1.2.1, fragile X syndrome is not characterised solely by attentional deficits, because of a complex atypical phenotype across domains. There remain, however, important theoretical reasons for particularly focusing on attentional processes in FXS. The integration of our current understanding of attentional processes and of fragile X syndrome suggests that the syndrome is an intriguing tool to study the development of attentional processes. It allows us to explore how a system with compromised synaptic plasticity and morphological dendritic changes develops to perform processes that rely particularly on such a property.

1.3.1. Research Questions and Empirical Predictions

I shall operationalise endogenously-driven attentional processes as the processes that allow us to match a template of our goal (e.g., the representation of task-relevant stimuli) to the input provided by the visual environment. This matching process is also strongly influenced by the perceptual characteristics of the visual input itself (like, for example, the perceptual salience of stimuli in a display). For heuristic purposes, I shall distinguish these two contributors to selection as endogenously-driven and exogenously-driven influences on selection (albeit simplistically, Yantis, 1998, 2000).

Question One.

It has been suggested that endogenous influences on attentional control processes and the functioning of frontoparietal circuits responsible for them rely on the integration of multiple inputs (i.e., integrative functions of dendritic trees are “process-relevant” to attentional control). These integrative functions are likely to be compromised in a neural system in which dendritic morphology remains immature, as is the case in fragile X syndrome. Indeed, adults and children with FXS have shown impairments in tasks testing attentional control processes over and above what is expected given their overall level of cognitive functioning. Do infants and toddlers with FXS also display these difficulties?

If the low-level neural properties affected in FXS are relevant to attentional processes involved in goal representations, then I hypothesise that these processes will be affected in very young children with the syndrome, as they are in adults, over and above what is expected given the overall developmental level.

Question Two.

Although attentional control processes may rely more heavily on the neural properties affected in FXS, the effects on the morphology of glutamatergic synapses are ubiquitous. This suggests measurable, albeit more subtle, impairments in processes that rely less heavily on such neural properties, like exogenously-driven processing of visual input. Impairments in endogenous control, therefore, will need to be considered in relative, rather than absolute terms. For the purpose of this thesis, I shall investigate this issue by simultaneously studying both endogenous and exogenously-driven influences on attentional control in very young children with fragile X syndrome. Are toddlers and infants with FXS vulnerable to exogenous manipulations of the visual environment, despite the fact that data on adults suggest that they are not?

As the low-level property characterising FXS at the cellular level has ubiquitous effects across cortex, then I hypothesise that exogenously-driven attentional processes will also (albeit more subtly) be differentially affected in infants and toddlers with the syndrome.

Question Three.

An understanding of the syndrome at the neural level suggests that the morphological changes are experience-dependent and that this plasticity, a basic neural process involved in development and learning, is affected in FXS (Greenough et al., 2002). Thus, the effects of FMRP reduction on integrative functions of frontoparietal networks will need to be studied in a developmental context, especially given the heterochronicity of development across areas involved respectively in endogenous and exogenous attention. How, if at all, does the early profile of attention change? Does the early profile predict later functioning?

If the low-level property characterising fragile X syndrome is important for developmental change, then I predict not only an initial difference in endogenous attentional processes between infants with FXS and control populations, but also an increase in this difference as endogenous control improves in typical development. Secondly, in terms of exogenously-driven processes, I hypothesise that early differences will gradually decrease, as suggested by the adult proficiency in tasks requiring visuo-perceptual discrimination. Thirdly, if endogenous and exogenous influences on selection do not develop independently, then I predict that there will be a relationship between markers of performance for the two sets of processes, at different times in development.

1.3.2. Structure of the thesis

Chapter 2 will provide general rationales for the methodological choices applying to all empirical chapters. In particular, it will focus on the need to determine the typical developmental trajectory for each construct tested experimentally, on issues of matching controls to atypically developing performance, and on questions of statistical design.

The experimental chapters are organised in separate sections addressing each of the above research questions and predictions. Altogether, attention theorists point to the importance of a goal-related, endogenously-driven representation of task requirements for efficient response selection. This will be operationalised more clearly in Part II, in order to investigate whether infants and toddlers with FXS display difficulties in endogenous control as do the adults and older children with the syndrome. In particular, I shall focus on saccadic

responses (Chapter 3) and inhibition, planning and switching of manual responses (Chapter 4). Current leading models of selection also highlight the importance of stimulus-driven effects based on intrinsic or learned biases of the perceptual system, that are largely independent of task demands. In Part III, I shall evaluate the differential stimulus-driven influences on attentional selection in infants and toddlers with fragile X syndrome compared to controls. I shall manipulate these factors temporally (Chapter 5, investigating the effects of abrupt peripheral onsets on visual orienting) and spatially (modifying the perceptual salience of objects presented simultaneously across the visual field, Chapter 6). Part IV will explore longitudinal changes in both endogenous and exogenous processes and the possible relationships amongst them.

Methodological Issues

Although each empirical chapter will contain a dedicated section on methods, there are a number of general issues that need to be considered before focusing on specific experimental paradigms. All testing was conducted on two sessions (composed each of multiple visits) that were approximately twelve months apart. Not all children contributed to all experiments treated in the empirical chapters at the same time, although the sample was treated as a unit and tested longitudinally. This chapter will treat issues related to the overall clinical sample as well as the choice of standardised assessment tools and statistical analyses.

2.1. Participant Groups

2.1.1. Rationale for selecting the age groups of interest

The need to investigate the early attentional profile of fragile X syndrome is apparent from a clinical perspective. Indeed, attention is indicated as an area of striking impairment by both clinicians and parents (Hagerman, 1987; Turk, 1998), but no published studies investigate this issue with children younger than 4 years of age. However, the lack of information on

infants and toddlers is not the sole motivation for the choice of age groups tested in the present thesis. Critical theoretical reasons point to the need to select a sample of infants and toddlers in order to address the research questions outlined in Chapter 1.

The first research question addressed in this thesis is the following: does the adult pattern of difficulties with endogenous control (e.g., Munir et al., 2000) characterise individuals with fragile X syndrome throughout the life-span or is it the result of a later atypical deviation from normal? Secondly, I aim to investigate whether exogenous factors also result in subtly atypical performance early in development, in contrast to the relative proficiency demonstrated later in life (Cornish et al., 1999). These two research questions suggest the need to assess endogenous and exogenous influences on attention at an early stage of development and therefore select as young a sample as possible, given that a full diagnosis often comes in the second year of life (Bailey et al., 2001a). Thirdly, I aim to investigate similarities and differences between developmental trajectories for endogenous and exogenous influences on attentional control in FXS. This question can be addressed using two approaches: on the one hand, studying age-related changes in performance in a sample of children within a relatively large age range; on the other hand, following longitudinal changes in performance tapping on endogenous and exogenous influences on attention. Either approach would benefit from a sample chosen within an age range characterised by rapid changes in exogenous and endogenous effects on attention. This is indeed the case for the infant and toddler years. Exogenously-driven processing of visual stimuli reaches adult maturity before other cortical systems: for example, contrast sensitivity improves dramatically within the first 10 months of post-natal life (Maurer & Lewis, 1998; 2001). These fast changes in maturity depend on faster myelination, dendritic development and pruning of primary visual cortices (Huttenlocher, 1990). In contrast, endogenous control and the systems upon which it depends develop within a much slower time-scale, reaching maturity only in late adolescence (Diamond, 2001; Huttenlocher, 1979, 2002), suggesting heterochronous developmental trajectories for exogenously and endogenously-driven processes. Therefore, the infant, toddler and early childhood years are a crucial period during which to investigate differences in the developmental trajectories in exogenously-driven processing and endogenous control, both in the typical and the atypical case.

In particular, at the neural level, the time-frame for changes in plasticity differs for circuits involved in exogenously-driven processing as opposed to endogenous control (Huttenlocher, 2002). Therefore, the effects of an early change in plasticity, as is the case for fragile X syndrome, could impact differently on the two processes relative to the typical developmental trajectory. Areas upon which visual processing depends most heavily will have developed sooner, already showing differences between toddlers with fragile X syndrome and typically developing infants. These will not necessarily increase during the toddler years. In contrast, the areas upon which endogenous influences on selection depend will not have developed as quickly, even in the typical case. Therefore, the effects of the changes in plasticity caused by the fragile X syndrome will increase in the toddler years, as the typical developmental trajectory is increasingly characterised by changes in endogenous control. This points, again, to the infant and toddler years as an important age group in which to investigate the heterochronicity of the effects of the low level biological changes characteristic of fragile X syndrome.

2.1.2. Characteristics of the samples

Infants and toddlers with fragile X syndrome

The project focused on boys rather than girls with FXS, because their phenotype is relatively more homogeneous than that of girls (who express variable amounts of FMRP depending on the activation ratio of their functional X chromosome). Furthermore, the prevalence and early diagnosis of FXS are higher in boys than girls with the condition, so that it is easier to recruit a relatively large and representative sample of male toddlers, rather than girls. The majority of infants and toddlers with fragile X syndrome were recruited through the family support association (the Fragile X Society, UK). Impact and relevance of the project were first assessed by the academic committee of the Society. Information on the project was then forwarded to the parents of 26 infants and toddlers with the syndrome (boys from 0 to 48 months of age) throughout the United Kingdom. Four additional families were recruited with the help of the Genetics Unit at the Institute of Child Health, University College London, and at the University of Nottingham. The status of the children as carriers of the full mutation (FRAX-A) was confirmed through the Fragile X Society by the relevant genetic services. Further details on the genotype were not provided. All children in the

sample, except for three, were diagnosed because of parental concerns in their early developmental milestones. The remaining three children received a diagnosis because a family member (older sibling or relative) had been previously diagnosed with the condition.

All families expressing an interest in the project were involved. As detailed in the section on procedures, all children were visited for at least one full testing session (labelled hereafter as “Time 1”) and all families were invited to take part in the longitudinal follow-up approximately 12 months later, depending on parental availability (“Time 2”). The final group of children who volunteered consisted of 30 boys at Time 1 and 26 boys at Time 2. Four boys seen at Time 1 discontinued their participation to the project: in three cases this was due to family choices and in one because of a conflict between the necessary testing schedule and the pre-school time-table. The mean chronological age for the group of children who volunteered (standard deviation, median and range) is presented in Table 2.1. The median represents the age distribution of the group in a manner that is unbiased by extremes: indeed, only 4 children were younger than 18 months of age, with the remaining children in the sample being 31-months-old or older.

Table 2.1. Chronological age (mean, median, and range) of all infants and toddlers with fragile X syndrome who volunteered to take part at Time 1 and, 12 months later, at Time 2.

Testing session	Mean Chronological Age (CA, months +/- standard deviation)	Median CA (months)	Chronological Age Range (lower and upper limit)
<i>Time 1 (N = 30)</i>	37 (+/- 11)	42	7-50 months
<i>Time 2 (N = 26)</i>	49 (+/- 12)	54	18-63 months

Of the sample of 26 boys contributing longitudinal data, 21 provided data to a combination or all of the empirical chapters reported in this thesis (see Appendix A for details of individual participation). The remaining five children did not because of: a) reduced visual acuity that would confound measures of visual selective attention (one of the boys had a large visual field cut); b) refusal to perform on any of the experimental tasks either at Time 1 or Time 2 (four boys). All children (including the children who refused the tasks) were

tested with the general cognitive assessment tool described in section 2.2.2 in order to provide parents and the Family Support Association with data on their early development. Furthermore, I deemed it necessary to provide unbiased details of the entire sample characteristics without excluding the initial data on the least able or compliant toddlers. However, I shall hereafter focus solely on the experimental sample. Table 2.2 presents the mean chronological age for the group of children who contributed experimental data (standard deviation, median and range).

Table 2.2. Chronological age (mean, median, and range) of all infants and toddlers with fragile X syndrome who provided experimental data at Time 1 and, 12 months later, at Time 2 (N=21).

Testing session	Mean Chronological Age (months +/- standard deviation)	Median CA (months)	Chronological Age Range (lower and upper limit)
<i>Time 1</i>	37 (+/- 11)	41	7-50 months
<i>Time 2</i>	49 (+/- 12)	54	18-60 months

Comparison groups

In the present thesis, I aimed to control for two factors that could account for atypical performance by children with FXS in experimental tasks tapping attentional processes. On the one hand, their overall delay in development could explain attentional difficulties. Thus, I selected a sample of typically developing children chosen to match children with FXS individually on the bases of their overall developmental level. On the other hand, regardless of their overall developmental delay, children with FXS have more experience with the world than their young typically developing counter-parts. This becomes a relevant performance factor when assessing performance on a number of experimental tasks. For example, their experience with computers and computer touch-screens could potentially provide atypically and typically developing older children with skills that younger children do not develop until later. Thus, for tasks that required interacting with computers and computer touch-screens (Chapters 4 and 6), I also selected a sample of typically developing

children matched individually to the children with FXS by chronological age, to control for their potential differential level of experience.

It is important to note that limiting oneself to comparing participants with fragile X syndrome with individually matched typically developing infants and toddlers is problematic if the cognitive processes underlying typical performance on a task are not well understood for the age groups of interest. In research investigating atypical development, it is common practice to employ tasks that have been designed for young typically developing infants in order to study performance in older atypically developing individuals. For example, habituation and preferential looking paradigms used to test processes in typical infants have been successfully employed for atypically developing infants (e.g., Brown, 2000; Paterson, 2000). In other occasions, the response demands of well-established tasks used with older children or adults are modified/simplified for less able atypically developing participants, in order to tap constructs that those paradigms tap in typically developing groups.

However, there are a number of concerns involved in using this logic. From a practical point of view, older atypically developing children may be bored by stimuli and paradigms that are appropriate for younger typically developing children (e.g., see discussions of these issues by Brown, 2000; Paterson, 2000). From a theoretical point of view, the assumption that a particular paradigm operates for the age group of interest as it does in younger typically developing infants, older children, or adults, would in and of itself assume no developmental change in performance on the task. This is a matter for empirical investigation and should not be implicitly postulated. The approach taken here was therefore to essentially consider typically developing children as an additional experimental group. Before individual matching, I investigated performance in a larger sample of typically developing infants and toddlers within the range of interest for mental age matching on the grounds that:

1. This would provide clearer information on the mechanisms underlying changes in typical performance specifically for the age group of interest.

2. This would therefore allow for a clearer understanding of how the atypical group may deviate from the typical trajectory, rather than simply highlight differences in performance that may not provide any mechanistic explanation.

However, if children in the FXS group were then directly compared to a larger sample of typically-developing children, real group differences in processing could have been confounded by heterogeneity of variance across the groups (a smaller sample is more likely to be heterogeneous) and by issues of statistical power. Therefore, for each experiment, I first investigated changes in performance in a larger group of typically developing toddlers, and then proceeded to match each child with fragile X syndrome individually to typically-developing toddlers on the bases of developmental level (and chronological age in Chapters 4 and 6).

2.2. Procedural Choices

2.2.1. Testing clinical groups: Individuals with fragile X syndrome

Atypically developing populations often display attentional difficulties that hinder their ability to maintain on task. This had implications for planning the general structure of testing sessions. A number of measures were taken to address the difficulties of testing children with developmental delay and children with fragile X syndrome in particular.

Children and adults with fragile X syndrome are known to find changes in routine and dealing with novel environments extremely anxiety provoking (e.g., Hagerman & Cronister, 1996), resulting in challenging behaviours that are associated to elevated cortisol levels (Hessl et al., 2002). To reduce these effects, all families received details regarding the precise characteristics of the testing equipment, both in writing and in photographic format to be shown to the children (including a photo of the experimenter). Within the limits allowed by the experimental apparatus used, sessions were conducted at the children's home, not on nursery days to avoid disruption to the children's normal routine. Parents contributed to the planning of the testing session by indicating the place within their home in which children were most used to work productively (for example, with their Portage

teacher or under parental supervision). At Time 1, all testing was also preceded by a session during which I visited the family home and played with the children, without performing any formal assessment. This allowed me to establish a rapport with the family and child, decreasing the anxiety-provoking effect of dealing with a stranger.

At Time 1 testing therefore consisted of the following meetings, as early during the day as possible to avoid the effects of fatigue. The length of each session was also kept to a minimum of an hour.

1. A preparatory meeting involving a semi-structured parental interview and informal play to build a rapport with the child.
2. A meeting during which the overall developmental level of the child was assessed (as discussed in more detail below) for later matching with a typically developing child.
3. An experimental session at the child's home during which he was presented with the portable experimental apparatus discussed in Chapter 4 and 6. Not all children performed these tasks at Time 1, as will be discussed in the relevant empirical chapters.
4. An experimental session at the Infant Testing Lab at the Neurocognitive Development Unit, involving recording of eye-movements discussed in Chapter 3 and 5, depending on whether the parents had expressed an interest in travelling to London.

At Time 2 (12 months later), testing consisted of the following meetings:

1. A meeting during which the overall developmental level of the child was re-assessed for later matching with a typically developing child.
2. An experimental session at the child's home during which he was presented again with the portable experimental apparatus to provide longitudinal data (discussed in Chapters 7 and 8).
3. For parents who had later decided to visit London, an experimental session at the Infant Testing Lab, involving recording of eye-movements discussed in Chapter 3 and 5.

2.2.2. Measuring the general cognitive phenotype for matching

Determining a level of general cognitive functioning in the clinical group is crucial in order to select matched control groups against which one aims to measure performance on any

tasks (e.g., treated in Moore, 2001). It therefore becomes vitally important to motivate the choice of the assessment tool that will be used to ascertain the overall cognitive level. In the case of populations characterised by developmental delay, this is a challenge exacerbated by uneven cognitive profiles. For example, Wishart and Duffy (1990) showed that, for infants and toddlers with Down's syndrome, overall delay in general cognitive scores masks an uneven pattern of performance with visuo-spatial skills exceeding scores in the verbal domain and instability in test-retest reliability. This has implications for matching based on overall cognitive functioning, because it will select matched controls who will tend not to be characterised by this uneven profile of performance. This will automatically result in relative advantages and disadvantages for individuals with Down's syndrome for the visuo-spatial and the verbal domains respectively. These may complicate the interpretation of group differences on tasks that tap more directly the constructs of interest for the experimenters.

This issue is further complicated by the fact that the uneven profile of cognitive functioning across domains is not static and varies across development, so that when recruiting across a relatively large age range the relative contribution of domains of strength and weaknesses varies. This has been shown for individuals with fragile X syndrome in particular (Hodapp et al., 1991). In sum, no matching tool will provide an absolutely perfect control group, and the appropriateness of each control group will depend on the experimental question of interest in each study.

What are the practical implications of these issues when choosing a particular matching tool? In this thesis, comparisons to control groups aims to answer the following experimental question: do individuals with fragile X syndrome display attentional difficulties over and above those that would be expected given their overall developmental delay? The assessment tool of choice therefore needs to satisfy three requirements. It would need to provide a reliable assessment for children with fragile X syndrome whose chronological age would fall below one year and whose expected developmental rate is most often approximately half than of typically developing children (Bailey et al., 1998). It would need to require a relatively brief administration time, given the pattern of behavioural difficulties with inattention and hyperactivity that are characteristic of the sample (Bailey et al., 2000). It would also need to provide reliable floor and ceiling scores for children whose

performance would fall considerably below or above this expected level, given that the population is characterised by a considerable level of variability in performance on general cognitive assessment tools (Bailey et al., 2000).

For this thesis, the general level of cognitive functioning, crucial for the selection of individually matched control participants, was assessed through a standardised ability test, the Bayley Scale of Infant Development II – Mental Scale (BSID-M; Bayley, 1993). This is the updated version of an earlier existing popular assessment tool (Bayley, 1969) and offers a comprehensive examination of cognitive developmental functioning in infants aged 1-42 months. According to the author, it assesses sensory-perceptual acuity and discriminations, object constancy, memory, learning, problem solving, early verbal communication, early abstract thinking ability, and early number concepts. This assessment tool was chosen amongst the few other scales available for the assessment of infants on a series of grounds. Firstly, it satisfies the three requirements outlined above. It allows assessment of children as young as 1 month of age. It is also characterised by discrete item sets for each age group, which make administration times relatively brief, and its floor and ceiling scores are reliable compared to other assessment scales available for the youngest children (Bradley-Johnson, 2001). Furthermore, it is the most commonly used test in assessing developmental levels in infants and toddlers for matching purposes in experimental studies and has been successfully used for studying early cognitive development in atypical populations (e.g., Brown et al., 2003; Moore et al., 2002; Paterson et al., 1999).

There are, however, a number of very important limitations to the use of the BSID-M for the assessment of cognitive development in atypical groups. The BSID-M consists of different items sets that have been tailored for different, but partly overlapping age groups of infants and toddlers. Crucially, the item set employed for the assessment has repercussions on the final scores, with typically developing children scoring worse if tested on lower item sets (Gauthier et al., 1999). This is particularly problematic for atypical populations (Washington et al., 1998), for whom the appropriate item set is rarely that of their chronological age, for which general delay would often result in floor performance. The choice of the appropriate item set used has to be based on a number of considerations. On the one hand, an item set that contains items that are too difficult could result in repeated failures to complete them,

frustration and finally refusal to complete the testing session; on the other, choosing too low an item set would misrepresent the child's level of ability. In particular, the literature on the level of cognitive functioning in children with fragile X syndrome in the age range of interest, indicates that on average toddlers with the syndrome function approximately at a level that is half of their chronological age (Bailey et al. 1998; 2000; 2002). However, the literature on the high degree of individual variability in functioning within this group (e.g., Hooper et al., 2000; Bailey et al., 2001b) suggests that there may well be children whose performance would be much lower and others who could perform nearly as expected given their chronological age. I motivated the choice of item set on the bases of the following criteria:

1. I would select the item set that would be appropriate for a child of approximately half the chronological age as that of the child with fragile X syndrome;
2. At Time 1, during the first preparatory meeting, I would observe the child's behaviour in free-play, to gather preliminary indications of whether the item set selected as indicated above could result in floor or ceiling performance.
3. At Time 2, this information was complemented by the scores obtained at Time 1.
4. During the session assessing the general cognitive functioning of the child, I would be prepared to flexibly change the item set following the instructions given in the manual of the BSID-M in case of repeated consecutive failures or successes.
5. When possible, clinical reports volunteered by the parents (assessments by clinical and educational psychologists) provided converging evidence for my assessment.

Having selected the appropriate item set for each child, items were administered as indicated by the manual for the BSID-M, except for the requirement for the experimenter to sit facing the child. Direct eye-gaze is an anxiety-inducing factor for children with fragile X syndrome (Hagerman & Cronister, 1996), who perform better when tested from the side (Saunders, 2000). This change was also applied to the assessment of the individually matched typically developing children with the BSID-M to ensure that changes in the administration procedures did not cause spurious group differences.

The BSID-M was used both at Time 1 and at Time 2. Using the BSID-M for all children in the sample allows assessing children on the same tool across time-points, rather than

introducing the confounding factor of a comparison across dissimilar tools. The original BSID-M provides a normalised standard score only for children whose chronological age falls within the standardised age range (1-42 months) and normalised standard scores have only more recently been extended to very low functioning children (Robinson & Mervis, 1996). The curators of the scale suggest that it may be appropriate for older children with significant cognitive delay, because they may only perform at floor on scales for older children.

However, testing children whose chronological age is above that of the upper limit for which the BSID-M has been standardised is problematic. In those cases, it is only possible to derive a mental age equivalent for children's performance and not a normalised standard score. While this is a viable strategy for selecting individually matched controls for experimental studies, the clinical significance of age equivalent scores for older atypically developing children has been questioned (Nellis & Gridley, 1994; Washington et al., 1998).

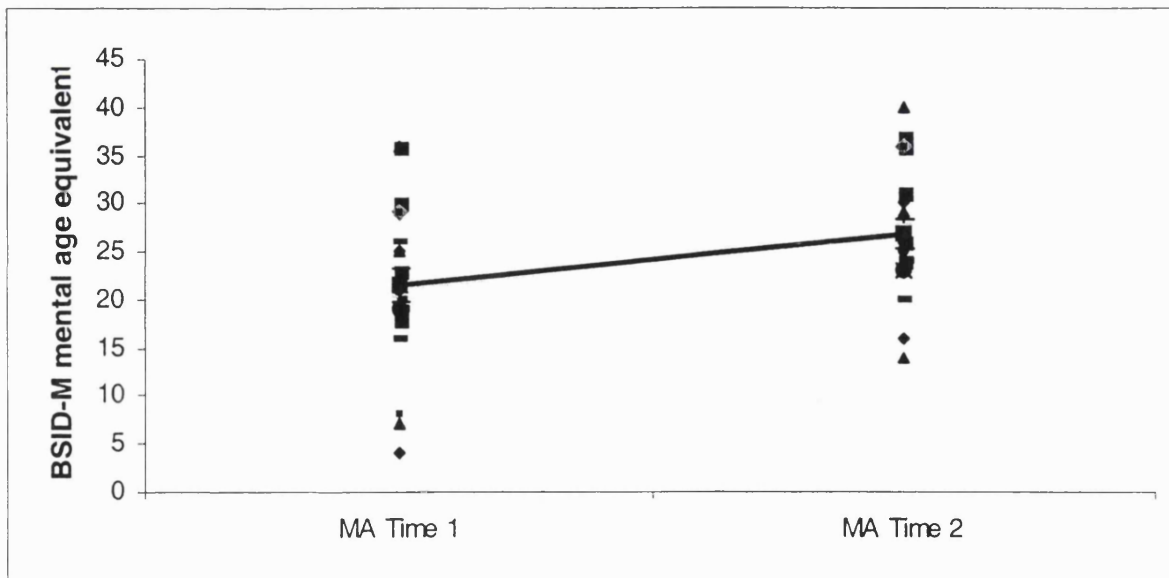
When relevant, the implications of using the BSID-M with older children will be considered for the individual data sets, given that each experiment tested infants and toddlers of slightly different age groups. In general, the criteria outlined above were used to determine the item set used for assessment on the BSID-M. If older/higher functioning children were assessed on the final item set on the scale, particular care was taken to determine whether their performance reached ceiling. I decided that, only in this case, I would use a different assessment tool that would be appropriate for older children (the British Ability Scale, Early Years, Elliott, 1983). This was eventually not necessary for any of the children in the experimental sample. Table 2.3 presents mean age equivalents for the group of children who contributed experimental data (standard deviation, median and range).

Table 2.3. Mental age equivalent (mean, median, and range) of all infants and toddlers with fragile X syndrome who provided experimental data at Time 1 and, 12 months later, at Time 2 (N=21).

Testing session	Mean Mental Age Equivalent (MA, months +/- standard deviation)	Median MA (months)	MA Range (lower and upper limit)
Time 1	21 (+/- 8)	21	4-36 months
Time 2	27 (+/- 7)	26	14-40 months

Longitudinal changes in the mental age equivalents for individual children are also represented graphically in Figure 2.1. Both the average level of functioning and the rate of change over a period of 12 months reflect similar results obtained for infants and toddlers with fragile X syndrome assessed using the Battelle Developmental Inventory (Bailey et al., 1998; 2000, 2002). This suggests that, despite all limitations discussed above, the use of the BSID-M for this sample provides a valid and conservative estimate of general cognitive functioning that is adequate for matching purposes.

Figure 2.1. Mental age equivalent of individual infants and toddlers with fragile X syndrome who provided experimental data at Time 1 and, 12 months later, at Time 2 (N=21). The average mental age equivalent for the group (+/- standard error) is represented by the bold black line.



2.2.3. The use of non-attentional control measures

As the overall aim of the present thesis is to investigate attentional difficulties in fragile X toddlers and infants, it was extremely important to collect non-attentional baseline measures, as well as develop tasks that would target attentional processes directly. This would allow me to disentangle group differences that could depend on factors other than attentional differences, like differences in motor control, overall slower motor speed and lower visual acuity. Each will be discussed within the context of specific experimental manipulations. Non-attentional baseline measures were either analysed separately or used as covariates (depending on individual experimental designs) to establish whether any group effects could be attributed to non-attentional factors.

2.3. Rationales for Statistical Choices

Individual chapters discuss the choice of statistical analyses that were more appropriate to address specific experimental questions. Here, I shall examine two important issues that are relevant to the interpretation of results and the statistical analyses of all empirical chapters.

First, it is important to consider *a priori* the implications of statistically significant differences amongst groups matched on the bases of developmental level or chronological age and, crucially, what the absence of differences would not entail. The finding of differences between the FXS group and the other groups would provide confidence in suggesting that infants and toddlers with fragile X syndrome display attentional difficulties over and above those that would be expected given their level of experience and/or overall developmental level. However, the absence of a difference between the atypical group and typically developing groups matched on general developmental level would need to be evaluated with caution for the following reasons. Firstly, the sensitivity of the experimental measures would have to be questioned. It could for example be the case that finer or alternative measures of performance could highlight differences amongst the groups, as has been repeatedly highlighted by comparing the absence group differences on gross standardised tasks and tasks of on-line processing (e.g., Tyler et al., 1997) or studies of the

neural correlates of equivalent behavioural performance (e.g., Grice et al., 2001). Secondly, when the clinical population shows equivalent behaviour to a group of younger typically developing individuals, one needs to remember that absence of a statistically significant difference implies at least gross delay, rather than indicating intactness of a particular cognitive process. This bears a particularly important implication for developmental disorders: the possibility that initial “simple delay” of a particular process may lead to deviant performance in other processes at various developmental time points. As will be discussed in Chapter 7, the dismissal of delayed performance carries the assumption that the processes under investigation do not interact with others throughout developmental time (Karmiloff-Smith, Scerif, & Ansari, 2003).

The second broader issue regarding statistical choices is the statistical power of analyses comparing small groups of typically and atypically developing individuals. There are inevitable practical constraints when seeking to recruit toddlers with FXS to complete experimental tasks. Some of the experiments presented here had relatively small sample sizes, limiting the statistical power of the analyses. Moreover, unless stated otherwise, significance levels for all statistics were two-tailed, increasing the probability of Type II errors, especially for small sample sizes.

This concern was addressed as follows. First, by noting that the weight of the theoretical arguments put forth here in terms of endogenous and exogenous influences on selection, as well as their longitudinal changes, rests on statistically significant differences between controls and toddlers with FXS. It does not rest on finding impaired performance on some tasks and not others, an argument that would require higher confidence in the power of analyses resulting in null findings. When unexpected null findings turned out to be of particular interest (e.g., in Chapter 3, Experiment 1b), these were illustrated with scatterplots presenting individual data-points, to provide more confidence in them through simple visual inspection.

Secondly, I conducted compromise power analyses (G-Power, Faul & Erdfelder, 1992) in order to establish whether the sample sizes were too small to yield statistically significant results on the variables of interest. Compromise analyses were favoured over post-hoc

analyses because the sample here was effectively the largest available sample of infants and toddlers with fragile X syndrome who may volunteer to take part in the project. I focused on calculating power for the main effects of group membership and for the interaction effects of group with the within-subject variables. Table 2.4 illustrates the power of the analyses assuming various effect sizes, according to the conventions set for ANOVA ($f = .10, .25, .40$ for small, medium and large effect sizes respectively, Cohen, 1988). Further assumptions of calculations in G-power that I adopted here (following Faul & Erdfelder, 1992) are: a) a population correlation between the individual levels of the repeated-measure effect of $\rho = 0.75$; b) sphericity, i.e., homogeneity of variance and equal correlations across repeated measures. However, If the assumption of sphericity is violated by the data, F values are artificially inflated and the probability of Type I errors is higher. This concern was addressed for each experiment independently (both for large and small sample sizes) and a number of measures were employed (the use of the Greenhouse-Geisser correction and the use of the appropriate non-parametric tests as converging statistical evidence).

For example, Experiment 5a (Chapter 7) contained the smallest number of participants: 16 in total (8 toddlers with fragile X syndrome and 8 individually matched controls). In this case, for a medium effect size and with the sample sizes employed here, the power to detect a significant effect would be considered satisfactory for an interaction effect of group with a within-subject variable, but not for a main group effect (Faul & Erdfelder, 1992). Beyond the general prudence necessary in drawing conclusions from null results (e.g., Howell, 1997), the analyses in Table 2.4 underscore that, for small sample sizes as those employed here, researchers should primarily focus on generating experimental tasks that hypothesise group differences, rather than null results. Furthermore, when null results are obtained, they should be interpreted with extreme caution. This is indeed the general strategy employed here.

Table 2.4. Compromise power analyses for the effect of Group and its interaction with other variables in all experiments in which infants and toddlers with fragile X syndrome (labeled FXS) were compared to mental age matched controls (labeled MA). For the interaction effects, different levels of power are reported depending on whether the within-subject variables has 2 (most experiments) or 4 levels (Experiment 3b). [Next page]

<i>Statistical Parameters</i>		<i>Exp. 1b: Endogenous Orienting</i>	<i>Exp. 2b: Control of Spatial Conflict</i>	<i>Exp. 3b: Exogenous Orienting</i>	<i>Exp. 4b: Visual Search and Target Salience</i>	<i>Exp. 5a: Longitudinal Changes in Visual Search</i>
<i>N</i>	<i>FXS</i>	10	10	9	14	8
	<i>MA</i>	10	10	9	14	8
	<i>CA</i>		10		14	
<i>Main Effect of Group: Assumed Effect Size</i>	<i>Large</i>	0.76	0.78	0.74 (2 levels) and 0.75 (4 levels)	0.84	0.72
	<i>Medium</i>	0.63	0.65	0.61 (2 levels) and 0.62 (4 levels)	0.69	0.61
	<i>Small</i>	0.52	0.53	0.52 (2 levels) and 0.53 (4 levels)	0.54	0.52
<i>Interaction Effects of Group: Assumed Effect Size</i>	<i>Large</i>	0.98	0.99	0.98 (2 levels) and 0.99 (4 levels)	0.99	0.97
	<i>Medium</i>	0.91	0.95	0.89 (2 levels) and 0.94 (4 levels)	0.98	0.87
	<i>Small</i>	0.64	0.70	0.63 (2 levels) and 0.66 (4 levels)	0.74	0.62

Table 2.4. Compromise power analyses for the effect of Group and its interaction with other variables in all experiments in which infants and toddlers with fragile X syndrome (labeled FXS) were compared to mental age matched controls (labeled MA). For the interaction effects, different levels of power are reported depending on whether the within-subject variables has 2 (most experiments) or 4 levels (Experiment 3b).

Endogenous Influences on Selection

Part II - Introductory Synopsis

As discussed in Part I, there are important theoretical reasons for investigating the early precursors of the difficulties with the endogenous control of attention that are characteristic of the late childhood and adulthood profile of fragile X syndrome. In Part II, I investigate endogenous attention by tapping distinct operationalisations of the construct of goal-directed attentional control. I hypothesize that, if the neural processes affected in fragile X syndrome are relevant to the early development of endogenous attention, these multiple measures should provide converging evidence for difficulties with the control of attention from infancy and toddlerhood.

Chapter 3 assessed whether infants and toddlers with fragile X syndrome display atypical control of endogenously-driven saccades by adapting paradigms that have been used with typically developing infants and adults, as well as with neuropsychological patients. In particular, I examine difficulties in inhibiting reflexive saccades to sudden peripheral onsets as well as difficulties in anticipating the appearance of targets at known locations.

Chapter 4 focuses on the ability to inhibit prepotent manual responses in a spatial conflict task adapted for use with toddlers. Both with typically developing toddlers and toddlers with fragile X syndrome, I also address the question of whether measures of everyday inhibitory control predict the ability to resolve spatial conflict and inhibit prepotent responses.

For all measures, particular attention will be drawn to the cross-sectional changes in performance by typically developing infants and toddlers as well as in the sample of children with fragile X syndrome.

Endogenous Control of Orienting

“Our eyes are on the move most of the time during our waking hours. We make about 3 saccadic eye-movements per second, some 170,000 a day and about 5 billion in an average lifetime. [...] Seldom does one hear about individuals complaining at the end of the day of having made those 170,000 saccades.” (Schiller, 1998, p. 3)

Eye-movements are necessary operations for our explorations of the daily visual world. Indeed, the ability to visually orient towards stimuli relevant to current goals is a crucial aspect of visual selection. Nevertheless, the relationship between eye-movements and attention has been a hotly debated topic (e.g., Klein et al., 1992; Klein & Pontefract, 1994). This is due to the fact that, while at any moment in time there is only one location to which we can direct our foveae, the use of a similar metaphor for attention has been heavily criticised in the last decades (e.g., cf. Posner, 1980; and Desimone & Duncan, 1995). However, although attention and eye-movements can be fully dissociated (Klein et al., 1992; Klein & Pontefract, 1994), there is nonetheless a great degree of overlap between the neural systems involved in both processes (Nobre et al., 2000). Indeed, eye-movements are preceded by the orienting of visual attention to the target location before the actual

execution of the saccade (e.g., Hoffman & Subramaniam, 1995), and attentional cues directly affect saccade execution evoked by direct stimulation of the primate superior colliculus (Kustov & Robinson, 1996). Furthermore, in studies investigating covert orienting of attention, processes like inhibition of return (the topic of Chapter 5) have been attributed to the preparation processes for saccadic eye-movements (Rafal et al., 1989; Reuter-Lorenz & Rosenquist, 1996). Most importantly, from a developmental perspective, while infants are relatively immobile, eye-movements are the major means for the infant to inspect the visual world during the first year of life, and therefore constrain their ability to select stimuli in their visual field (Johnson, 1990). Collectively, these studies make eye-movements a powerful marker of attentional development.

As discussed for attentional processes in general in Chapter 1, researchers working on the control of eye-movements distinguish between different factors contributing to saccade planning and execution, both in the adult (e.g., Fischer, 1998) and in children (e.g., Hood, Atkinson, & Braddick, 1998). Eye-movements are under the control of goal-directed endogenous factors, whose effects can be measured by the ability to control saccades to peripheral stimuli or anticipate the appearance of interesting targets at expected locations. However, many successful models of saccade execution also take into consideration the interaction between endogenous (also termed voluntary or intentional) and exogenous signals (i.e., directly visually guided) at multiple levels of online neural processing (e.g., Grossberg et al., 1997; Lefevre et al., 1998; Trappenberg et al., 2001). The differentiation between endogenously controlled saccades and saccades triggered by exogenous factors at the cognitive level is grounded in distinctions between the neural substrates of each process, both in the adult and in the developing brain. I shall therefore review the literature on the typical and atypical development of saccadic control, with a special emphasis on its neural substrates and its implications for fragile X syndrome.

3.1.1. Typical development of saccadic control

Visual orienting is the primary way in which infants explore their visual world during the first year of life. Therefore, studies of the development of oculomotor control have influenced much of the literature on the early development of attention (Bronson, 1974;

Atkinson, 1984; Johnson, 1990). These models drawn from the literature on the neural correlates of oculomotor control (Schiller, 1985, 1998). These will be reviewed in the section below, followed by a discussion of the literature on the development of the neural correlates of saccadic control in human adults and non-human primates.

Behavioural and cognitive level of description

Studies of eye-movements in infants have focused on the production of visually-guided saccades towards peripheral stimuli under varying conditions and have revealed striking changes in the development of visual orienting during the first year of life as well as continuities with later development and adulthood (Atkinson, 1984; Johnson, 1990; Maurer & Lewis, 1998). For example, newborn babies exhibit orienting towards sudden onsets within the temporal as opposed to the nasal visual field (e.g., reviewed in Maurer & Lewis, 1998). This effect is maintained to a lesser degree in the adult, with stronger effects of exogenous cues presented in the temporal visual field (Posner, 1980). In contrast, the ability to orient to a peripheral stimulus in conditions in which a central fixation stimulus remains visible as opposed to when it disappears develops dramatically over the first months of life. Two-month-old infants indeed exhibit prolonged periods of fixation, with difficulties (and often ensuing frustration!) in looking away from salient visual stimuli, a behavioural pattern termed “obligatory attention” (Stechler & Latz, 1966) or “sticky fixation” (Hood, 1995). A longitudinal investigation of this effect between birth and 6 months revealed an inverted U shape for visual fixation, with infants fixating for longer periods at two-months than at any of the other ages (Hood et al., 1996).

What are the cognitive mechanisms driving these developmental changes? Hood (1995) proposed that this is likely to reflect deficiencies in mechanisms that allow a new stimulus to override the capture of fixation, a suggestion that is supported by the decrease in this effect when multiple competing stimuli are present. “Sticky fixation” may be an extreme example of the normal effects of stimulus competition on saccade execution, and it can be measured by manipulating the temporal gap between the offset of a fixation stimulus and the onset of peripheral targets in infants (Hood & Atkinson, 1993) and in adults (Saslow, 1967). Executing saccades to peripheral stimuli while a competing central stimulus is present requires the ability to voluntarily disengage from the central stimulus, but it is also driven

exogenously by the visual capture effect of the peripheral stimulus. The control of goal-directed saccades has been studied more directly by examining the production of saccades anticipating the appearance of a target at a known location (Haith et al., 1988). It has also been investigated elegantly by manipulating the location of the appearing stimulus and its relationship to predictive central cues (e.g., Johnson, Posner, & Rothbart, 1991) as well as peripheral cues (Johnson, 1995), as will be discussed in more detail below in relation to Experiment 1. In sum, these studies suggest that infants as young as 4-months can develop expectancies from predictive spatiotemporal events and guide their eye-movements accordingly.

Comparatively little is known about the development of saccadic functions in older children and adolescents. Amongst the reported findings are the following: in children and adolescents between 5 and 16 years of age, saccades towards peripheral stimuli (prosaccades) are slower and exhibit a larger effect of the temporal gap between fixation point and peripheral stimulus (Cohen & Ross, 1977, 1978). Eight- and 9-year-olds produce more reflexive saccades towards peripheral distractors during fixation trials (Paus et al., 1990). Furthermore, participants between 6 and 26 years display age-related reductions in reaction times, in proportions of direction errors and in the error correction latencies in antisaccade tasks (Klein & Foerster, 2001). In particular, Klein and Foerster (2001), studying performance in three age groups: 6-7, 10-11, and 18-26 years, and Fischer et al. (1997a), with 10 age-groups of participants aged 8-16, highlighted differences in developmental changes for various parameters from pro- and antisaccade tasks. In the largest study to date on the developmental changes of eye-movement parameters, Klein (2001) tested 199 participants from 6 to 28 years of age using pro- and antisaccade tasks using both gap and overlap conditions for the offset of fixation points compared to the peripheral stimuli. The author carried out multiple regression analyses, analyses of variance and covariance, and a principal components analysis to investigate developmental changes in performance on these tasks. Of relevance here, age accounted for up to 51% of the variance in the percentage decrease of erroneous looks towards peripheral stimuli in the antisaccade paradigm and was also a significant predictor of the onset of antisaccades, both of which are considered, according to Klein (2001), the core antisaccade parameters. In contrast, other measures like the proportion of express saccades (i.e., saccades with an onset

between 80 and 130 ms after stimulus onset) did not vary significantly with age. The author also highlighted the importance of always investigating age effects when studying eye-movement effects over a relatively large age range of children or adolescents, whether they are developing typically or atypically. However, thus far no data have been gathered regarding the development of pro- and antisaccade production between the ages of 1 and 5 years of age and this will be the focus of Experiment 1a, treated in section 3.2.1.

Neural systems requirements

Figure 3.1 illustrates the large network of areas that have been implicated in oculomotor control in adults through neuroimaging studies (O'Driscoll et al., 1995; Sweeney et al., 1996; Doricchi et al., 1997), electrical recordings from non-human primates (e.g., Munoz & Wurtz, 1992, 1993) and patients with localised brain lesions (e.g., Guitton et al., 1985; Pierrot-Deseilligny et al., 1995; Rivaud et al., 1994).

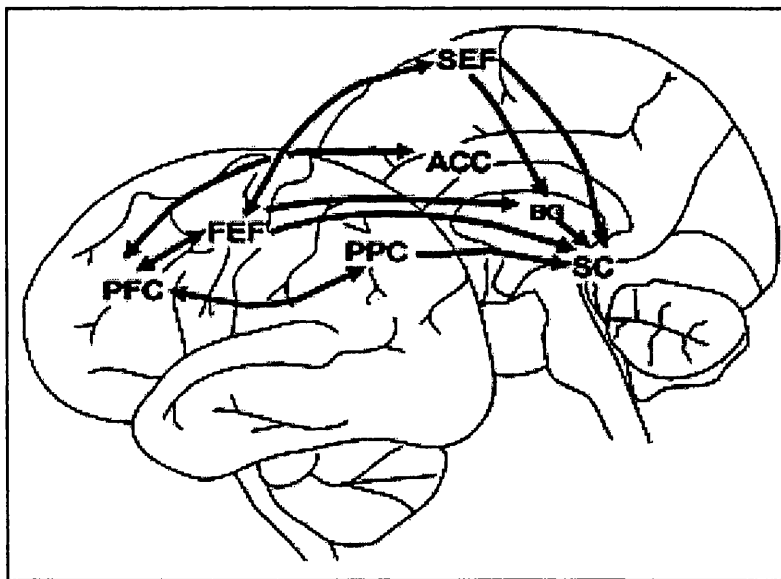


Figure 3.1. Structures believed to be involved in eye-movement generation. The figure shows the cortical and subcortical structures which are involved in the correct performance of the antisaccade task in humans and it illustrates a simplified schematic of their connectivity. ACC, anterior cingulate cortex. BG, basal ganglia. FEF, frontal eye field. PFC, prefrontal cortex. PPC, posterior parietal cortex. SC, superior colliculus. SEF, supplementary eye field. (From Everling & Fischer, 1998).

These studies implicate a large number of cortical areas in eye-movement control. Notably, these overlap with areas involved in visual selective attention: lateral intraparietal area (Zhang & Barash, 2000), supplementary eye-fields (Schlag-Rey et al., 1997), frontal eye-

fields (Everling & Munoz, 2000). All these areas have extensive projections to the superior colliculus, a midbrain structure whose function is crucial for the integration of endogenous and exogenous signals for saccade generation. Functionally, adult oculomotor control seems to be implemented by two systems playing different roles in eye-movement control (for a seminal review and update, see Schiller, 1985, 1998). The posterior system reaches the brainstem through the superior colliculus and appears central for the generation of exogenously-driven eye movements. Outputs from the superior colliculus are modulated by converging excitatory inputs from primary visual cortex, middle temporal area and parietal cortex and as well as by an inhibitory pathway from substantia nigra and basal ganglia. The anterior system is probably constituted of two distinct but integrated subsystems, the frontal eye fields and the dorsomedial prefrontal cortex. The latter is involved in carrying a place code for saccade planning, while the former seems more involved in the planning of eye movement sequences, predictive tracking and memory-guided saccades (Schiller, 1998).

How do these functions develop? Bronson (1974) first addressed this question by suggesting that visually-guided behaviour in the newborn is controlled primarily by means of a subcortical retinocollicular pathway, with control progressively shifting to cortical pathways. However, more recently both Atkinson (1984) and Johnson (1990) have argued that a cortical versus subcortical dichotomy is too simplistic to capture the complexity of the observed transitions (see section 3.1.1). Further, Johnson (1990) maintained that the characteristic sequence of visually guided behaviours emerging in infancy would depend on the developmental state of the primary visual cortex. The proposal was grounded on neuroanatomical data suggesting that: (1) primary visual cortex is a major gateway for both the anterior and the posterior cortical pathways (Schiller, 1985); (2) the pattern of growth of primary visual cortex follows an inside-out pattern, with deeper layers showing greater dendritic branching and length (Huttenlocher, 1990, 2002) than upper layers; (3) inputs and outputs from primary visual cortex are restricted to particular layers. Johnson (1990) argued that as layers of primary visual cortex reach their mature state, different pathways involved in oculomotor control come on line. This proposal accounted for the sequence of changes in infants' visual orienting behaviour. However, more recently Johnson et al. (1998) and Johnson (2001) have highlighted how a simple maturational account does not provide mechanistic explanations for all observed transitions, nor does it account for all the

neuroanatomical data. For example, saccadic control by the superior colliculus on eye-movement in adult animals depends on cortical input (Schiller, 1998). To what extent do these cortical projections regulate exogenous saccades earlier in life? What are the mechanisms involved in these quantitative improvements?

Csibra et al. (1998, 2000, 2001) have begun to address this question by investigating the electrophysiological correlates of neural processes leading to the production of saccades to peripheral stimuli, by manipulating the fixation offset parameters as described for behavioural studies of the gap effect reviewed above. They showed a gradual development over the first year of life of the saccadic spike potential, a parietal marker of saccade planning in adults (Csibra et al., 1997). Although 12-month-old infants exhibit the spike potential, this has smaller amplitude than the potential found in adults, suggesting gradual development of cortical (parietal) processes leading to saccade generation. However, no research thus far has investigated these processes in toddlers, and the production of antisaccades (as defined in the adult literature) has not been reliably demonstrated in children younger than 6 years of age (Everling & Fischer, 1998). A viable strategy for investigating low-level neural requirements for the development of this ability is the study of populations whose atypical development is due to known neurobiological factors, as is the case in fragile X syndrome. Before generating specific hypotheses, I shall review the literature on the atypical development of oculomotor control.

3.1.2. Atypical development of saccadic control

Oculomotor control has been widely investigated in a variety of neurodevelopmental conditions known to affect the endogenous control of attention. For example, several studies reported that schizophrenia and schizotypal behaviours are associated with high error rates on smooth pursuit and antisaccade tasks (e.g., Fukushima et al., 1988; O'Driscoll et al., 1998). In addition, antisaccade error rates were found to be elevated in patients with obsessive-compulsive disorder (e.g., Tien et al., 1992) and depression (Katsanis et al., 1997). Klein and colleagues (2002, 2003) investigated pro- and antisaccade parameters in children and adolescents with ADHD, showing marked atypical developmental changes in

antisaccade parameters (see section 3.2.1. for a description of the task) in the ADHD group compared to controls.

Although there is growing knowledge on the development of oculomotor control in atypically developing populations, there are relatively fewer studies investigating parallel issues early in atypical development. Brown and collaborators (2002), for example, first studied saccade planning and sustained attention in infants with two neurodevelopmental conditions of known genetic origin, Williams syndrome and Down's syndrome, and found different patterns of performance by the two groups. Like adults with Down's syndrome, infants with this syndrome displayed difficulties in sustaining attention, whereas infants with Williams syndrome did not perform poorly contrary to what would be predicted from their adult attention profile. However, infants with WS were significantly less successful than DS and control groups at combining extra-retinal information with retinal positions to produce saccades correctly, a pattern of performance that may relate to the visuospatial difficulties that are documented in the condition in adulthood. The findings stressed the need for investigations of early performance. Note, however, that the above study investigated productions of saccades in response to rapidly presented visual stimuli whose locations were unpredictable, thereby tapping the responses driven (exogenously) by the stimuli. In contrast, there are no infant studies investigating the atypical endogenous control of saccades in antisaccade tasks, even though these are so prominently used in research with neurodevelopmental conditions later in life. My second aim was therefore to investigate the early inhibition of reflexive saccades and the production of antisaccades in fragile X syndrome, as this is a condition known to affect the endogenous control of attention later in life.

3.2. Experimental data

3.2.1. Experiment 1a. The inhibition of reflexive saccades in typical toddlers

In a seminal paper in 1978, Hallett instructed subjects to perform eye-movements in the opposite direction from the location of a stimulus that appeared in their right or left peripheral visual field while they were fixating on a central stimulus. This task became known in the literature as the “antisaccade task” and was brought to fame by Guitton and colleagues (1985), who used it to investigate eye-movement control in patients with frontal lesions (adapting Hallett’s paradigm as illustrated in Figure 3.2a). Deficits in patients with localised brain lesions, neuroimaging of normal subjects and monkey neurophysiology have highlighted a large network of areas involved in the production of antisaccades, grossly corresponding to all regions depicted in Figure 3.1. Relatively few studies have investigated the normal parameters of performance on the task (Everling & Munoz, 2000; Everling et al., 1998, 1999; Schlag-Rey et al., 1997; Zhang & Barash, 2000), and there have been even fewer studies of the typical developmental changes in eye movement parameters for antisaccades.

My first aim was therefore to adapt existing paradigms to test toddlers as well as infants in order to detect age-related changes in the ability to inhibit pro-saccades, as well as the ability to produce saccades that anticipate the appearance of a target at the opposite location. These combined measures should provide a converging assessment of the typical trajectory of saccadic control in toddlers and this would complement what is known about oculomotor control in infants. This required adapting existing paradigms to investigate the control of saccades to peripheral targets. Furthermore, it was necessary to integrate methodologies and constructs used by developmentalists testing saccadic controls in young infants and those investigating developmental changes on the antisaccade task from childhood to old age. Indeed, the infant and adult studies focusing on the production of antisaccades differ on a major dimension.

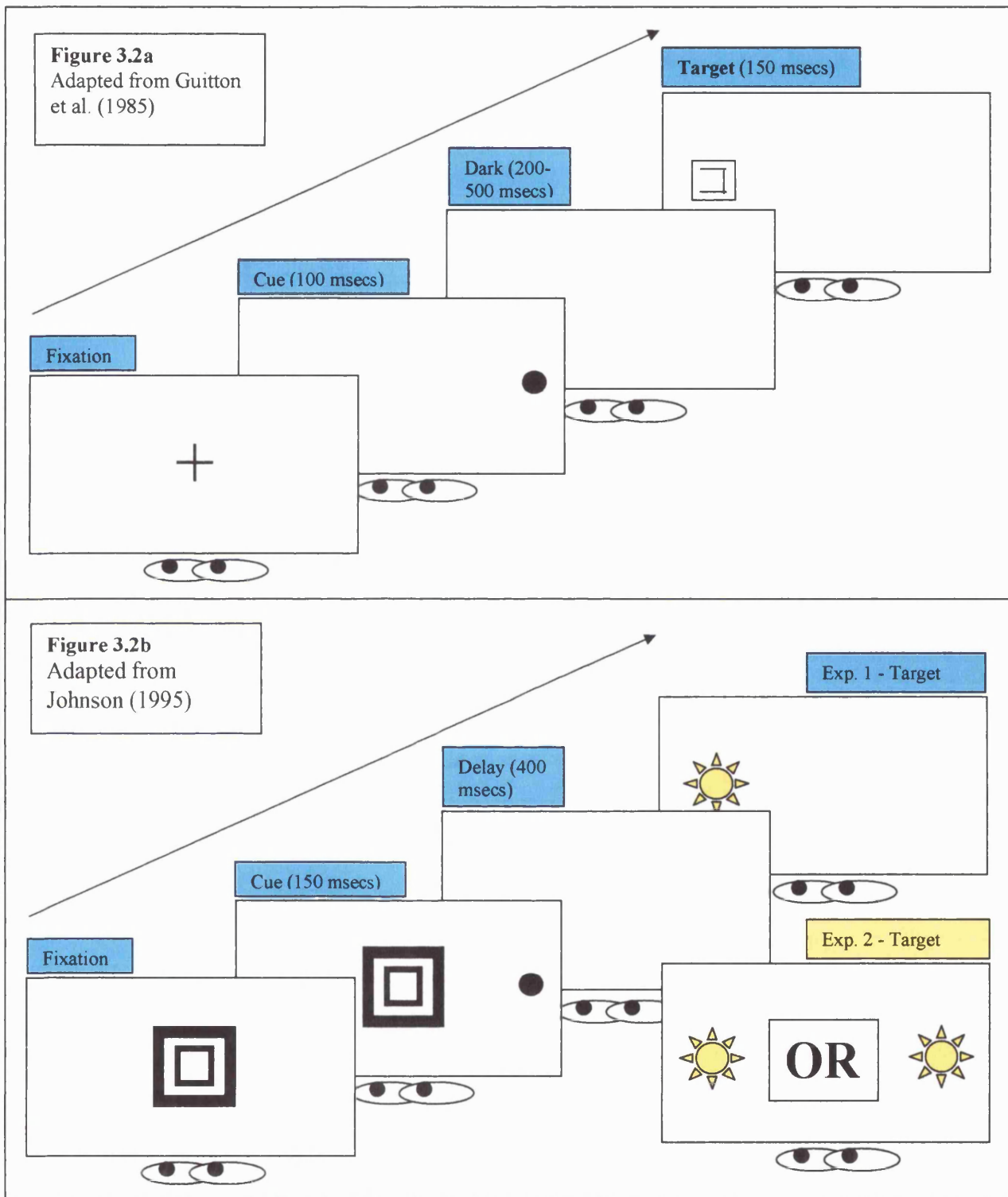


Figure 3.2. Stimulus sequence used by (a) Guitton et al. (1985), (b) Johnson (1995) in Experiments 1 and 2. Note the similarities and differences between the two adaptations of the antisaccade task. On the one hand, both Guitton et al. (1985) and Johnson (1995, Exp. 1) required (or trained) participants to saccade to the location opposite to the cue. However, in the adaptation used by Johnson, fixation stimulus and cue overlap, decreasing the probability of looks towards the cue (SEE TEXT). Also cue and target differ in terms of how attractive and animated they are intended to be

Firstly, most studies of antisaccades in adults require participants not to orient towards a peripheral onset (equivalent to the cues used here) and to direct a saccade to the opposite direction in the absence of a stimulus appearing there (with the exception of the study by Guitton et al., 1985, see Figure 3.2a). This methodology is impossible to use in this form with infants or toddlers with little language. Therefore Johnson (1995) trained 4-month-old infants to orient away from an informative cue by presenting a rewarding stimulus at the opposite location and took the decrease in saccades towards the cue as a measure of saccadic control (illustrated in Figure 3.2b). He found that infants as young as four months of age decreased looks towards peripheral cues when these predicted the appearance of a target at the opposite location, but not when these cues were not predictive, suggesting that they could learn to inhibit reflexive looks towards the peripheral cue. Although it differs from the standard antisaccade task used with adults, Johnson (1995)'s adaptation was groundbreaking. Indeed, it made possible, with preverbal infants, the investigation of both the production of reflexive saccades towards the predictive peripheral cue and the ability to look towards the target location before the appearance of the target. Both of these components have been pinpointed as important aspects of the standard antisaccade task (Fischer et al., 1997b). Interestingly, Johnson (1995) did not find saccades towards the opposite location prior to the appearance of the target stimulus, equivalent to the antisaccades measured in the adult paradigms. This potentially indicates that inhibition of reflexive saccades and production of antisaccades are not only distinct processes on-line, as suggested by Fischer et al. (1997b), but that they may also emerge at different points across developmental time. However, there is a considerable gap in knowledge about developmental changes in performance between 4 months and 5 years of age.

Therefore, the present study has two main aims. First, it samples from an understudied age range: toddlers. Secondly, it investigates developmental changes in performance across a wide age range, rather than focusing on a single age group. This was achieved by adapting the methodology used by Johnson (1995) to engage older children. Previous studies suggest that typically developing infants and toddlers will decrease looking towards predictive but uninteresting peripheral onsets. This pattern should be more marked in older than in younger toddlers, indicating a developmental improvement in the ability to control saccades. However, the production of antisaccades (i.e., saccades directed towards the target location

before target onset, in the absence of a look towards the cue) has not been demonstrated in younger infants. It will therefore be critical to try and measure this type of saccades and age-related changes from infancy through toddlerhood in typical development.

Method

Participants

Participants were 30 infants and toddlers from the age of eight to 34 months, all with no known birth or other complications. The data from 14 infants and toddlers (age range 8 to 30 months) were discarded because they failed to register a sufficient number of codable trials, according to the criteria described below. One further toddler did not look towards cues on at least 40% of training trials. This yielded a final sample of 15 infants and toddlers (4 girls), whose age ranged from 8 to 34 months (mean: 21 months, median: 22 months). This rate of subject attrition is not unusual in similar studies on infants' attention (Johnson et al., 1991, 1994; Johnson, 1995; Johnson & Tucker, 1996).

Procedure

The methodology employed here aimed to closely replicate stimulus conditions used in studies of younger infants (Johnson, 1995). Participants sat on their caregivers' lap, 70 cm from the centre of a large colour monitor. The display on this monitor was controlled by a Pentium III computer. The experiment started by presenting an introducing image containing all fixation stimuli (cartoon characters, the Teletubbies) to engage infants and toddlers with the screen. Each trial began with the presentation of an attractive fixation display that served to ensure that the infant or toddler was looking at the centre of the screen at the start of each trial. Four different characters were employed, but they all subtended 20 degrees of visual angle from the viewing distance indicated above. The experimenter could see the infant by means of a video camera mounted above the display screen.

Acuity trials.

For each participant, the first four trials aimed at determining whether he could detect the cue, also providing a baseline measure of the accuracy and speed of orienting. As soon as the experimenter judged that the infant was looking at the fixation display, she activated the

computer mouse to initiate a trial. A trial started with a bleeping sound and the animation of the fixation stimulus, which zoomed in and outwards in steps of 500 ms for a total of 2 secs. One hundred milliseconds after the offset of the fixation, the cue stimulus for experimental trials, a black circle (subtending 5.5 degrees angle from the viewing distance specified above) was presented to the right or left of fixation (18 degrees to the right or left) until the child oriented towards it. Then the experimenter clicked on the mouse to make the (initially static) fixation stimulus re-appear in the centre of the screen and waited for the child to re-fixate to initiate a new trial. During video coding (see below), the amplitude of saccades during these initial trials was also used to calibrate individually for each child the relative positions of left vs. right appearing stimuli as well as the fixation stimulus.

Experimental trials.

The sequence of events composing each experimental trial is depicted in Figure 3.3. As the fixation stimulus disappeared at the centre of the screen, the cue stimulus, a black circle (5.5 degrees angle), was presented for 100 ms to the right or left of fixation (18 degrees to the right or left). In contrast to the overlap condition used by Johnson (1995), in which the fixation stimulus remained on while the cue was presented, here I adopted a step procedure, in which the cue appeared immediately after the offset of fixation. I decided to do so because overlap conditions are well known for reducing the probability of orienting towards such a briefly presented cue (e.g., Fischer & Weber, 1998) and thus would automatically reduce looks towards the cue, one of the variables that I was aiming to measure. Indeed, Johnson (1995) incurred in high participant attrition because some 50% of the infants tested did not produce sufficient looks towards the cue during training trials and it was crucial for me to avoid such a situation, especially with a limited clinical population. On the other hand, a standard gap condition, with 200 ms between fixation offset and cue onset, may result in the complete inability of infants and toddlers to inhibit saccades to the cue at all (Abrams & Dobkin, 1994; Fischer & Weber, 1992, 1997, Reuter-Lorenz et al., 1995, 1996; Tam & Ono, 1994). Therefore, I settled for the intermediate setting, with the cue onset immediately after fixation offset. The cue duration was selected as it has been shown to elicit the effects of interest both in infants younger than the age of choice here and in older children and adults (Johnson, 1995).

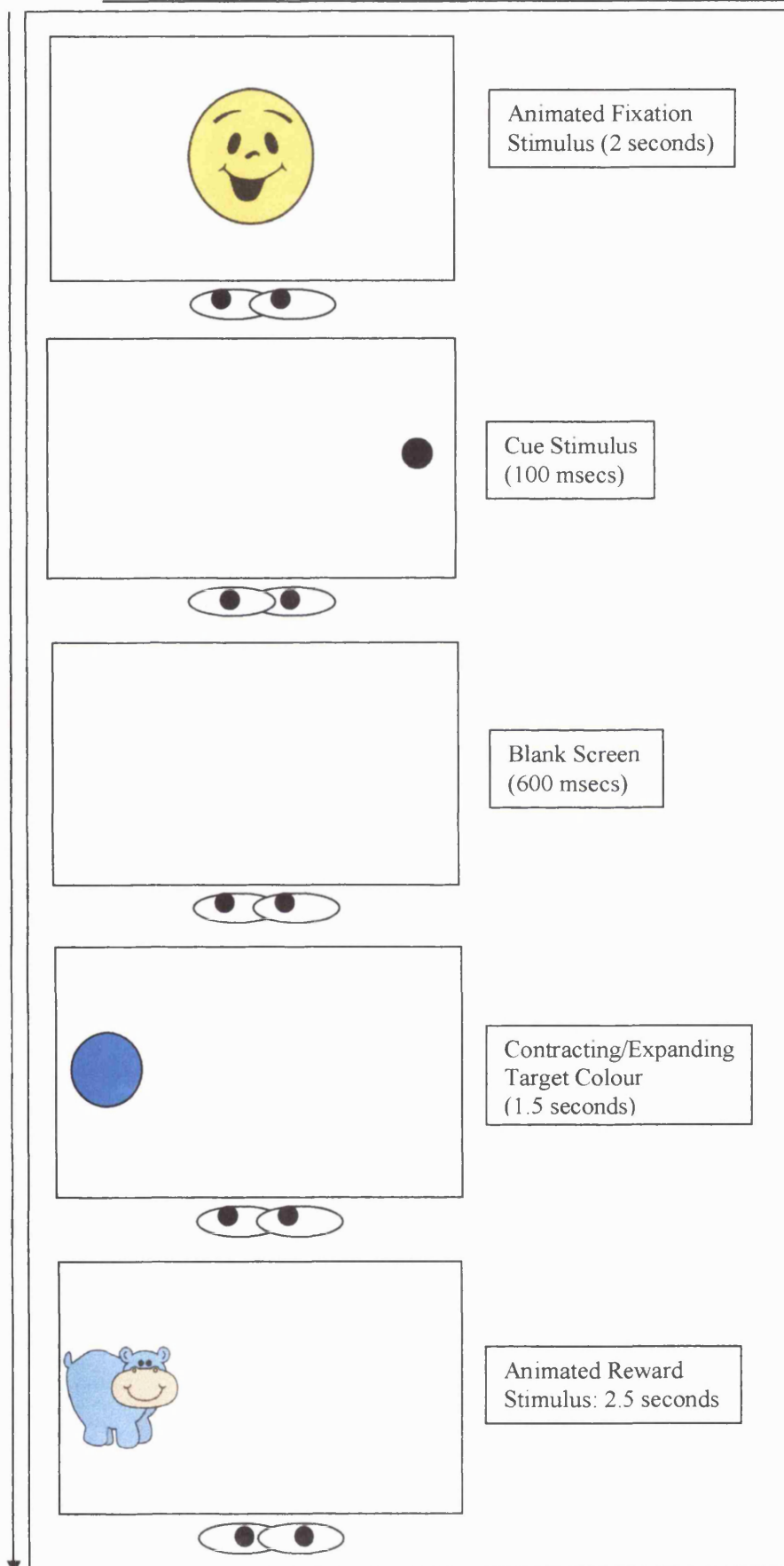


Figure 3.3. Stimulus sequence for Experiment 1a and 1b. Notice the similarities and differences between this adaptation of the antisaccade task and that used by Johnson (1995) with 4-month-olds. Although both experiments use multi-coloured and animated target stimuli, here the cue is presented in isolation (following Guitton et al., 1985), to facilitate orienting towards it during the training phase.

A blank screen was then presented for 600 ms before presentation of a target stimulus (an expanding and contracting coloured circle, subtending a maximum of 9.2 degrees angle) at the opposite location. After 1.5 seconds of successive expansions and contractions, the coloured circle was replaced by a cartoon animal or object (20 degrees angle), which animated on screen for 2.5 seconds. The (static) fixation stimulus re-appeared and the experimenter waited for the child to re-fixate to the middle before starting the following trial. The side of presentation of the cue stimulus was determined by a pseudo-random computerised sequence, which lasted a minimum of 12 and a maximum of 32 experimental trials or until the infant/toddler fussed or was no longer attending to the stimulus display. The experimental session terminated with a final image presenting the fixation stimuli (the Teletubbies) and all target cartoon characters so that the parent could name them for the child if he/she desired to do so, and to keep infants and toddlers occupied while their parents were debriefed.

Video coding protocol and inter-rater reliability.

Videotapes of children's eye movements during the task were coded off-line (using the Observer video coding equipment, after digitising the videotaped material). A time code generator imprinted the time on each video frame and the auditory signal indicating the beginning of each trial was mixed onto the videotape to indicate the onset of the trial for coding. All trials were coded with the off-line observer being blind to the precise onset of the cue and target stimuli. The observer recorded the onset of the initial auditory signal, the direction (centre, left, right) and onset of saccades, as well as eye-blinks and frames spent looking elsewhere. Saccade direction was coded relative to left/right/centre positions on the video-screen established during the initial acuity trials individually for each child. Saccade onset (in ms) was recorded by selecting the first frame in which an eye movement to a discrete centre/left/right location was detected. Saccade onset was used as an indication of reaction time only if the saccade went directly to the indicated centre/left/right locations. After blind coding, the coding record from the Observer and the recorded sequence of events (E-Prime) were synchronised. I then recorded the different types of saccades produced for each scorable trial. Trials were most commonly rejected because the child was not looking at

the fixation stimulus at the start of the trial, because he was not looking at the fixation stimulus at cue onset, because he oriented towards the cued side before the appearance of the cue, or because he looked elsewhere throughout the duration of the trial. Following the exclusion criteria employed by Johnson (1995), data from each toddler were included in the final analyses only if he completed at least 6 training trials and 6 test trials and if he produced looks to the cue on at least 40 % of training trials. Reliability between the experimenter and a trained coder blind to children's identity, age or group membership (on 20% of videotapes) was 0.8 (Cohen's K) for whether trials should be rejected or scored, and 1.0 for direction of saccades.

I operationalised saccade types of interest as follows:

Looks towards the Cue.

Looks towards the cues in trials that satisfied the criteria specified above were classified, according to the literature, as pro-saccades. The first variables of interest here were the percentage of prosaccades (i.e., looks towards the predictive but uninteresting peripheral onsets) during the training phase and during the following testing phase. Johnson (1995) took the percentage decrease in these saccades as a measure of the ability to control reflexive saccades, reasoning that this would be a reliable indicator of the extent to which infants had learnt to control saccades to peripheral but uninteresting stimuli.

Looks towards the Target.

In adult studies of antisaccades, experimenters instruct participants not to orient towards a peripheral onset (equivalent to the cues used here) and direct a saccade to the opposite direction, in the absence of a stimulus appearing here. This methodology is prohibitive with infants or toddlers with little language, and therefore Johnson (1995) used a rewarding stimulus appearing reliably at the opposite location to the (relatively uninteresting) cue. While saccades prior to the appearance of the target can be clearly labelled as anticipatory, several previous studies have classified saccades onsetting shortly after the target's appearance as anticipatory, rather than reactive (e.g., Haith et al., 1988; Csibra et al., 2001; Johnson & Tucker, 1996). The time limit provided varies from study to study, depending on the age of the participants tested. Given that children in the present study varied in age across a relatively large age range, the arbitrary cut-off of 100 ms post-stimulus was chosen

for considering saccades as anticipatory. This is the lower limit in the studies with infants, is close to the limit used with adults (Clohessy et al., 1991) and would therefore provide a conservative estimate of anticipations.

It is important to note, however, that the 4-month-olds in the study by Johnson (1995) did not produce antisaccades as defined in adult studies, i.e., saccades towards the target location prior to the appearance of the target stimulus. I speculated that this could be due to a number of reasons. It could be that the cue-to-target time interval used by Johnson (1995), 500 ms, is too brief to allow for anticipations in such young infants. Furthermore, anticipations measured by Johnson do not correspond to the measure of antisaccades most commonly employed in studies using the antisaccade task with older children and adults. While Johnson defined antisaccades as “saccades to the target location while the first stimulus is being presented in the opposite spatial location” (p. 288), in adult studies correct antisaccades are directed to an empty location in space (regardless of cue offset), away from the cue location, but only when the subject successfully inhibits looking at the cue (e.g., Klein & Foerster, 2001; Klein, 2001). With these caveats in mind, I lengthened the cue-to-target interval to allow more time for anticipations and decided to measure correct antisaccades, defined as anticipatory looks towards the target location in the absence of a look towards the cue location.

Statistical Analyses

Percentage of trials during which a saccade was made to the peripheral cue, and percentage of anticipatory saccades (of two types, see above) were calculated for each toddler. These were then plotted and analysed using standard statistical packages (SPSS, G-Power). These dependent measures were checked for normality and homogeneity of variance before being entered in repeated-measures parametric statistics (paired samples t-tests), with Trial Type (training, test) as the within-subject independent variable. Given that the children in this sample spanned a relatively large age-range, I investigated age effects by (a) plotting scatter diagrams of the relationships between age and the dependent variables to explore the distribution of individual data points; (b) investigating correlations between age and performance measures; (c) following Klein (2001), I investigated correlations with both age

and Age⁻¹ and performance; and (d) using multiple regression analysis to evaluate age as a predictor of performance.

Results

In summary, typically developing toddlers decreased looking towards the peripheral cue, even with the modifications to the procedure presented here. They did not, however, increase the number of antisaccades between training and test trials. Nevertheless, both decrease in looks towards the cue and number of saccades were correlated with age, with older toddlers decreasing cue looks more than younger toddlers and infants and producing more antisaccades during test trials. These results were statistically supported as follows.

Training and Test trials

All variables were plotted, tested for normality (Kolmogorov-Smirnov test, lowest $p = .108$) and homogeneity of variance (Levene test, lowest $p = .262$). As these did not violate the assumptions of parametric tests, parametric statistics were employed without the need to transform or trim the data. A preliminary analysis comparing trials in which the cue had been presented to the left or right of fixation did not reveal statistically significant differences. Therefore trials with the cue appearing to the left or right of fixation were collapsed.

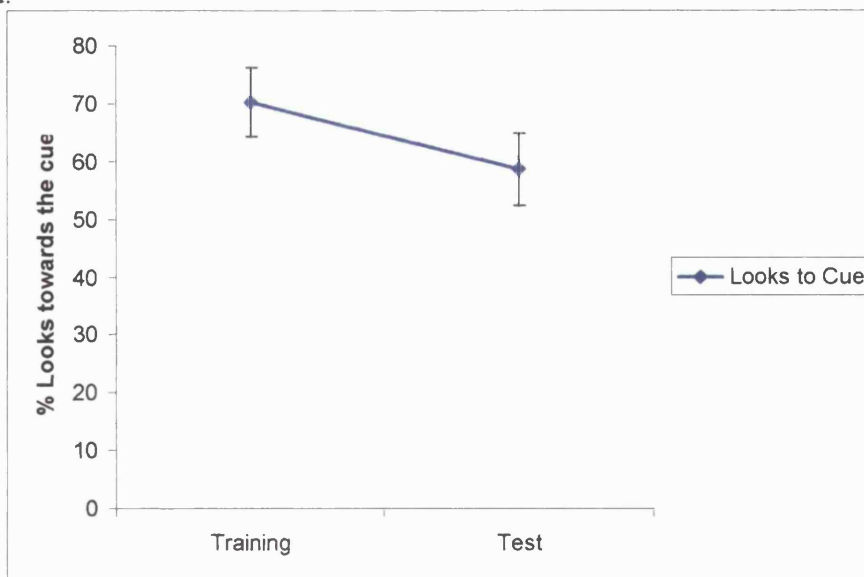


Figure 3.4. Percentage of trials during which typically developing infants and toddlers as a group looked towards the cue (represented on the y-axis) during training and test trials. Bars represent standard errors.

Saccades towards the cue.

Figure 3.4 represents the percentage of trials in which toddlers oriented towards the cue during training and test trials. Infants and toddlers looked at the cue on 70.25 % of training trials (\pm SE = 5.9) and 58.62% of testing trials (\pm SE = 6.3), showing a statistically significant decrease in looks to the cue from training to test, $t(14) = 2.149$, $p = .05$.

Saccades anticipating the appearance of targets.

The four-month-old infants tested by Johnson (1995) did not produce antisaccades towards the target locations. In contrast, the toddlers tested here did produce them, but the overall number of antisaccades did not differ during test compared to training trials. During training trials, toddlers tested here produced this kind of antisaccades on an equal percentage of training (12.79% \pm 3.9) and test trials (12.77% \pm 2.9), $t(14) = -.004$, $p = .997$, n.s.

Age-related changes in performance.

Age did not correlate with the percentage of looks to the cue during training trials, Pearson's $r(15) = -.312$, $p = .258$, but it did correlated with cue looks in the test trials, $r(15) = -.606$, $p = .017$. In other words, older toddlers produced fewer reflexive looks towards the cue during the test trials. This is illustrated in Figure 3.5. The correlation of Age⁻¹ with looks towards the cue during test trials was stronger, $r(15) = -.673$, $p = .006$. The combined age predictors significantly predicted the percentage of cue looks during test trials cue looks, $F(2, 12) = 4.959$, $p = .027$.

Age did not correlate with the production of antisaccades in training trials, $r(15) = .224$, $p = .422$, n.s., but there was a highly significant correlation between Age and the number of antisaccades produced on test trials, $r(15) = .776$, $p = .001$, suggesting that older toddlers produced more antisaccades than younger toddlers during test trials, as illustrated in Figure 3.6. Furthermore, Age⁻¹ correlated with this type of saccades, $r(15) = -.628$, $p = .012$. Indeed, the combined age predictors significantly predicted the number of antisaccades in general, $F(2, 12) = 3.978$, $p = .047$, and especially so in test trials, $F(2, 12) = 10.331$, $p = .002$.

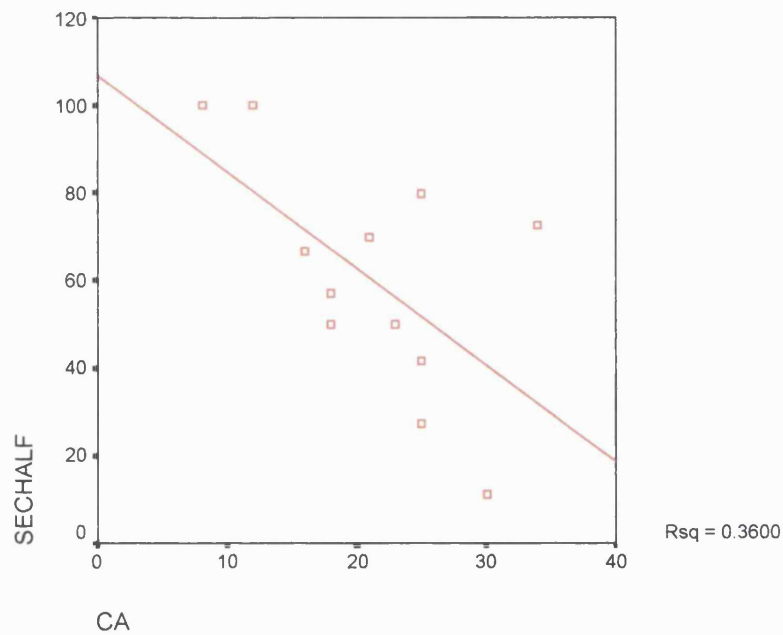


Figure 3.5. Percentage of test trials during which infants and toddlers looked towards the cue as a function of their age. The graph also shows that chronological age predicts 36 % of the variance in cue looks during test trials.

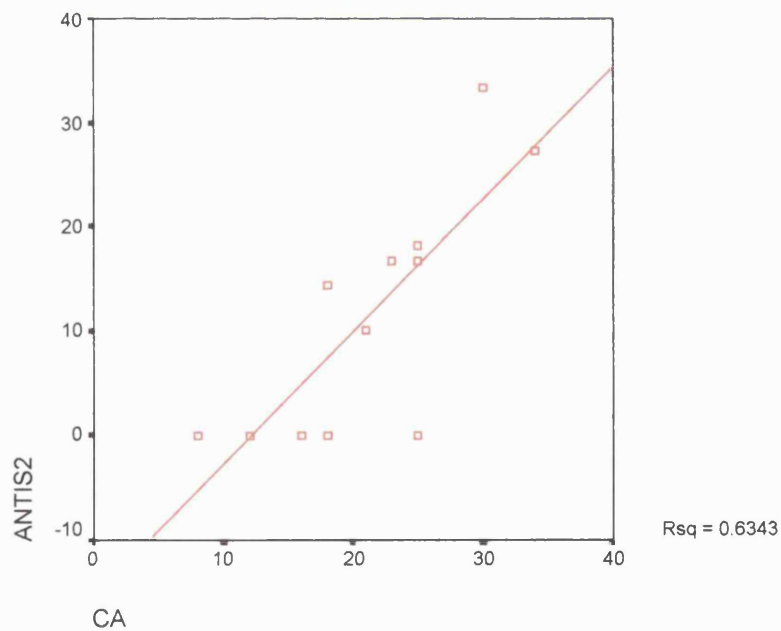


Figure 3.6. Percentage of test trials during which infants and toddlers produced correct antisaccades (i.e., they did not look at the cue and anticipated the appearance of the target) as a function of their age. The graph also shows that chronological age predicts 63 % of the variance in antisaccades.

Discussion

Section 3.2.1 sought to investigate whether typically developing toddlers tested with this paradigm would decrease looks towards a peripheral stimulus and how this ability may change with age. It is therefore the first study addressing this question in children between the ages of 4 months (Johnson, 1995) and 6 years of age (the youngest age group tested by Fischer et al., 1997; and Klein, 2001). The results suggest that, like 4-month-old infants, toddlers tested with this paradigm decrease looks towards informative but uninteresting sudden peripheral onsets. Furthermore, and unlike younger infants, they produce correct antisaccades, i.e. looks towards the target location prior to the appearance of the target and in the absence of looks towards the cue. Crucially from a developmental perspective, both measures of performance change with age: during test trials, older toddlers produce fewer looks towards the cue and more correct antisaccades than younger toddlers.

The percentage of looks towards the cue during test and training trials is similar to those found with 4-month-old infants by Johnson (1995, extrapolated from Figure 2, p. 285), who produced cue looks on approximately 62% of training trials and 50% on test trials. It is important to remember that methodologies for these experiments differ, in that Johnson (1995) maintained the fixation stimulus on during cue presentation, whereas I did not (compare Figures 3.2b and 3.3). Furthermore, while more than 50 % of the infants tested by Johnson did not reach the 40 % criterion of looks towards cues during training trials, most of the toddlers tested here did. However, the similarity remains intriguing, especially as age did not predict cue looks during training trials, suggesting that the initial production of these types of saccade is less amenable to developmental change than the ability to control them after training.

This study explores for the first time antisaccades equivalent to those measured in adult tasks, and most importantly it shows that age is a strong predictor of this measure during the toddler years, accounting for more than 60 % of the variance. The percentage of saccades produced is, however, low compared to the findings reported by Klein (2001), but again direct comparisons are unwarranted because of methodological differences. These results underscore the value of the information provided by following developmental changes using

multiple measures of performance across age ranges, rather than focusing on a single age group. It would be extremely important to validate these results on a larger sample of toddlers and young children up to 6 years of age and beyond, to test similarities and differences in results obtained with this paradigm compared with the standard instructions used on the antisaccade task.

There are, however, a number of limitations to this study. An alternative explanation for the decrease in looks towards the cue could be low-level habituation to the cue itself. This is, however, unlikely. As illustrated in Figure 3.2a, Johnson tested a different group of infants to peripheral cues with no predictive value and found that they did not decrease looking towards the cue, a finding that would have been expected if the infants in Experiment 1 had simply habituated to the cue. However, this would need to be investigated further using the present paradigm. In sum, the antisaccade task revealed meaningful changes in performance and in particular changes that correlated with age as a simple measure of typical development. Section 3.2.2. examines performance on the same task in infants and toddlers with fragile X syndrome. Control children were individually matched to them on the bases of the overall level of cognitive functioning, in order to identify difficulties in the endogenous control of saccades over and above those expected given general developmental delay.

3.2.2. Experiment 1b. Inhibition of reflexive saccades in infants and toddlers with fragile X syndrome

It was the use of the antisaccade task to investigate performance in populations of patients with localised brain lesions that brought fame to Hallett's task. Indeed, this was not well known until, in 1985, a study on patients with frontal lobe lesions demonstrated that these individuals produced larger numbers of errors in the antisaccade task (Guitton et al., 1985). Since then, atypical saccadic control has been investigated in a number of neurodevelopmental conditions. Two issues are of relevance here. First, the pervasive nature of difficulties in the production of antisaccade across neurodevelopmental and psychiatric populations could be related to the fact that, as discussed above, a large network of areas is involved in the generation of goal-directed saccades, making them very vulnerable.

Secondly, for a number of the disorders displaying atypical antisaccades, a dysfunction of glutamatergic transmission has been suggested. For example, in the case of schizophrenia, the leading monoamine hypothesis of the disorder (Frith, 1992) has been replaced by hypotheses that conceptualise the interactions between dopamine and glutamate (Takahata & Moghaddam, 2003). Indeed, this is a logical step because of glutamate's importance in cortical function and because glutamatergic cortical projections interact with the activity of monoaminergic neurones. An understanding of these issues is crucial when examining neurodevelopmental outcome in a condition that, like fragile X syndrome, is characterised by altered responsiveness to glutamatergic transmission.

A further motivation for the use of the antisaccade task with fragile X syndrome is embedded in the nature of the task itself. While it loads particularly on endogenous control, the task involves the interaction of endogenous and exogenous signals for saccade generation and is therefore relevant to the issues discussed in Chapter 1. Indeed, a recent model of activation in the superior colliculus during antisaccades suggest that performance on the task is biased by an endogenous signal, based on the antisaccade instruction coming from cortical processing and an exogenous signal coming directly from visual areas (Trappenberg et al., 2001). Both of these signals activate the superior colliculus, in particular build-up neurones, but at the same time the two signals inhibit each other (Everling et al., 1998; 1999). The successful inhibition of the reflexive signal could be mediated by the interplay of fixation and saccade-related activity at the level of the superior colliculus. This interplay is in turn dependent on the integration of activity from cortical areas mediating endogenous control.

Thus far, no studies on fragile X syndrome have focused on eye-movements as measures of attentional control, in any age group. The task has, however, been used successfully with older children and adults with attentional difficulties (ADHD: Rothlind, Posner, & Schaughency, 1991; Klein et al., 2002; Klein, Raschke, & Brandenbusch, 2003). In particular, Klein et al. (2003) tested a large sample of children with ADHD and matched controls, showing an increased number of errors on the antisaccade task, augmented proportions of fast responses and an atypically reduced decrease in antisaccade reaction times compared to prosaccade reaction times with increasing age in patients. These results

suggest a number of crucial points: first, the usefulness of the task in studying atypically developing children with known attentional difficulties; second, the importance of investigating age-related changes in the experimental effect in both the control and atypical group, rather than simply comparing them as a group. This latter point underscores the need to look at factors that may underlie variability within a clinical group, rather than simply focusing on comparison with typically developing individuals. Furthermore, age is a crucial factor to evaluate as a predictor of variability in any developmental disorder.

Implications for fragile X syndrome: Empirical predictions

Using methodologies appropriate to older children, Munir et al. (2000) found that children with fragile X syndrome display a weakness in inhibiting repetitions of previously successful responses. It is unknown, first, whether these difficulties in inhibitory control are characteristic of response requirements other than button-presses or mouse-clicks, that are relatively more complex responses than eye-movements. Secondly, it remains unclear whether infants and toddlers with the syndrome display difficulties that are similar to those displayed by older children and adults.

If infants and toddlers with fragile X syndrome already exhibit these difficulties over and above what is expected given their overall developmental delay, they should show reduced decrease of looks to the cue compared to controls individually matched on the basis of overall developmental level. If this is also accompanied by difficulties in planning antisaccades, we may observe reduced antisaccades. Following Klein et al. (2003), it will be crucial to investigate also whether performance of the children with FXS correlates with either chronological or mental age or whether it follows an atypical pattern. This will allow us to investigate variability in performance within the group, rather than simply collapsing information on the children by comparing them as a group with typically developing toddlers.

Method

Participants

Toddlers with FXS were recruited as discussed in Chapter 2. Fifteen boys and their families agreed to visit the Infant Testing Laboratory of the Neurocognitive Development Unit, in London. Of these, 4 boys did not produce a minimum of 12 scorable trials and 1 did not produce the minimum of 40% trials with looks towards the cue. This left 10 boys who completed the task (chronological age range = 14-55 months, mean = 35.9 months, SD = 12.7 months). Their developmental level measured using the BSID-II, Mental subscale, was equivalent to 20.0 months on average (range = 12-30, SD = 5.1). These boys were individually matched by mental age equivalent within one month, to ten typically developing boys (mental age equivalent: mean = 21.1, SD = 5.2, range = 12-30), all of whom had contributed to Experiment 1a in section 3.2.1., henceforth referred as MA controls. Toddlers with FXS and MA controls did not differ in the overall level of development, $p = .639$, n.s.

Procedure, video-coding and inter-rater reliability

As in Section 3.2.1.

Statistical analyses

As in section 3.2.1., except that age alone was used as a predictor of performance (as opposed to both Age and Age⁻¹) given the limited number of children in each group and the recommendation to use multiple predictors only with approximately 8 children per predictor (e.g., Howell, 1997). For children with FXS, the correlation between chronological age and performance was also explored, as their mental and chronological age differed significantly. In addition, due to the relatively small sample size, I conducted compromise power analyses using G-Power statistical software (Faul & Erdfelder, 1992). These are reported in Table 2.4 in Chapter 2.

Results

Overall, and in contrast to typically developing toddlers, toddlers with FXS did not decrease looks towards the peripheral cue during test trials, compared to training trials. However, they produced just as many correct antisaccades towards the target location as their individually matched controls. Nevertheless, while general developmental level predicted

the decrease in looks towards the cue and the percentage of antisaccades in controls, it did not do so for toddlers with FXS. All these findings were supported statistically as follows.

Acuity trials.

Toddlers with FXS and typically developing toddlers did not differ in either the number or speed of looks towards the cue ($p = 1.0$ and 0.8 respectively).

Training and Test trials.

Decreases in saccades towards the cues.

Figure 3.7. illustrates the percentage of trials during which toddlers looked at the cue, during training and test. In blue are MA controls and in red toddlers with FXS. There was a statistically significant interaction between Group and Trial Type, $F(1, 20) = 5.835$, $p = .025$. Independent t-tests confirmed that the MA controls decreased looks towards the cue during test ($52.17\% \pm 9.38$) in comparison to training trials ($67.28\% \pm 8.35$), $t(10) = 2.281$, $p = .04$, whereas toddlers with FXS did not, $t(10) = -.931$, $p = .374$. Furthermore, the MA controls produced significantly fewer looks towards the cue than toddlers with FXS during test trials, $t(20) = 2.357$, $p = .03$. However, the two groups produced equal looks towards the cue during training trials, $t(20) = .098$, $p = .923$, n.s.

Increases in saccades anticipating the appearance of targets.

Figure 3.8 illustrates the total number of correct antisaccades towards the target location before the appearance of the target object (equivalent to the antisaccades measured in the adult tasks) for the toddlers with FXS (in red) and individually matched MA controls (in blue). None of the differences was statistically significant, p ranging from .555 to .984.

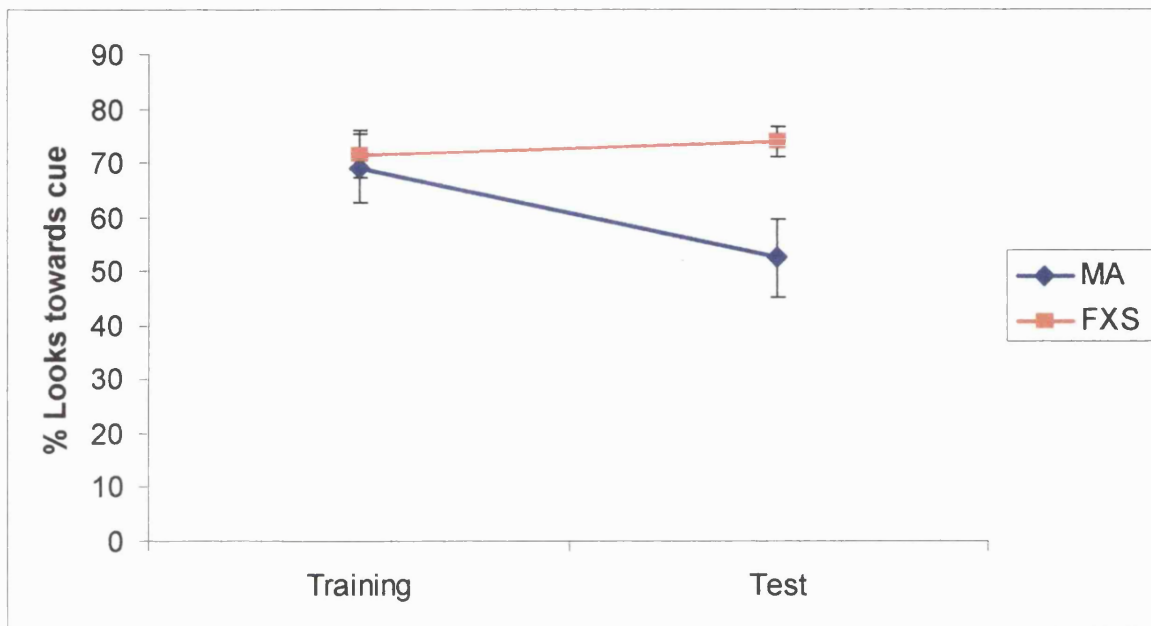


Figure 3.7. Percentage of trials during which typical and atypical toddlers looked towards the cue during training and test. In red are toddlers with fragile X syndrome, in blue are individually matched controls. Bars represent standard errors.

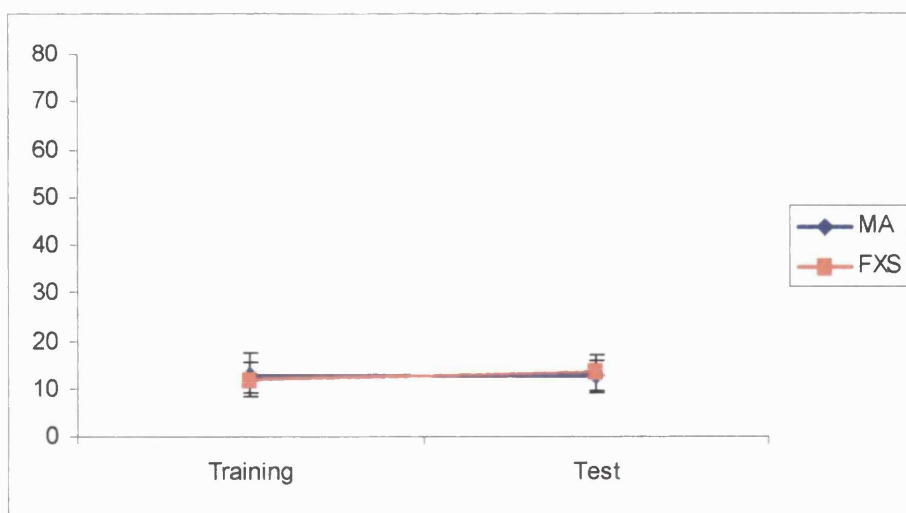


Figure 3.8. Percentage of correct antisaccades performed by toddlers with FXS (in red) and individually matched controls (in blue) during training and test trials. Bars represent standard errors.

Differential age-related changes in performance.

I investigated differential effects of mental age on both looks towards the cue and anticipatory looks towards the target location for the two matched groups initially by correlating mental age and percentage of looks for the two groups. Figure 3.9. illustrates the percentage of looks towards the cue during test trials, for toddlers with FXS (red) and MA controls (green). Older MA controls produced less looks towards the cue than younger controls during test trials, $r(10) = -.908$, $p < .001$. In contrast, for toddlers with FXS mental age did not correlate with the percentage of looks towards the cue either during training trials, $r(10) = .173$, $p = .633$, n.s.; or during test trials, $r(10) = -.280$, $p = .433$, n.s. Their chronological age also did not correlate with either measure, $r(10) = .163$ and $-.377$, $p = .653$ and $.283$, n.s.

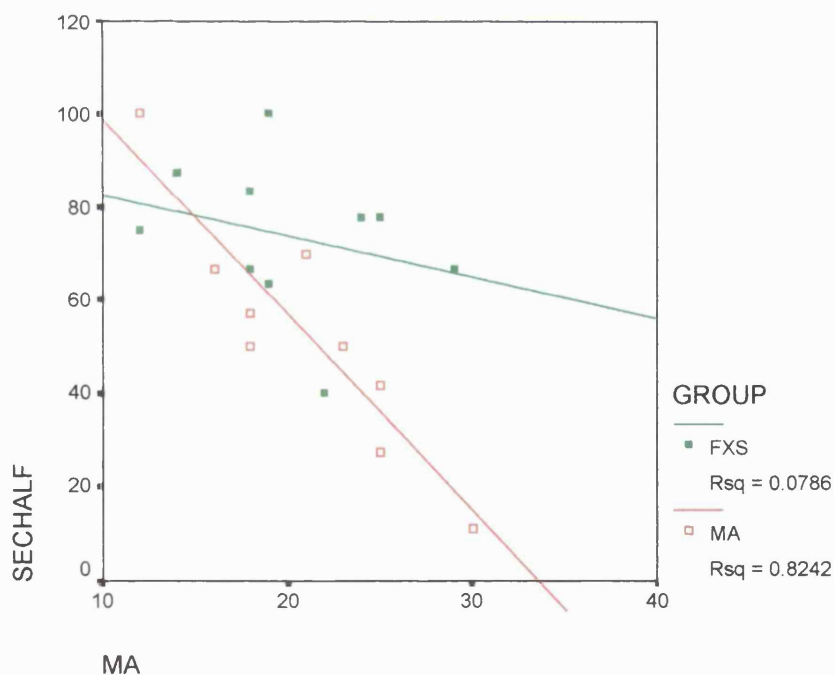


Figure 3.9. Percentage of test trials during which toddlers with FXS (in green, full squares) and MA controls (in red, empty squares) oriented towards the cue during test trials. Mental age predicted 82% of the variance in cue looks for MA controls, but only 7.8% for toddlers with FXS.

With regard to looks towards the target location, for MA controls mental age correlated with the percentage of correct antisaccades during test trials ($r = .912$, $p < .001$). In contrast, for toddlers with FXS the percentage of correct antisaccades did not correlate with either mental age ($r = -.039$, $p = .915$) or chronological age ($r = -.142$, $p = .695$). Figure 3.10 illustrates the relationship between mental age and antisaccades to the cue during the test phase. Entering age as a covariate in the analyses of antisaccades did not result in any statistically significant effect in addition to those discussed above.

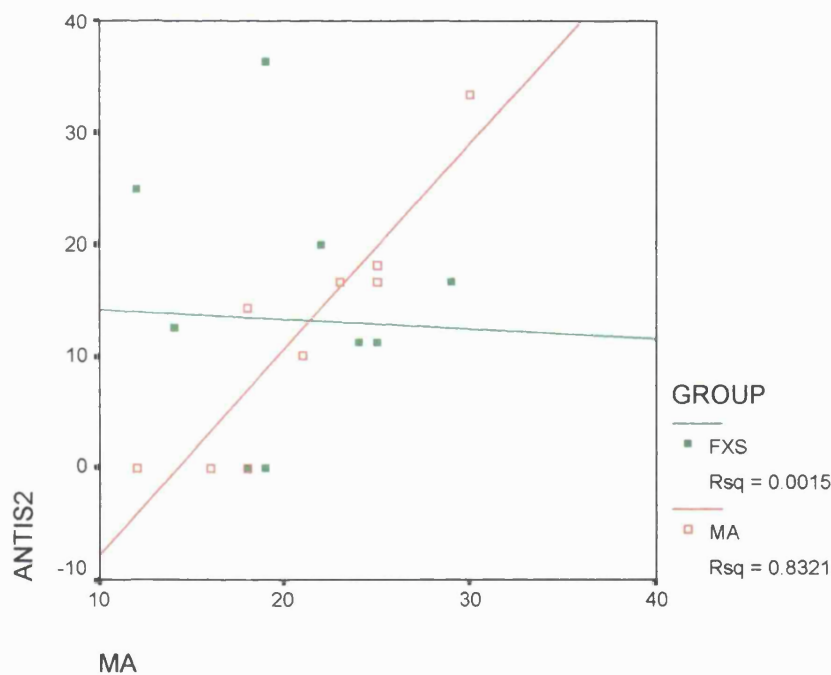


Figure 3.10. Percentage of test trials during which toddlers with FXS (in green, full squares) and MA controls (in red, empty squares) produced antisaccades during test trials. Mental age predicted 82% of the variance in cue looks for MA controls, but only 0.15% for toddlers with FXS.

Discussion

Section 3.2.2. is the first study to investigate oculomotor control in a sample of individuals with the fragile X syndrome. It aimed to compare pro and antisaccades in typically developing toddlers and toddlers with the condition. Results suggest that toddlers with FXS did not inhibit looks towards uninteresting but predictive peripheral cues, in contrast to the behaviour displayed by MA control children. Furthermore, although the clinical group produced an equivalent number of correct antisaccades as the controls, this did not correlate with either mental or chronological age in the sample of toddlers with the condition. Similarly, and in contrast with their individually matched controls, the number of looks towards the cue did not correlate with either age or mental age within the clinical sample, suggesting an atypical pattern of performance that does not vary consistently with either increasing chronological or mental age. It is important to note that multiple aspects of performance by toddlers with FXS appear atypical, from the ability to decrease exogenously-driven looks towards the cue, to the age-related changes in both cue looks and antisaccades. These latter results in particular underscore the importance of investigating not only group performance, but also the factors contributing to within-group variability. Given the developmental nature of the condition, it was of particular interest to investigate age-related changes in these measures, but these turned out not to be consistent in this group. It will therefore become of paramount importance to use a similar approach with the other constructs investigated throughout this thesis.

These results suggest that infants and toddlers with FXS as young as 14 months of age (the youngest child in the group) display an atypical pattern of endogenously controlled eye-movements. This is consistent with the findings obtained with older children and adults with the syndrome using pen and paper as well as computerised tasks (e.g., Munir et al., 2000; Wilding et al., 2002). Indeed, Chapter 4 will investigate whether difficulties in the control of responses are present within this younger group when manual responses are required.

3.3. General Discussion

3.3.1. Typical and atypical endogenous control of saccades

Taken together, results from these experiments suggest that the endogenous control of saccades can be successfully measured in both typically and atypically developing toddlers, starting to fill a gap in the published records between the ages of 4 months and 6 years. Typically developing toddlers of this age decrease looks towards an informative but uninteresting cue and produce antisaccades in the opposite direction. Both of these measures change within the age range tested, with older toddlers producing fewer reflexive saccades towards the cue and more antisaccades. How does performance on these tasks compare with that measured on standard versions of the antisaccade task, used with older children and adults? Errors (measured here as the percentage of looks towards the cues) have been found to reflect the largest age effects in all studies investigating developmental changes in performance on such tasks (Fischer et al., 1997; Klein, 2001; Klein et al., 2002). Furthermore, higher percentages of errors also best characterise atypically developing individuals with attentional difficulties (e.g., schizophrenia, ADHD).

In contrast to typically developing toddlers, toddlers with FXS do not decrease looks towards the cue, with their performance neither correlating with mental nor chronological age. In fact, their performance does not change consistently with increasing developmental level or chronological age. This suggests that toddlers with FXS display a highly atypical pattern of oculomotor control, which is consistent with their later difficulties in tasks requiring manual responses. However, it is not clear whether these early difficulties in inhibiting reflexive saccades are also accompanied by difficulties in controlling manual responses or whether the latter emerge later. To address this question, Chapter 4 will focus in particular on another measure of inhibitory control, a directional Stroop task, in which participants have to solve conflict of responses. If the inhibitory control difficulties revealed here extend to manual responses, toddlers with FXS should show deficits in the ability to control responses when these conflict with the location of a target stimulus, as described in more detail in Chapter 4.

3.3.2. Limitations and future research questions

A number of issues for future investigation emerge from the data presented in this chapter, both with regard to the response requirements tested here using oculomotor tasks and with respect to older age groups. Because an accurate temporal analysis was precluded by the limited number of trials, it was not possible to investigate concurrently whether failures to inhibit reflexive looks to cues were due to a failure of suppression or to a failure to generate saccades to internally defined locations. Further experiments could address this issue by modifying the methodology used by Fischer and Weber (1998), who manipulated systematically the cue-target interval and the eccentricity of cues and targets. This modification allowed them to measure independently effects on fast (“express”) and slower saccades and in turn to suggest a dissociation between automatic and voluntary temporal and spatial effects.

Moving beyond the antisaccade task itself, would toddlers with FXS also display difficulties on other oculomotor tasks requiring inhibition? In a very elegant series of studies of tasks testing attentional control in inhibitory tasks, Karatekin and Davenport (2003) modified inhibitory control tasks that traditionally require manual response to oculomotor tasks and included the production of antisaccades amongst their measures. They found interesting correlations in measures across tasks, with errors being most representative of inhibition abilities. It would therefore be informative to modify other inhibitory control tasks to test control of saccades in infants and toddlers with FXS. This would provide converging evidence of inhibitory difficulties, as well as clarifying the precise locus of these difficulties. In particular, future experiments could examine whether children with fragile X syndrome continue to have such striking difficulties in controlling looks to peripheral onsets when an antisaccade is not required. Csibra and collaborators have indeed designed a task requiring infants to focus on a central animated cartoon character and inhibit looks towards a peripheral stimulus (Csibra, pers. comm.). Peripheral looks result in the “freezing” of the animated central stimulus, making it far less rewarding than it is when it moves. Combined with the antisaccade task, the “freeze-frame” experiment would allow teasing apart the sources of difficulties by toddlers with fragile X syndrome.

Another, crucial issue remains unanswered. By using the current paradigm, I accepted the view that considers attention and oculomotor control as being tightly linked (e.g., Hood et al., 1998). I defended this approach in the introduction to this chapter, and, while there is more to attention than eye-movements, interactions between saccade planning and perceptual discrimination tasks suggest that they share a limited, common processing capacity (Kristjansson, Chen, & Nakayama, 2001). However, it would be valuable to investigate the issue of attentional control in young infants with FXS by adapting attentional tasks that differentiate between oculomotor and attentional control (e.g., Klein et al., 1992). Furthermore, it will become very important to assess whether these issues apply to the inspection of more naturalistic displays. The seminal studies of Yarbus (1967) investigated eye-movements while participants inspected more natural scenes, showing an interaction between aspects of goal-directed control and the perceptual characteristics of the visual displays presented. In another study, for example, Mannan, Ruddock and Wooding (1995, 1996) investigated eye-movements performed automatically in response to unfamiliar images and found that it is in fact the perceptual characteristics and statistical regularities of the images drive inspection patterns. What implications would the reduced oculomotor control measured in the toddlers with FXS tested here have on naturalistic scene inspection? This issue will be partially addressed in the chapter 6, examining visual search in these toddlers.

3.4. Chapter Summary

This investigation of endogenous control of orienting began by asking whether it would be possible to examine oculomotor control in typically and atypically developing toddlers. I opted for the antisaccade task as a measure to target both oculomotor development in general and the issues of interest for fragile X syndrome in particular. I focused on saccades that, in typically developing infants, toddlers and young children can be modified by the predictive value of a cue. These goal-directed changes in saccades, be they the decrease in looks towards peripheral cues or the antisaccades towards locations at which the rewarding stimuli would appear, seems to be driven by the predictive nature of peripheral onsets (section 3.2.1). In contrast to the typical case, infants and toddlers with fragile X syndrome did not change their reactions to peripheral onsets. Importantly, the atypical pattern of performance was also evident in the lack of a correlation with mental and chronological age in the clinical group, in contrast to the controls. Taken together, these findings suggest that eye-movement control is impaired in infants and toddlers with the fragile X syndrome. Chapter 4 will investigate whether this difficulty is also characteristic of manual responses by toddlers with the syndrome, a finding that would be predicted by the literature on older children and adults with FXS (e.g., Munir et al., 2000; Cornish et al., 1999).

Chapter 4

Control of Response Conflict

At any time, multiple stimuli and their associated responses compete for selection and action. Resolving this conflict in information processing is a crucial component process of attentional control (e.g., Allport, 1987; Ninio & Kahneman, 1974; Kahneman et al., 1983) and this ability is characterised by prolonged changes through infancy, early childhood, adolescence and adulthood (e.g., Diamond, 1985; Barkley, 1997).

Control of conflict has been investigated with classical paradigms that are all predicated on the interference of irrelevant stimulus dimensions with task-relevant responses. For example, the Stroop task (Stroop, 1891, reviewed in MacLeod, 1991) and the Flanker task (Eriksen & Eriksen, 1974) both involve over-riding an over-learned or habitual response in favour of the task relevant one. In what is now known as the “Simon task”, Simon and colleagues (e.g., Simon, 1990) investigated the interference of irrelevant stimulus dimensions (e.g., the location of the stimulus) on the processing of visual stimuli and the production of relevant responses. Various theoretical accounts attempt to model the

cognitive factors underlying adult control of response conflict (e.g., Eimer, Hommel, & Prinz, 1995; Eimer, 1999). Many invoke the activation of two routes: a fast, direct route that is preferentially dedicated to learnt or habitual responses, and an indirect route, that influences behaviour through controlled stimulus-response translation rules (e.g., Zorzi & Umiltà, 1995). When stimulus and response dimensions overlap, stimuli automatically activate compatible responses through the direct route, regardless of whether this compatible dimension is relevant.

While the existence of stimulus-response compatibility effects is undisputed, recently the notion that these can be accounted for by a simple combination of automatic and goal-relevant factors has been seriously challenged. The effects of stimulus-response incompatibility can be eliminated and even reversed on the bases of previous responses, questioning the automaticity of the processes driving the original Simon effect (Lu & Proctor, 1995, 2001). For example, if conflict trials are very frequent, the compatibility effect decreases. In contrast, it increases for infrequent incompatible trials and this strongly suggests that effects of the overall context within which subjects perform the task modulate the ability to control conflict (e.g., Ridderinkhof, 2002). Moreover, it is possible to find effects of previous response context from trial to trial (Gratton, Coles, & Donchin, 1992; Valle-Inclan et al., 2002). Incompatible trials result in faster responses if they are preceded by an incompatible trial than if they are preceded by a compatible one, suggesting improving inhibitory control whenever a previous trial requires an incompatible response. These findings pushed a number of researchers to propose the existence of a mechanism monitoring the context in which responses are made (e.g., Carter, Botvinick, & Cohen, 1999; Botvinick, Braver, Barch, Carter, & Cohen, 2001). The nature of contextual effects in adults is hotly debated: do they depend on trial-by-trial monitoring of responses and/or on the fading of mnemonic traces (e.g., Mayr et al., 2003)? To what extent are they under the influence of stimulus-driven or goal-driven factors (e.g., Los, 1996; Stoffels, 1996)? A parallel literature on the development of control has accumulated over many years, but the implications of the issues permeating the current debate on response conflict in adults are influencing research on development in a slower fashion. How does the ability to resolve conflict develop? Does the monitoring of response context develop independently of the ability to deal with conflict on a trial-by-trial basis?

4.1.1. Response Conflict: The typical developmental trajectory

It is well accepted that the ability to override competing actions becomes more efficient with age, with older individuals being characterised by less susceptibility to interference from competing actions (e.g., Diamond, 1985; Munakata & Yerys, 2001). In adults, executive attention comes into play in any task requiring control, but is most evident when the task requires resolving conflict between habitual responses and those that are appropriate. This is also the case for young infants, for example when they are tested with classical paradigms like the A-notB task or the delayed response task (e.g., Diamond & Goldman-Rakic, 1989; Diamond & Doar, 1989; Diamond, 1990). One crucial concern for those interested in tracing a life-long developmental trajectory of control is whether the measures collected from adults and young infants are really commensurable (Wright et al., 2003). Various attempts have aimed to bridge the gap between infant and adult conflict tasks. Indeed, young children performing Stroop tasks (Tipper et al., 1989; Wright et al., 2003) and go-nogo tasks (Casey et al., 1997a,b) show higher susceptibility to interference than older children and adults.

There remain, however, at least three considerable gaps in our understanding of the development of control. First, few studies investigate conflict between 18 and 36 months of age, at least partly because of the limited and variable verbal competence of toddlers and young children. A notable exception is the study by Gerardi-Caulton (2000, also reported in Posner et al., 1998). The author required toddlers from 24 to 36 months of age to respond to the identity of a visual object appearing on a computer screen while ignoring the relation between the object itself and the location of the appropriate response key. The task therefore modifies the Simon task used to test response conflict in adults to be used with toddlers (Simon, 1990; Lu & Proctor, 1995; Umiltà & Nicoletti, 1990). Children responded more slowly and less accurately when location and identity conflicted, showing that, as young as two years of age, they were influenced by stimulus-response incompatibility in a paradigm similar to the one used in adults. A second gap in the literature depends on the focus on compatibility effects on a trial-by-trial basis. As discussed above, the adult literature is currently questioning this approach, as compatibility effects are strongly modulated by context (e.g., Botvinick et al., 2001). Thirdly, in adults these efforts have been combined with a number of studies investigating the neural substrates involved in resolving conflict.

Relatively less is known about developmental changes in such substrates, and even less about how these may be affected in neurodevelopmental conditions.

Neural requirements

Classically, the frontal cortex has been the focus of research on the development of executive control in human infants and non-human primates (e.g., Diamond, 1985; Diamond & Goldman-Rakic, 1989). Indeed, neuroimaging studies of conflict resolution in adults reveal activation in a number of striato-frontal circuits, but particularly in regions of the frontal midline, including the anterior cingulate cortex (Carter et al., 1999; Botvinick et al., 2001). Increased activity is detected in dorsolateral prefrontal and anterior cingulate regions, as well as in superior parietal cortex (e.g., Bunge et al., 2002; Carter et al., 1995, 1999; Van Veen et al., 2001). These areas seem to serve distinct but complementary roles in the neural bases of the control of conflict. Anterior cingulate cortex is involved in the detection of conflict when there are competing responses (Botvinick et al. 2001; Nieuwenhuis et al., 2001; Van Veen et al., 2001). A distributed network of regions including parietal cortex and dorsolateral prefrontal cortex makes it possible to attend to relevant information by biasing the processing of relevant information over irrelevant information, resulting in the reduction of conflict (Cohen & Servan-Schreiber, 1992). In addition, a network of posterior areas seems to be involved in detecting unattended, but behaviourally relevant stimuli appearing in different locations of the visual field. This network would include intraparietal and posterior cingulate cortex (Corbetta et al., 1993, 2000; Nobre et al., 1997).

Casey et al. (2000) dissociated between these circuits by manipulating the type of trials preceding an incompatible trial within a version of the flanker task, where flanking stimuli are compatible or incompatible with the target stimulus (Eriksen & Eriksen, 1974). On the bases of the literature on the context of conflict, they hypothesised that, with consecutive incompatible trials, attention may be increasingly directed to the target, rather than to the flanking stimuli, resulting in increased target selection. However, if preceding trials have compatible flankers, a current trial with incompatible flankers would result in increased conflict. The authors found that an anterior network increased in activity in conditions of high conflict, whereas activity in posterior attentional circuits increased for increasing target selection. Furthermore, circuits including the basal ganglia and insular cortex showed higher

activation for simple changes in compatibility across trials, regardless of the direction of these changes. Interestingly, they manipulated the overall percentage of compatible and incompatible trials across blocks, a contextual manipulation that is also known to behaviourally modulate compatibility effects (e.g., Ridderinkhof, 2002). More recently, Durston, Thomas, Worden, Yang and Casey (2002) parametrically manipulated the number of preceding compatible or incompatible trials before an incompatible trial and found a monotonic increase in prefrontal and anterior cingulate regions with increasing conflict.

Are similar mechanisms at play with younger children? Casey et al. (1997) obtained fMRI data from 7-year-old children and adults performing a go no-go reaction time task, in which withholding the no-go response results in conflict. They found reliable activation of anterior cingulate, inferior, middle and orbitofrontal gyri areas for both children and adults. How did children differ from the pattern observed in adults? Overall volume of prefrontal activation was greater in children than in adults. Furthermore, they found that activity in dorsal prefrontal areas was less sensitive to contextual manipulations in children than in adults, suggesting that activity in children is less specific and less efficient in representing information relative to adults. Although those initial results were obtained using block designs, converging results also come from event-related studies investigating similar questions. Durston et al. (2002) manipulated parametrically the number of go trials preceding nogo trials. They found that ventral prefrontal cortex, cingulate gyrus and superior parietal regions increased activity monotonically to nogo trials that were preceded by increasing numbers of go trials. More recently, Durston et al. (2003) found that younger children could not modulate prefrontal activity as effectively as adults did, and this correlated with their ability to successfully perform on the task. The advantage of these parametric manipulations is that they allow for the comparison of different groups, across different levels of difficulty. This is crucial when trying to dissociate differences in activity due to different behavioural performance from differences in activity due to actual improvements with age. The circuits involved in inhibitory control of different types of responses can be differentially affected by disorders of known genetic origin (e.g., Casey et al., 2002). Indeed, Durston et al. (2003) found differential modulation of activation in children with ADHD compared to typically developing children and adults performing the same conflict task (go-nogo).

4.1.2. Atypical control of response conflict

Disorders of genetic origins have provided a window into our understanding of the neural mechanisms involved in the development of executive control. Many of the genes of interest are chosen on the bases of their heavy expression in areas that are involved in control of responses in adults, such as prefrontal and cingulate cortex (e.g., Casey et al., 2002). Most of the studies have focused on conditions that would specifically affect striato-frontal circuits or dopaminergic neurones in prefrontal cortex. For example, the expression of the dopamine D4 receptor (DRD4) gene in areas involved in the resolution of conflict (anterior cingulate in particular) has attracted wide interest amongst researchers interested in control. Therefore, conditions that are characterised by dysfunctional polymorphisms of the DRD4 gene have been the focus of developmental studies of inhibitory control (Casey et al., 2002). Diamond (1996, 2001) discusses an elegant example of this approach. The author and her colleagues investigated executive control in infants and toddlers with phenylketonuria (PKU), a genetically inherited condition that, when treated early and continuously (through a strictly regimented diet), does not result in mental retardation, but affects subtly and specifically dopaminergic neurones projecting to prefrontal cortex. They predicted that tasks relying heavily on the functioning of such projections would be selectively impaired in infants and children with PKU. The tasks chosen to assess this ability tested in multiple ways the capacity to control competing responses and inhibit inappropriate actions. As predicted, infants, toddlers and children with PKU displayed selective difficulties on tasks recruiting striatofrontal circuits, supporting the crucial contribution of dopaminergic pathways to the development of control.

And yet, a number of disorders are characterised by similar core inhibitory control difficulties, despite the fact that effects of the genotypic dysfunction do not affect dopaminergic circuits directly. For example, fragile X syndrome is known to affect glutamatergic transmission, not dopaminergic modulation, and yet older individuals with the syndrome display dysexecutive difficulties. Could the paradigms used to investigate control of responses in conditions affecting striato-frontal circuits also be employed to assess similar control difficulties in conditions like fragile X syndrome?

Implications for fragile X syndrome

Individuals with fragile X syndrome encounter great difficulties in controlling competing actions. Munir et al. (2000) tested executive control in children and adolescents with the syndrome. She found that children with FXS were less able to withhold previously appropriate responses than children with Down syndrome and than typically developing children matched for verbal mental age. Furthermore, children with the syndrome performed worse than typically developing children on a task testing the ability to maintain and execute a rule that is conflicting with an over-learned response. In Chapter 3, I provided compelling evidence for early difficulties in controlling eye-movements adaptively on the basis of informative cues in the environment. It is unclear, however, whether these difficulties span different response modalities as early as during the toddler years. In the present Chapter, I aimed to address this question by modifying a spatial conflict paradigm that has been used with both typically developing adults and young toddlers. The literature suggests a number of predictions: toddlers with fragile X syndrome may be differentially affected by response conflict. Furthermore, they may not modulate behaviour according to previous responses. In order to test these hypotheses, it was crucial to trace first the typical developmental trajectory of performance on the task. This is the focus of Experiment 2a.

4.2. Experimental Data

4.2.1. Experiment 2a. Typical development of response conflict

As I discussed above, a number of issues remain unresolved in the literature on the development of control. Firstly, toddlers tend not to be studied, with most of the published studies focusing on younger infants (e.g., Diamond, 1990) or older children (e.g., Diamond, 2001; Casey et al., 1997, 2000; Wright et al., 2003). Secondly, it has never been investigated whether, like older children (Casey et al., 1997; Durston et al., 2002) and adults (Botvinick et al., 1999; Carter et al., 1995), toddlers are also sensitive to the previous response context. Thirdly, it is not clear whether the ability to deal with context changes, and if so, independently from the control of conflict, from 24 to 48 months of age.

While recent studies have investigated the ability to deal with spatial conflict in older children (Diamond, 2001), the study by Gerardi-Caulton (2000) was the first to address this in toddlers. She required 24- to 36-months-olds to respond to the identity of a visual object appearing on a computer screen while ignoring the relation between the object itself and the location of the appropriate response key. At every age tested, accuracy was higher and reaction times were faster for spatially compatible relative to spatially incompatible trials, replicating results with adults (Simon, 1990; Umiltà & Nicoletti, 1990; Lu & Proctor, 1995). The author did not find any interaction between age and trial type, and suggested that improvements may be due to increasing ability to contend with general task demands, rather than an improvement in the ability to deal with conflict. However, the age range selected for this study was relatively limited and changes, if they exist, should occur within a larger developmental time-window.

The present experiment aimed to address concerns expressed above, while extending the findings obtained by Gerardi-Caulton (2000). First, I aimed to replicate the results obtained by Gerardi-Caulton with typically developing toddlers and young children, extending the age range to 48-months. This would test whether the author's failure to reveal developmental changes in the ability to deal with conflict depended on the sensitivity of the measure or on the restricted age-range used. I predicted that all children would be affected by stimulus-response conflict, but that the size of this effect would be differentially larger for younger toddlers. Secondly, and building on the literature on conflict in older children and adults, the effects of previous responses on compatible and incompatible trials were investigated. This issue has never been investigated in a spatial response conflict task in toddlers. The literature on older children and adults leads to the following predictions: if toddlers are sensitive to the conflict generated by previous responses, they should be slower and less accurate on incompatible trials that had been preceded by compatible trials, than in those preceded by incompatible trials. Similarly, they should be slower and less accurate on compatible trials preceded by incompatible, rather than compatible trials.

Method

Participants

Forty-seven typically developing toddlers were recruited through local nurseries and advertisements. They came predominantly from middle-class Caucasian families. Parents and teachers reported children's vision as normal or corrected. Thirty-seven toddlers completed the task, satisfying the inclusion criteria listed below: 17 two year-olds (range: 24-35 months, mean: 30 months, SD: 3.1 months, 7 girls), 20 three year-olds (range: 36-48 months, mean: 42 months, SD: 3.2 months; 8 girls).

Apparatus and Materials

Stimuli were presented on a laptop Dell computer (14" screen). A standard computer keyboard was modified to shield all keys except for two, the "p" and "w" keys. These were covered by two buttons (measuring 5 x 5 cm) marked by two large coloured circles (4 cm in diameter). The buttons were one red and the other blue in the first half of trials, one yellow and the other green for the second half. Coloured circles identical to those on the buttons were presented on the screen one at a time, either centrally, on the left or right of the screen. The experimenter initiated each trial, clicking on a separate computer mouse, to avoid distracting the child from the response buttons (full keyboards are inherently much more attractive, even for two-year-olds).

Procedure

Toddlers were tested in a quiet room either at their nursery, home or in the Neurocognitive Development Unit infant testing lab. Children sat at a little table approximately 50 cm from the laptop computer-screen, either on their caregiver's lap or on an appropriately sized chair, and within reach of the computer keyboard. Testing consisted of two separate blocks, one for each pair of coloured buttons. Each block consisted of 4 practice trials, followed by 8 trials during which target circles were presented centrally (henceforth referred to as "Central" trials) and a maximum of 16 trials during which the target circles were presented either to the left or right of fixation (henceforth referred to as "Lateral" trials). Figure 4.1 represents the different conditions graphically. This choice of trial sequences differs from the

methodology used by Gerardi-Caulton (2000), who employed a different pair of target pictures for each set of 8 trials and alternated between numerous central and lateral trial blocks. This could indeed be particularly problematic for younger children because it would require them to learn novel mappings between target stimuli and response buttons every 8 trials. I opted instead for minimising the number of target colours and preferred to vary the animated characters that rewarded a correct response, maintaining the task interesting. Before each trial started, the experimenter asked the child to place both hands centrally in front of the keyboard and reminded him of the game's rules. The child was instructed to press the button that was of the same colour as the circle presented on the screen. Each trial started with the presentation of two cartoon characters (the Teletubbies) at the centre of the screen. When the child's hands and eyes were centrally placed, the experimenter initiated the trial. Each trial began with the two centrally presented cartoon characters disappearing to be followed by a fixation cross (for 500 ms). A coloured target circle (subtending 6 degrees angle in diameter) was then presented until the child made a response or for a duration of 10 seconds. If the child responded correctly, the target circle was followed for 2.5 seconds by an animated cartoon character from a selection of eight characters of the same colour as the targets, accompanied by sounds. If the child responded incorrectly, a blank screen replaced the target circle and no sounds were presented, for the same duration as the animated character.

Practice, central and lateral trials.

Four practice trials (with the coloured circle presented centrally) began the first and second half of trials. During practice trials, the experimenter encouraged the child "to press the button that was the same as that (pointing to the circle on the screen)". If the child was reticent to do so, the experimenter demonstrated pressing the button. During practice trials, the coloured circle remained on screen until a correct response was given. Figure 4.1 represents the following trial types. After practice trials, children were always presented with a block of eight central trials, to ensure that they learnt the mapping between colour and response, as well as highlighting the fact that colour was the relevant dimension, before introducing lateral trials. During lateral trials, the coloured circle appeared either on the left or the right of fixation. In both central and lateral trials, trials were terminated after 10 seconds if the child did not respond and the trial continued as if it were incorrect.

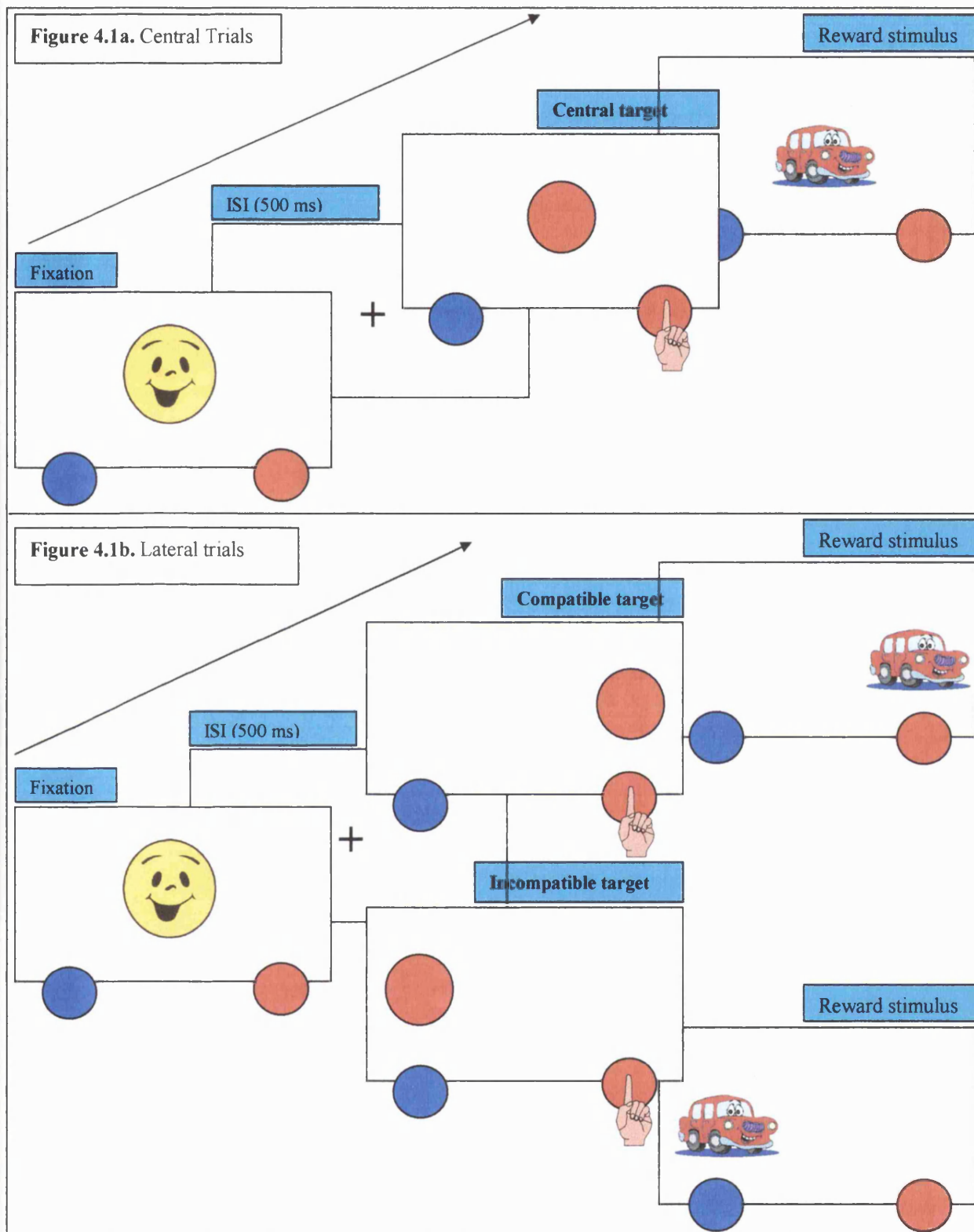


Figure 4.1. The sequence of events in each trial type in Experiments 2a and b (a) Central trials and (b) Lateral trials, varying in compatibility between location of the target stimulus and of the appropriate response: in compatible trials the target location and side of response are congruent, in incompatible trials they conflict.

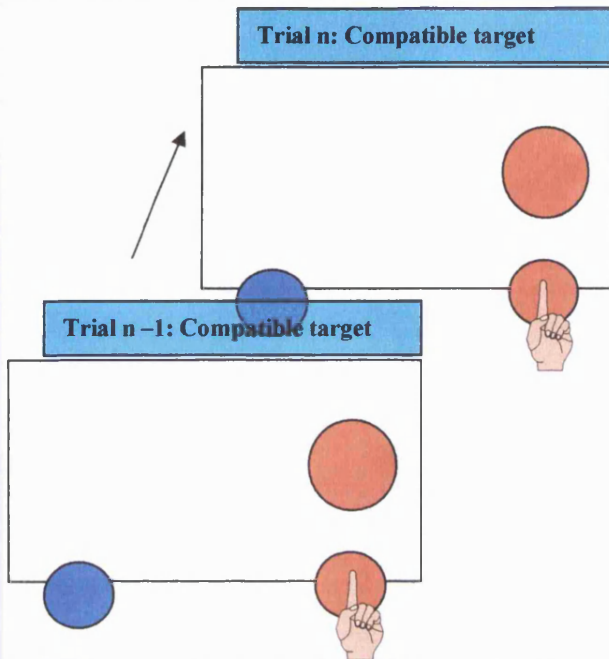
Performance was measured in terms of median response speed and percentage accuracy for central and lateral trials. Data-points from trials yielding an average reaction time of 2 standard deviations above or below the mean were discarded. Furthermore, median response times were calculated to limit the bias of outliers on other measures of central tendency, like the mean. I also set an additional exclusion criterion on the basis of performance on central trials. Data from 10 toddlers (all two-year-olds) were discarded because either they refused to play the game beyond the central trials ($N = 5$) or because they did not respond correctly on more than 60% central trials ($N = 5$). I chose this latter criterion to ensure that, within the limited number of central trials, children had learnt the association between the target colours and the response button to above chance level. Although 60% is a very liberal criterion, I considered it a satisfactory compromise between keeping brief the total duration of central trials (to avoid boredom and subject attrition) and establishing the association between target colours and response buttons.

Statistical Analyses

Analyses were organised according to two types of dependent measures, speed and accuracy. Median response times in milliseconds (speed measure) were calculated for each toddler, and accuracy was calculated as a percentage of the total number of trials per condition. This yielded separate speed and accuracy measures for central trials, lateral trials in which stimulus location and response side were compatible (hereafter named “compatible” trials) and lateral trials in which stimulus location and response side conflicted (hereafter named “incompatible trials”). In order to investigate the effects of previous response context, I then calculated two separate median reaction times and percentage accuracy for incompatible trials preceded by a compatible trial (hereafter labelled “CI”), as opposed to incompatible trials preceded by an incompatible trial (“II”). Compatible trials were also separated into those preceded by an incompatible trial (“IC”) and those preceded by a compatible trial (“CC”, see Figure 4.2 for the diagram summarising these differences). All analyses were preceded by an exploratory phase during which I plotted all variables of interest to explore distribution and variances. Dependent variables were checked for normality, homogeneity of variance and transformed where necessary. Bonferroni adjustments for multiple comparisons were used for post-hoc tests of all main effects.

Figure 4.2a. Compatible trials

CC Trial: Compatible trial in a compatible previous response context.



IC trials: Compatible trials in an incompatible previous response context.

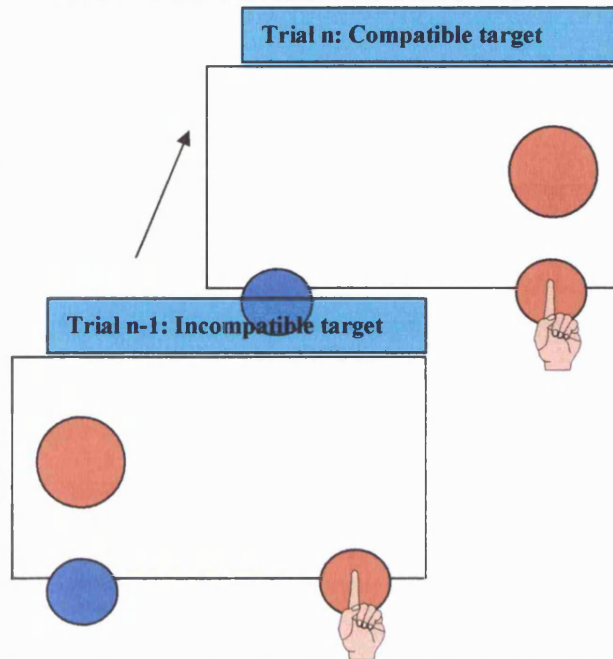
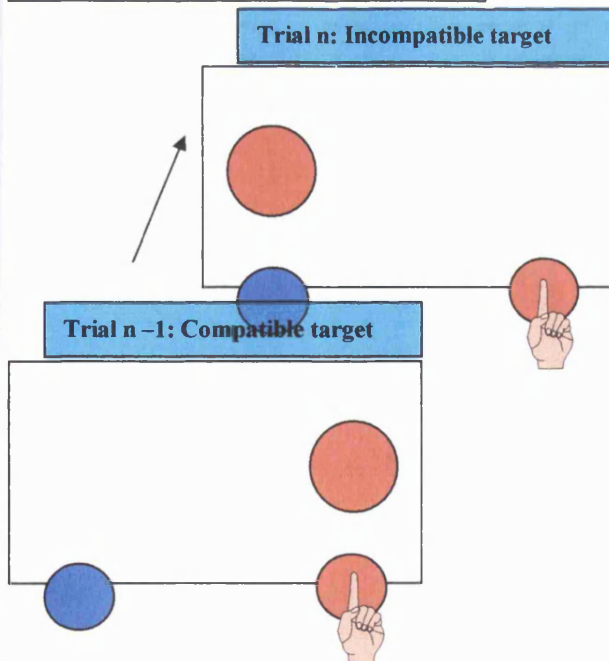


Figure 4.2b. Incompatible trials

CI Trial: Incompatible trial in a compatible previous response context.



II trials: Incompatible trials in an incompatible previous response context.

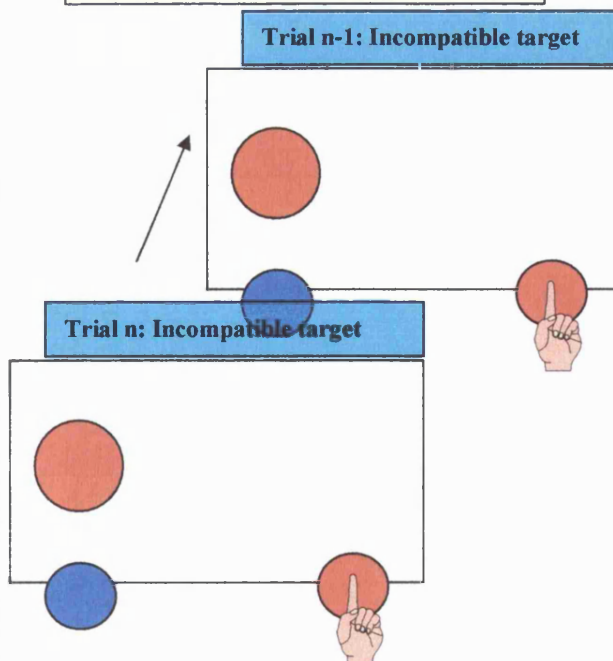


Figure 4.2. Trial types varying stimulus-response compatibility on trial *n* for (a) compatible trials and (b) incompatible trials; and the context created by the immediately preceding response. CC = compatible trial preceded by a compatible trial; IC = compatible trial preceded by an incompatible trial; CI = incompatible trial preceded by a compatible trial; II – incompatible trial preceded by an incompatible trial.

For both speed and accuracy, I first investigated the effects of stimulus-response compatibility, by running a paired t-test comparing compatible and incompatible trials. Secondly, I calculated different speed and accuracy measures as a function of preceding trial types. I then examined the effects of previous response context on each type of lateral trial (compatible, incompatible), by running a 2x2 repeated measures ANOVA with Compatibility (compatible, incompatible) and previous response Context (compatible, incompatible) as the within-subject variables. Thirdly, I investigated the effects of age, treating age both as a continuous variable (as a covariate in ANCOVA) and as a dichotomous variable, splitting the group into two-year-olds and three-year-olds and using Age Group as a between-subject factor. In order to study the effects of age on response time, accuracy and error type, I analysed these variables with a 2x2 mixed factorial ANOVA with trial type (lateral compatible, lateral incompatible) as the within-subject variable and age (two year-olds versus three year-olds) as the between-subject variable. To investigate the effects of preceding response context on compatible and incompatible trials, reaction time and accuracy were entered in a 2 x 2 mixed factorial ANOVA with trial type (CC, IC, CI, II) as the within-subject variable and age (two year-olds versus three year-olds) as the between-subject variable.

Finally, in order to characterise in detail the types of errors committed by the children, I calculated the percentage of correct switches in responses from one response button to the other. Gerardi-Caulton (2000) calculated the percentage of times a child pressed the left or right button twice in succession as a perseveration index using data from the central condition alone. This was due to too few of the youngest children completed trials in the lateral conditions, but here I calculated correct switching for both central and lateral trials. This would become crucial when trying to understand the sources of potential performance differences between typical and atypical children. For example, would children with fragile X syndrome produce more perseverations than their matched controls on lateral trials only (i.e., when faced with potential response conflict) or would they perseverate regardless of trial type? But first let us examine performance in typically developing toddlers.

Results

In summary, toddlers were significantly faster at responding to targets that were in a compatible location with their response button than in an incompatible location. Their accuracy reflected a similar trend. As a whole, toddlers did not reveal differential effects of previous response context. However, introducing their age as a factor revealed different effects of compatibility and context for older children's accuracy compared to younger toddlers. While older children showed contextual effects that were similar to those found in adults, with higher accuracy to incompatible trials preceded by incompatible than compatible trials, younger children did not. In contrast, they showed a trend in the opposite direction, with responses that were more accurate when response context changed from one trial to the next. Furthermore, younger children made more errors than older children when responses required to switch from the response given on the previous trial, but not when a switch was not required. These findings were supported statistically as follows.

First, preliminary analyses with gender as a between-subject factor did not reveal any statistically significant difference between boys and girls on any of the dependent variables (p levels ranged from .707 to .102) and therefore gender was dropped from the further analyses described below. All dependent variables were tested for normality (1-sample Kolmogorov-Smirnov test) and homogeneity of variance (Levene's test).

Analyses of Response Speed

Figure 4.3 represents median reaction times to targets that appeared at a compatible or incompatible location with their appropriate response button. Median reaction times to targets were not all normally distributed (Kolmogorov-Smirnov test, p values ranging from .259 to .021) and were therefore transformed (natural logarithms). The transformation succeeded in normalising the distribution of the data (Kolmogorov-Smirnov test, lowest p = .224).

Reaction times to targets in compatible trials were faster than in incompatible trials (on average 1.62 seconds \pm SEM = .09 and 1.81 seconds \pm .10 respectively), a statistically

significant difference, $t(36) = 4.229$, $p < .001$. When I analysed separately the effects of stimulus response compatibility, of previous response context and their interaction on median reaction times, compatibility continued to have a statistically significant effect, $F(1, 34) = 5.159$, $p = .03$. However, the effects of either previous response context or the interaction were not significant, $F(1, 34) = .001$ and 1.082 respectively, $p = .982$ and $.306$.

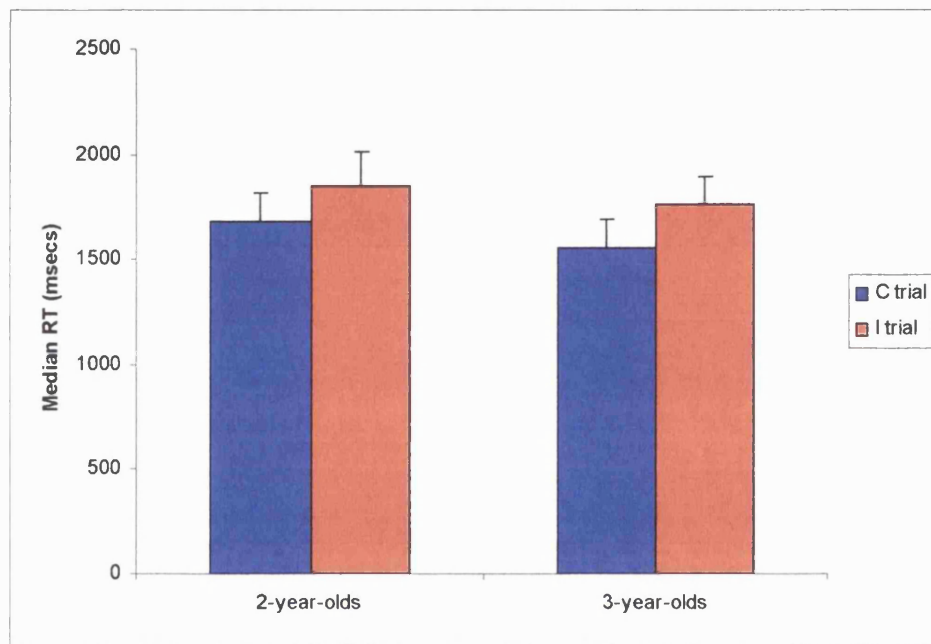


Figure 4.3. Median Reaction Times to target stimuli appearing at a location that was compatible (C trial, in blue) or incompatible (I trial, in blue) with the appropriate response button, for 2- and 3-year-olds. Error bars represent the standard error of the mean. Bars represent standard errors of the mean.

Analyses of Response Accuracy and Error Types

Percentage accuracy measures were not all normally distributed (Kolmogorov-Smirnov test, p values ranging from .612 to $< .001$) and therefore they were transformed (square root transformation). The transformation succeeded in normalising the distribution of the data for accuracy on central, compatible and incompatible trials (p values ranging from .522 to .058). However, transforming the data did not normalise accuracy when this was calculated separately for compatible and incompatible trials preceded by compatible and incompatible responses (p values ranging from .024 to $< .001$) and I therefore decided to assess the effect

using non-parametric statistics. The compatibility of previous responses did not have differential effects on accuracy, as shown when I compared percentage accuracy across compatible and incompatible trials preceded by compatible and incompatible trials, Friedman test, $\chi^2(35) = .518$, $p = .915$.

Toddlers tended to be more accurate on compatible (91% of trials ± 1.8) than on incompatible trials (87.8% of trials ± 1.7), but this difference was not statistically significant, $t(36) = 1.514$, $p = .139$. On average, toddlers committed errors both during trials that required repeating the response produced in the previous trial (no-switch trials, average percentage accuracy = 90.2% ± 1.8) and during trials that required switching response (switch trials, average accuracy = 89.1% ± 1.8). Their perseveration index, a measure of how much toddlers repeatedly pressed response buttons over and above what was required by the computer program, was significantly smaller than 0, binomial test, $N = 37$, $p = .003$. This indicated that on average toddlers repeated pressing the previous response button more than required by the trial sequence.

Age-related Changes in Performance

After analysing toddlers' data as a large group, I investigated potential differential effects of age on both the reaction time and accuracy measures above. The overall effect of compatibility on reaction times, $F(1, 35) = 17.048$, $p < .001$ did not vary with age, $F(1, 35) = .504$, $p = .482$ (when age was considered a dichotomous variable) and $F(1, 35) = 1.134$, $p = .294$ (when age was entered as a covariate). Furthermore, when the effects of both previous response context and compatibility on reaction times were tested, age did not have a significant effect, $F(1, 33) = 2.123$, $p = .155$ (dichotomous) and $F(1, 33) = 1.509$, $p = .228$ (continuous).

Accuracy measures revealed age trends and statistically significant age differences. Older toddlers were more accurate on central trials than on lateral trials (91.3% vs. 81.3% accurate), $t(26.58) = 2.593$, $p = 0.015$, equal variances not assumed. When context and compatibility effects were analysed in the same analysis, entering age as a co-variate

revealed that previous response context and compatibility interacted, $F(1, 33) = 6.128$, $p = .019$. This interaction is represented in Figure 4.4. Accuracy was highest for compatible trials preceded by compatible trials (CC, 90.7% accuracy ± 2), followed by compatible trials preceded by incompatible trials (IC, 88.7% accuracy ± 3), then by incompatible trials preceded by incompatible trials (II, 87.7% accuracy ± 3) and finally by incompatible trials preceded by compatible trials (CI, 86.2% accuracy ± 3). Furthermore, age interacted with compatibility and previous response context, $F(1, 33) = 10.754$, $p = .002$ (dichotomous variable) and $F(1, 33) = 7.080$, $p = .012$ (continuous). The sources of this interaction were investigated by analysing the interaction of compatibility and context separately for 2- and 3-year-olds. For the younger toddlers, the interaction was marginally significant, $F(1, 15) = 4.649$, $p = 0.048$. Older toddlers' interaction reached statistical significance, $F(1, 18) = 6.556$, $p = 0.02$. The interaction between compatibility, context and age remained statistically significant when I took into account the variability in accuracy on central trials, $F(1, 32) = 8.523$ and 5.151 , $p = .006$ and 0.03 (age as a dichotomous and continuous variable respectively).

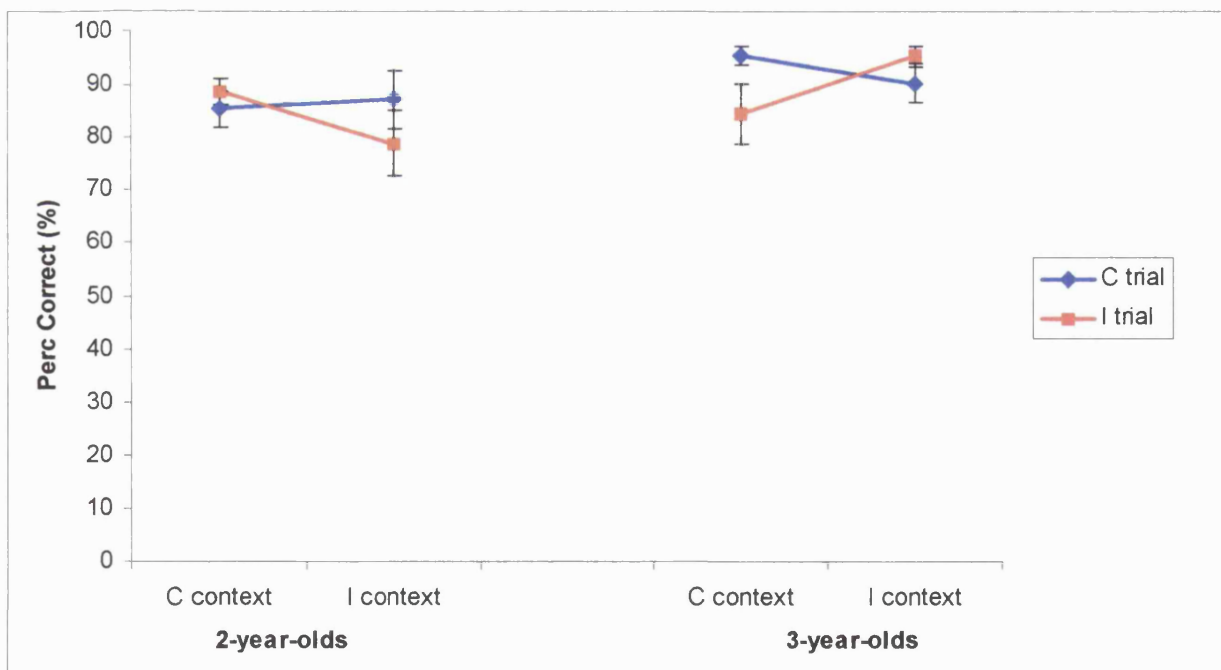


Figure 4.4. Mean accuracy for compatible (C trial in blue and diamonds) and incompatible trials (I trial in red and squares) that were preceded by compatible (C context) and incompatible trials (I context). The graph shows differential effects of previous response context for the two age groups. Error bars represent standard error of the mean.

The latter analyses need to be treated with caution because, as reported above, accuracy measures in CC, IC, CI and II trials were not normally distributed and variances were not homogeneous, minimum $p = .002$ (Levene's test). These violations of the assumptions of ANOVA and ANCOVA increased the risk of incorrectly rejecting the null hypothesis (type I errors). This concern was addressed as follows. First, 2- and 3-year-olds' accuracy was compared on CC, CI, IC and II trials using independent t-tests (equal variances not assumed) and, second, using Mann-Whitney tests (less influenced by violations of normality). These comparisons revealed that 3 year-olds were more accurate than 2 year-olds on compatible trials that had been preceded by compatible trials (95% vs. 85% accuracy, equal variances not assumed, $t(1, 22.65) = 2.522$, $p = .019$), but not when compatible trials were preceded by incompatible trials ($p = .652$). They were also more accurate than younger toddlers on incompatible trials preceded by incompatible trials (95.2% \pm 1.9 vs. 78.8% \pm 6.3 accuracy, equal variances not assumed, $t(1, 17.78) = 2.504$, $p = .022$), but not when compatible trials were preceded by incompatible trials (84.3% vs. 88.6%, $p = .652$). Secondly, these differences were also tested with non-parametric statistics (Mann-Whitney U) and a similar pattern of age differences emerged: CC, $p = .024$, IC, $p = .953$, CI, $p = .753$, II, $p = .018$. Thirdly, paired t-tests and Wilcoxon Signed Rank tests were used to assess differences across conditions for the two groups: two year-olds tended to be more accurate on CI trials than on II trials (88.5% vs. 78.8%), $t(15) = 1.782$, $p = 0.095$, Wilcoxon, $Z = 1.723$, $p = .085$. Three year-olds, in contrast, tended to be more accurate on II than CI trials (84.3% vs. 95.2%), $t(15) = 1.757$, $p = .096$, Wilcoxon, $Z = 1.653$, $p = 0.098$. None of the other paired comparisons were statistically significant.

Furthermore, I investigated whether these differential effects of context could be due to differential speed-accuracy trade-offs for the two groups. Were younger toddlers slower, as well as more accurate, at CI trials than at II trials? A larger speed-accuracy trade-off for this condition could explain their surprisingly higher error rates on II trials. An inspection of median reaction times across conditions suggests that this is not the case, because reaction time differences across conditions were in the same direction as accuracy scores (although the interaction effect was not statistically significant in this case). Critically, younger toddlers tended to be faster in CI than in II trials (1.97 seconds vs. 2.03 s), whereas older toddlers tended to be slower for CI than II trials (1.68 seconds vs. 1.61 s). Similarly, younger

toddlers tended to be faster in IC than in CC trials (1.77 seconds vs. 1.84 seconds), whereas older toddlers tended to be slower for IC than for CC trials (1.64 seconds vs. 1.47s).

Finally, age differences emerged also in the type of errors made by the children. Two-year-olds were less accurate than 3-year-olds on trials that required a switch in response compared to the previous trial, both on central (75.2 % accurate vs. 97.9 %, $t(16.586) = 2.467$, $p = 0.024$; Mann-Whitney U, $p = .037$) and on lateral trials (84.8% vs. 92.8%, $t(35) = 2.416$, $p = 0.021$; Mann-Whitney U, $p = .005$).

Discussion

In experiment 2a, I aimed to investigate the effect of stimulus-response conflict and of previous response context in an adaptation of the adult spatial conflict task. Furthermore, the study aimed to investigate differential changes of these effects between 24 and 36 months of age. Toddlers were slower (and tended to be less accurate) when the location of the target stimuli and the appropriate responses were incompatible. When data from all toddlers were analysed together, the context of previous responses did not have a significant effect on either their accuracy or their response times. However, considering their age as a variable revealed that the initial group analyses masked developmental changes in the effect of context. Older toddlers were more accurate on compatible and incompatible trials preceded by compatible trials than incompatible ones and they were more accurate on incompatible trials preceded by incompatible trials, an effect that is similar to the effect found in adults' and older children's reaction times on this task. Younger toddlers did not show this effect: in contrast, their accuracy was higher for a trial during which response context changed compared to the previous trial.

Spatial conflict affected toddlers' reaction time, replicating the findings by Gerardi-Caulton (2000) and extending them to young children from 36 to 48 months of age. As for toddlers between 24 and 36 months, for children in this group the overall effect of spatial compatibility did not vary across age groups. However, intriguingly, there were age-related changes in the effect of previous response context on accuracy. I had originally predicted that younger children might be insensitive to manipulations of context, whereas older toddler's performance could bear the hallmark of strategic contextual modulation that is

found later in life. Indeed, older toddler's accuracy showed the pattern that is characteristic of older children and adult performance. They were most accurate on trials that repeated the previous response context (CC and II trials). In contrast, and surprisingly, younger children were more accurate for trials that were characterised by a change in context (CI and IC trials).

A number of reasons could account for the findings with younger children. First, the larger variability and non-gaussian distribution of their accuracy could have biased the parametric statistics I used. However, non-parametric statistics supported the effects obtained with parametric analyses. Second, the effect could be a spurious result of the relatively limited amount of practice that toddlers were given with the task with central trials. It could be that 12 central trials (practice and central trials taken together) were sufficient for older children to master the task and therefore engage in response strategies that would be manifested in context effects. In contrast, 12 trials may not have been sufficient for younger children. However, this suggestion hardly explains why younger toddlers would be more accurate with some types of trials and not others. This concern could nevertheless be addressed further with an experiment in which younger and older toddlers are trained on central trials to equal accuracy levels (although this may result in subject attrition on lateral trials, because of boredom or fatigue). Thirdly, perhaps the statistically significant differences in accuracy are the result of differential speed-accuracy trade-offs in younger and older children across conditions. Were younger toddlers slower, as well as more accurate, at CI trials than at II trials? A larger speed-accuracy trade-off for this condition could explain their surprisingly higher error rates on II trials. An inspection of median reaction times across conditions suggests that this is not the case, because reaction time differences across conditions were in the same direction as accuracy scores.

Fourthly, and more interestingly, this difference in performance could be grounded in our current understanding of the developmental changes in neural processes of control. In adults, trials that are characterised by a change of context (CI and IC trials) recruit areas like the basal ganglia and insular cortex, in addition to cingulate and dorsolateral prefrontal cortices that are differentially more recruited for CI trials (i.e., for high conflict trials). Casey et al. (2000) proposed that recruitment of the basal ganglia might be involved in the detection of a

contextual change or violation of expectancy. Younger children (as young as 7 years of age) have been shown to recruit subcortical areas like the basal ganglia more extensively than adults when engaged in tasks involving control and violation of expectancies (Casey et al., 1997b; Casey et al., 2002). For example, Casey et al. (2002) found that striatal activity correlated with the percentage of errors made in over-riding an old stimulus-response association and that the volume of striatal/pallidal regions recruited was larger than in adults. This pattern of activation only gradually shifts to the adult pattern of cortical activation (in particular, prefrontal) activation in similar tasks (Duncan, 2001; see also Bunge et al., 2002 for developmental changes in prefrontal recruitment). It is possible then, that performance by the younger children in the current sample was mainly driven by mechanisms involved in the detection of change. In contrast, the older children's performance shifts towards the monitoring of conflict and context that is characteristic of older individuals as cingulate and dorsolateral prefrontal areas gradually become more effective.

Error types also discriminated between younger and older children. Indeed, younger toddlers were less accurate on trials that required a response switch compared to the previous. These results complement the findings by Gerardi-Caulton (2000), who focused on central trials and found that perseveration decreased significantly during this period, with the large majority of errors in 24-month-olds being due to perseveration. This finding suggests that error types, rather than overall speed and accuracy, may be a more sensitive measure of changes in the ability to deal with task demands.

4.2.2. Experiment 2b. The control of response conflict in toddlers with fragile X syndrome

Individuals with fragile X syndrome encounter great difficulties in controlling, planning and executing competing actions. Munir et al. (2000) tested executive control in children and adolescents with the syndrome on a number of tasks testing selective attention and executive control. Amongst these tasks, two experiments, both part of the Test of Everyday Attention for Children (TEA-Ch, Manly et al., 2001) targeted the ability to control responses in

particular. In a task measuring the ability to maintain a rule in mind and inhibit responses accordingly, children with FXS were less able to withhold responses than both children with DS and typically developing children matched for verbal mental age. Furthermore, in a task requiring a response to the Arabic numerals “1” and “2” as “2” and “1”, similar to a Stroop task (run by blocks of incongruent trials), children with the syndrome performed worse than typically developing children, but not worse than children with DS. However, this latter finding may be biased by the fact that a much larger proportion of children with FXS did not actually complete the task.

Predictions for the control of conflict by toddlers with FXS might be derived from the attentional profiles of adults with the syndrome and from the difficulties displayed by older children with FXS (Munir et al., 2000). Experiment 1b presented compelling empirical evidence for difficulties in inhibiting reflexive looks towards peripheral stimuli. If this pattern of performance is not merely related to eye-movement control, but is a general feature of their inability to control responses, children’s performance should be firstly characterised by difficulties in controlling response conflict on a trial-by-trial basis. Secondly, effects of previous response conflict have not been investigated in this population, but may open a different window on the syndrome’s phenotype. Toddlers with FXS may be differentially affected by either the requirement to control conflict or by the context in which they make responses. Furthermore, they may also make quantitatively and qualitatively different errors from those expected given their developmental level. For example, switching responses may be differentially harder than it already is for typically developing young children matched for mental age.

Method

Participants

Twenty boys with FXS attempted the present task. However, three toddlers did not comply with the experimental procedure beyond the initial central trials and seven did not achieve the criterion set at 60 % minimum accuracy on central trials.

Therefore, ten boys with FXS fulfilled the inclusion criteria set above for Experiment 2a (age range = 41 to 60 months, mean chronological age = 47.1 months, SD = 6.1 months). Their developmental level was assessed using the Bayley Scale of Development II – Mental Subscale (BSDM-II; Bayley, 1993), which revealed a mean mental-age equivalent of 25.6 months (SD = 4.8 months, range = 18 to 36). Although I attempted to match all children individually to typically developing toddlers of the same developmental level (within one month), it was particularly challenging to find an 18 month-old who would perform the task within the set criteria and match the lowest functioning child with FXS in the group. Children were therefore group-matched by mental age equivalent to ten typically developing toddlers, all of whom had participated in Experiment 2a and had been also been assessed with the BSMD-II (mean = 28.6 months, SD = 2.8 months, mental age range: 24 to 32 months), henceforth referred to as the MA controls. The FXS toddlers were also matched by chronological age (within one month) to fourteen typically developing children (mean = 46.8 months, SD = 6.3 months, range = 42 - 60), six of whom had contributed to the data presented in Experiment 2a, henceforth referred to as the CA controls. There were no significant differences in chronological age between the CA controls and toddlers with FXS (paired t-test, $p = .91$), nor in mental age between the MA controls and toddlers with FXS ($p = .11$).

Apparatus and procedure

As in Experiment 2a.

Statistical Analyses

As in Experiment 2a. As discussed in Chapter 2, I conducted compromise power analyses (G-Power, Faul & Erdfelder, 1992) in order to establish whether the present sample size was too small to yield statistically significant results on the variables of interest and these are reported in Chapter 2, Table 2.4.

Results

In summary, toddlers with fragile X syndrome were slower and less accurate than both the MA and CA controls, and their accuracy suffered particularly when asked to respond to lateral targets, more than expected given their lower accuracy on central trials. Nevertheless, they did not show differential effects of stimulus-response compatibility or of context. However, they produced a large proportion of errors on trials involving switching responses on lateral trials.

All these empirical conclusions were supported statistically, as follows.

Analyses of Accuracy and Error Types

Mean percentage accuracy was calculated for targets in incompatible and compatible trials for the three groups of toddlers (Figure 4.5). Kolmogorov-Smirnov tests for normality revealed that these measures were normally distributed for the MA controls and the toddlers with FXS ($p > .200$), but not for the CA controls, lowest $p < .001$. Square root transformations did not normalise these data. However, homogeneity of variance was satisfactory for the following analysis (Levene's test, minimum $p = .169$). A 2 (compatibility) \times 3 (group) mixed ANOVA on the untransformed data revealed a main effect of target compatibility, $F(1,27) = 7.061$, $p = 0.013$, with all toddlers being more accurate on compatible than incompatible trials (84.2 vs. 78.9% accurate on average). The main effect of Group was also significant, $F(2, 27) = 41.046$, $p < .001$. This was due to toddlers with FXS being less accurate than both the MA and CA controls. On average, they were accurate on 63.9 % of lateral trials, compared to an accuracy of 86.9 % for the MA controls and 93.9 % for the CA controls (both differences, $p < .001$, Bonferroni corrected). CA and MA controls did not differ statistically ($p = .162$). The main effect of Group and pair-wise differences remained significant when accuracy on central trials was co-varied, $F(2, 26) = 31.477$, $p < .001$, suggesting that toddlers with FXS were less accurate than both the other groups on lateral trials, even when the variability on central trials was accounted for.

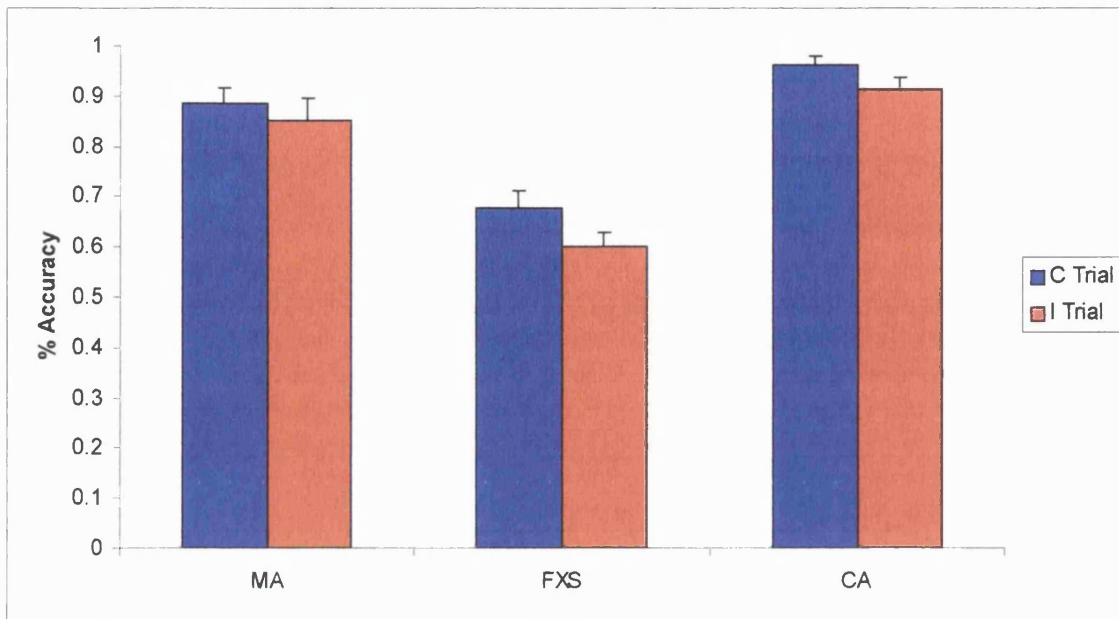


Figure 4.5. Mean percentage accuracy for compatible (C trials) and incompatible trials (I trials) by toddlers with fragile X syndrome (FXS), matched MA controls (MA) and CA controls (CA). Error bars are standard errors of the mean.

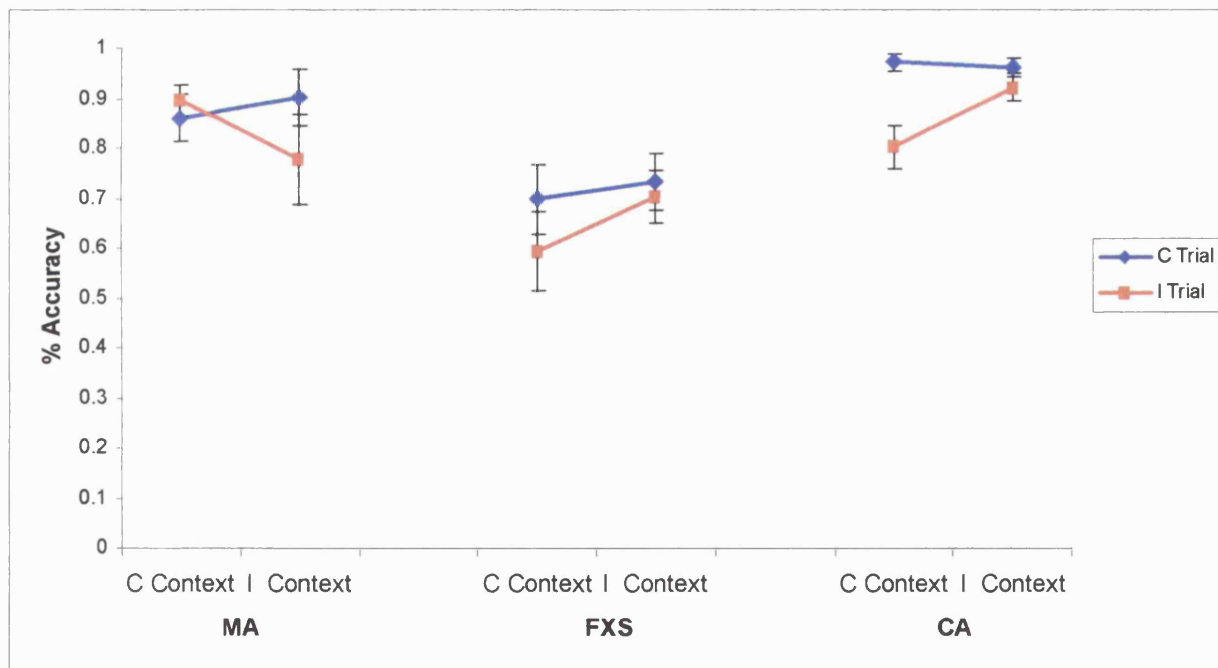


Figure 4.6. Mean accuracy for compatible (C trial in blue and diamonds) and incompatible trials (I trial in red and squares) that were preceded by compatible (C context) and incompatible trials (I context). The graph shows differential effects of previous response context for the three groups. Error bars represent the standard error of the mean.

Accuracy for compatible and incompatible trials was then calculated separately for trials preceded by compatible (CC and CI) and incompatible trials (IC and II) (Figure 4.6). However, these measures were normally distributed for toddlers with FXS (Kolmogorov-Smirnov test, lowest p value, $p = .095$), but not for the CA and MA controls (lowest p value $< .001$). A 2 (Compatibility) \times 2 (context) \times 3 (group) mixed ANOVA on the untransformed data revealed a main effect of Group, $F(2, 27) = 18.434$, $p < .001$. These effects were treated with caution because of the violation of normality as well as homogeneity of variance (Levene's test, lowest $p = .001$), by running both parametric and non-parametric post-hoc comparisons. The main effect of group was due to toddlers with FXS being less accurate than both the MA and CA controls (on average, on 68 % of trials, vs. 85.9 and 91.5 % respectively, $p < .001$ in both comparisons, Bonferroni corrected; Wilcoxon test, p ranging from .008 and .034). In contrast, MA and CA controls did not differ from each other significantly, $p = .538$. Compatibility had a statistically significant main effect on accuracy, $F(1, 27) = 6.415$, $p = .017$, with toddlers being accurate on average on 85.5 % of compatible (± 1.7) and on 78.2 % of incompatible trials (± 2) (Mann-Whitney U, $p = .008$). None of the other effects was statistically significant, p ranging from .840 to .220.

The effect of Group and the pair-wise group differences remained statistically significant when accuracy on central trials was entered as a covariate in the analysis, $F(2, 26) = 14.223$, $p < .001$, suggesting that toddlers with FXS were differentially less accurate than controls on lateral, compared to central trials. Indeed, toddlers with FXS did not differ in accuracy on central trials from the MA controls, $t(18) = .628$, $p = .538$. However, both groups were less accurate than the CA controls on central trials, $t(18) = 2.906$ and 2.203 , $p = .009$ and $.041$ respectively for the FXS toddlers and the MA controls.

I then analysed the type of errors made by the toddlers, calculating the number of correct response switches as a percentage of the total number of switches required by the computer program. A One-way ANOVA with Group as the between-subject factor revealed a main effect of Group, $F(2, 29) = 19.659$, $p < .001$. This was due to the toddlers with FXS being less accurate at switching responses than both the MA (on average 63.8% accurate ± 5 vs. 86.1% ± 3 , $p < .001$, Bonferroni corrected) and the CA controls (on average 94.4 % accurate ± 1 , $p < .001$, Bonferroni corrected). MA and CA controls did not differ

significantly from each other, $p = .328$. However, group differences were not statistically significant for central trials, $F(2, 29) = 2.050$, $p = .148$, suggesting differentially larger switching difficulties for toddlers with FXS on lateral than on central trials.

Analyses of Response Speed

Median reaction times to targets in compatible and incompatible trials were calculated for all groups. Tests of normality revealed that these measures were not normally distributed for all three groups (Kolmogorov-Smirnov test, p values ranging from .012 to $> .200$), and they were therefore \ln transformed. The transformed variables were normally distributed (p ranging from .06 to $> .200$). A 2 (compatibility: compatible, incompatible) \times 3 (group: FXS, MA, CA) ANOVA revealed a main effect of Group, $F(2, 27) = 8.620$, $p = .001$. A post-hoc Bonferroni test revealed that toddlers with FXS were slower than both the MA (2.75 seconds on average vs. 1.69 s, $p = .011$) and the CA controls (2.75 seconds vs. 1.49 s, $p = .002$), whereas the two control groups did not differ significantly from each other, $p = 1.0$. Furthermore, there was a marginally significant interaction between Group and Compatibility, $F(2, 27) = 3.374$, $p = 0.049$. These effects were treated with caution because of the violation of normality as well as homogeneity of variance (Levene's test, lowest $p = .001$), by running both parametric and non-parametric post-hoc comparisons. Paired t -tests for each group revealed that only the CA controls were significantly faster at responding to compatible targets than to incompatible targets, $t(9) = 2.748$, $p = .023$, whereas the MA controls and toddlers with FXS did not differ in median reaction times across conditions ($p = .547$ and $.195$ respectively). The difference between reaction times to compatible and incompatible targets for CA controls was confirmed non-parametrically (Wilcoxon Signed-Rank Test, $Z = 2.293$, $p = .022$). None of the other effects were statistically significant. The main effects of Group and the interaction of Group and Compatibility no longer held ($p = .202$ and $.092$ respectively) when reaction time in central trials was entered as a covariate, suggesting that toddlers with FXS were not differentially slower than the other groups on lateral than on central trials. Rather, they were slower overall. Toddlers with FXS, but not MA controls, were slower than CA controls on central trials, $t(10.6 \text{ and } 11.2, \text{ equal variances not assumed}) = 3.419$ and 1.183 , $p = .006$ and $.252$. They were also close to being slower than MA controls on central trials, $t(18) = 1.930$, $p = .069$.

When median reaction times were calculated separately for compatible and incompatible trials preceded by compatible and incompatible trials respectively, these variables were normally distributed for the toddlers with FXS and the CA controls (Kolmogorov-Smirnov test, p values ranging from .08 to $> .200$), but not for the MA controls, lowest p value = .002. Natural logarithms did not normalise these data. A 2 (compatibility) \times 2 (context) \times 3 (group) ANOVA on the untransformed reaction times revealed a main effect of Group, $F(2, 27) = 7.397$, $p = .003$, with toddlers with FXS being again slowest ($p = .022$ and $.003$ compared to the MA and CA controls respectively, Bonferroni corrected). None of the other effects nor interactions were statistically significant.

Differential effects of developmental level on conflict and context effects.

When Mental Age was entered as a covariate in all the analyses above, it did not have any statistically significant main effects (lowest $p = .097$, when it was entered as a covariate for the analyses investigating the effects of conflict and context on accuracy). None of its interaction effects with the within-subject variables of interest were statistically significant (lowest $p = .663$ for its interaction effect with compatibility on accuracy in the analyses of conflict effects alone). Furthermore, all statistically significant effects treated above remained significant after co-varying the variability due to age. This suggested that there were no differential effects of developmental level on the variables of interest across the three groups.

Discussion

Experiment 2b aimed at investigating the ability to control spatial conflict in toddlers with fragile X syndrome. The results revealed both similarities and differences between performance in typically developing toddlers and toddlers with the condition. Although children with FXS performed slower and less accurately than the control groups, they showed a similar magnitude of the effects of conflict and context. However responding to lateral, rather than central targets, was differentially more difficult for them compared to the typically developing controls. In particular, their accuracy was poor on trials requiring switching of responses, and differentially more so for laterally presented targets.

Let us first examine the differences in performance between the toddlers with FXS and the typically developing controls. Toddlers with FXS were slower and less accurate when they were required to respond to lateral targets compared to central targets. This was the case regardless of the compatibility between the stimuli and the response and of the previous response context. FXS children's ability to focus on peripheral target may be differentially worse than that to focus on a central target, perhaps because shifting attention in the direction of lateral targets makes it more difficult to also maintain task demands on-line and to respond appropriately. These difficulties may depend on two factors. First, introducing two potential target locations, as opposed to a single central one, introduces a further dimension of complexity in the processing of the target, regardless of whether location is compatible or not with the required response. Secondly, the ability to voluntarily attend to the features of peripheral as opposed to foveal stimuli, in contrast to simply orienting towards a peripheral stimulus, develop at differential rates (Goldberg et al., 1998; Posner et al., 1998; Maurer & Lewis, 1998; 2001). The former may be differentially delayed in toddlers with FXS. This factor would therefore relate the current results to the findings of Chapter 3, in which infants and toddlers with FXS showed atypical control of reflexive looks towards peripheral targets. While children with the syndrome reflexively orient to such stimuli (as shown in Chapter 3), their ability to respond to the targets' relevant features seems differentially impaired when compounded with the need to make a shift in attention to the periphery. Furthermore, toddlers with FXS displayed large difficulties in switching to different response sides, especially during lateral trials, another hallmark of the inhibitory difficulties documented in Chapter 3. Difficulties with switching responses when required are documented both in neuropsychological patients (e.g., Shallice, 1980) and in a number of developmental disorders (Casey et al., 2002).

What of the similarities in performance between the controls and the toddlers with FXS? I predicted that, if toddlers with the syndrome were differentially more sensitive to conflict and contextual manipulations than expected given their developmental level, they should show differentially slower and less accurate performance on conditions that revealed the effects in typical toddlers. These predictions were only partially confirmed. Indeed, toddlers with FXS were slower and less accurate than typically developing toddlers, but they were

not differentially more affected by conflict or context of responses, suggesting overall delay, rather than deviance, on these measures of performance at this time point in development. First, there are processing explanations for this similarity: Eimer et al., (1995) and Hommel (2002) reviewed evidence suggesting that the size of the Simon effect is influenced by the timing allowed for irrelevant response codes to interact with the task-relevant responses. It could therefore be the case that potentially higher vulnerability to response conflict by FXS toddlers is masked by their slower reaction time overall.

Furthermore, it becomes crucial to consider the implications of findings of this type of finding for our understanding of performance in developmental disorders. When comparing typical and atypical populations, the finding of overall slower or less accurate performance compared to matched controls is generally dismissed as an uninteresting “simple” delay, with no further implications nor need of investigation. However, this approach ignores two observations. Firstly, “simple” delay for a cognitive process/domain at a particular time-point in development may well correlate with atypical performance on another process/domain at that same time-point. Secondly, delayed performance at a point in development may actually predict deviant performance at a later time point. To assume otherwise is to a priori assume the independence of processes and of measures across development. Ultimately, these issues can only be addressed in longitudinal designs, as I discuss in more detail in Chapter 7.

4.3. General Discussion

4.3.1. Typical and atypical control of conflict: Compatibility and Context

In Experiment 2a, I aimed to investigate the effects of stimulus-response conflict and of the context set by previous responses on typically developing toddlers’ performance on a spatial conflict task. Conflict between the location of target stimuli and the associated response buttons affected toddlers’ performance, a finding that replicated and extended the results first presented by Gerardi-Caulton (2000). In addition, the toddlers’ accuracy was differentially affected by the responses made on previous trials depending on their age.

While older toddlers tended to display the performance pattern that is characteristic of adults (e.g., Botvinick et al., 2001; Gratton et al., 1992), younger toddlers were more accurate for incompatible trials preceded by compatibles. These developmental differences appear counter-intuitive at first sight. Interestingly, the finding for younger children of a shift from more accurate reaction times on CI and IC trials to more accurate reaction times on CC and II trials, could be grounded in our current understanding of developmental changes in neural mechanisms of control. Indeed, in adults, the former type of trials seems to be recruiting areas like the basal ganglia and insular cortex, involved in the detection of changes in context and violations of expectations. But, as mentioned above, younger children (as young as 5 years of age) have been shown to recruit subcortical areas like the basal ganglia more extensively than adults when engaged in tasks involving control and violation of expectancies (Casey et al., 1997, 2002). This pattern of activation only gradually shifts to the adult pattern of cortical activation (in particular, prefrontal) in the same tasks (see also Bunge et al., 2002). It is possible that performance by the younger children in the present sample was mainly driven by mechanisms involved in the detection of change, whereas the older toddlers' performance shifted towards the monitoring of conflict and context that is characteristic of older individuals.

In Experiment 2b, I investigated the ability to deal with response conflict in children with FXS. Their accuracy and reaction times were worse than those of controls, but these effects on accuracy appeared to be larger for conditions that required children to select responses for lateral, as opposed to central trials. This relatively greater difficulty in identifying correctly peripheral stimuli could depend on a deficit in orienting attention voluntarily to the relevant features of peripheral stimuli and/or on difficulties in ignoring the irrelevant location dimension, regardless of its compatibility with the appropriate response. Furthermore, children with fragile X syndrome displayed large difficulties for trials that required them to switch from the previous response side. In conjunction with the results of Chapter 3, difficulties on switch trials suggest that toddlers with the syndrome, like adults and older children with FXS, experience difficulties in inhibiting responses (eye-movements or button presses) that are inappropriate to the task at hand.

4.3.2. Future research questions

A number of issues for future investigation emerge from the new data presented here.

Modifying a spatial conflict task revealed changes even in performance for typically developing toddlers. Further manipulations of previous response conflict could throw light on the level at which contextual effects operate and on how this changes through early typical development. The current findings point to changes in the effects of the context set by immediately preceding responses. The adult literature suggests further ways in which context can modulate conflict. Indeed, contextual effects have also been shown when the overall probability of compatible and incompatible trials is manipulated. For example, Ridderinkhof (2002) showed adaptive changes in reaction times and accuracy depending on how probable incompatible trials are. When incompatible trials are very frequent, adults are faster and more accurate at responding to them than to incompatible trials that are infrequent. An intriguing (and testable) hypothesis is the following: younger typically developing toddlers seem affected mainly by simple changes in compatibility (regardless of their direction), whereas older toddlers exploit sequential changes in response context. However, perhaps the ability to modify behaviour on the bases of the larger probability of a trial type is even slower to develop. This would support proposals, made in the adult literature, that the ability to control response conflict can be modulated by multiple contextual effects (e.g., Proctor & Vu, 2002; Valle-Inclan et al., 2002). A developmental perspective would enrich our understanding of how these multiple contextual effects emerge and interact with each other to lead to the ultimate adult performance. Furthermore, many authors have argued that the existence of contextual effects on conflict does not clarify the level at which this modulation occurs. Is it at the level of stimulus processing? Or is it restricted to the selection of responses? This issue has been previously addressed in adults by using paradigms that require mapping multiple stimuli to identical responses, and manipulating perceptual aspects of the stimuli to be mapped (e.g., Duncan, 1977). Modifying these tasks to be used with younger children could allow us to tease apart the effects that are due to stimulus versus response repetition and alternation (Valle-Inclan et al., 2002; Mayr et al., 2003).

Interesting differences and similarities emerged also when comparing performance by typically developing toddlers and toddlers with FXS. However, a number of concerns that arose could be addressed by modifying the experimental paradigm used here. There were large group differences in accuracy, so that it remains unclear whether any group effects and interactions were masked by near floor performance in toddlers with FXS and by near-ceiling performance in typically developing children. It would therefore be beneficial to use the approach adopted by Durston et al. (2002, 2003). These authors manipulated parametrically the number of go trials preceding no-go trials in a go-nogo task, as well as the number of compatible trials preceding incompatible trials in a flanker paradigm. This allowed them to titrate behavioural performance across typically developing children and children with ADHD. They could therefore compare various indices of behavioural performance and neural activity across groups at equivalent levels of task difficulty. Such an elegant approach would be very powerful when trying to understand the difficulties encountered by toddlers and older children with fragile X syndrome.

4.4. Chapter Summary

In this chapter, I asked whether toddlers with fragile X syndrome display difficulties in controlling conflict between target stimuli and manual responses. In order to understand typical developmental changes in this ability across the toddler years, I modified a spatial conflict task for use with 24- to 48-month-olds. I investigated both changes in the ability to deal with spatial conflict and in the effects of previous responses on both accuracy and reaction time. Typically developing toddlers revealed intriguing changes in the effects of context. Toddlers with fragile X syndrome did not show differential difficulties in the ability to deal with conflict; rather they displayed striking deficits in identifying correctly peripheral target identity and in switching responses effectively. These findings converge at least partially with those of Chapter 3: infants and toddlers with fragile X syndrome, like older children and adults with the condition, displayed difficulties in the ability to inhibit inappropriate responses. However, the pattern of relative deviance and delay in their performance suggests complex interactions between processes involved in the processing of stimuli and in the control of responses.

Part II – Concluding Remarks

Part II investigated whether infants and toddlers with fragile X syndrome, like older children and adults with the syndrome, display difficulties in the endogenous control of responses. I hypothesised that the low-level neural changes associated with the syndrome may influence more substantially the functioning of systems involved in endogenous control.

Chapter 3 examined adaptive changes in eye-movements to cues that predicted the location at which interesting stimuli would appear. Typically developing toddlers decreased looking towards predictive but uninteresting cues, in order to anticipate the appearance of dynamic and colourful stimuli, and this ability improved dramatically with age. In contrast, infants and toddlers with FXS continued to orient towards the peripheral cues, a pattern of performance that has been documented in adult neuropsychological patients with lesions of prefrontal cortex as well as in adults and children with neurodevelopmental disorders such as ADHD and schizophrenia. Intriguingly, these difficulties did not decrease with increasing developmental level, suggesting that they affect even relatively able toddlers with FXS. Chapter 4 focused on whether these difficulties extend to manual responses. I manipulated the spatial conflict between target stimuli, their associated responses, and the modulatory effects of previous responses on children's ability to make button presses. Typically developing toddlers were affected by spatial conflict, as well as showing developmental changes in the effects of previous responses. Toddlers with FXS produced slower and less accurate responses than expected given their developmental level. Furthermore, they displayed larger difficulties in dealing with peripherally presented targets and in switching responses appropriately.

Taken together, these results show that toddlers with FXS display a striking deficit in the ability to modify behaviour adaptively on the bases of previous events and/or responses, a hallmark of endogenously-driven selection and action control. Chapter 1 treated how the neurobiology of the syndrome predicts such an outcome, even at an early stage in development. However, the neurodevelopmental nature of the condition highlights the need to investigate exogenous as well as endogenous attention. This will be the focus of Part III.

Manipulating Exogenous Influences on Selection

Part III - Introductory Synopsis

Chapter 1 addressed various interpretations of the terms “core” and “selective” to describe deficit in the adult neuropsychological literature, and discussed the limitations and flaws of applying such a framework to developmental disorders, particularly in the context of a neurodevelopmental condition like fragile X syndrome. Part III of this thesis addresses more directly the issue of whether the early attentional profile in fragile X syndrome is associated not solely with large difficulties with endogenous attention, but also with atypical influences of stimulus-driven processes. I hypothesised that the low-level neural changes associated with the syndrome may influence more substantially the functioning of systems involved in endogenous control. However, the ubiquitous nature of these changes across cortex, as well as the neurodevelopmental nature of the condition, lead to the need for caution against merely assuming early selective deficits in endogenous control.

Chapter 5 investigates the temporal dynamics of exogenously-driven shifts of visual orienting by groups of typically developing infants and toddlers. The effects of non-predictive peripheral onsets on the speed and direction of eye-movements are used as measures of exogenously-driven orienting that is, at least in part, independent of endogenous attentional control. If fragile X syndrome is not solely characterised by selective attention deficits, subtle but measurable atypical responses will emerge to peripheral stimuli that are thought to attract visual orienting automatically.

Chapter 6 examines potential implications of atypical effects of peripheral onsets for more naturalistic tasks, like visual search for targets amongst distractors. I manipulate the perceptual salience of the targets in multiple ways and relate these changes to measures of temperament designed to load on perceptual sensitivity as well as on inhibitory control. I then proceed to test the hypothesis that performance in toddlers with fragile X syndrome is not only characterised by perseverative behaviours, a hallmark of difficulties with endogenous control, but also by atypical effects of perceptual salience.

Exogenously-driven Orienting

“In passive immediate sensorial attention the stimulus is a sense-impression, either very intense, voluminous, or sudden [...]: strange things, moving things, wild animals, bright things, pretty things, metallic things, words, blows, blood, etc., etc., etc.” (James, 1890/1950, pp. 417-418)

As discussed in Chapter 3, the ability to visually orient towards stimuli in the environment is a crucial aspect of visual selection. It is under the control of goal-directed endogenous factors, whose effects can be measured by the ability to produce antisaccades or anticipatory saccades. However, stimuli that are suddenly appearing in the environment also exert strong influences on visual orienting and thus on visual selection, even when they do not elicit overt eye-movements. Such covert shifts in visual attention have been classically studied in adults by cueing a spatial location and assessing the speed of detection of targets at the cued location compared to other locations. When a shift in attention is triggered by an abrupt peripheral stimulus, such as a luminance change, the orienting resulting from it is labelled as

exogenously-driven. The most commonly used method to investigate exogenously-driven orienting is a cueing paradigm developed by Posner and his colleagues (e.g., Posner, 1980; Posner & Cohen, 1984). It involves presenting observers with a cue that precedes the appearance of a target stimulus requiring a response (either target detection or discrimination). Cues can indicate the target's spatial location either correctly or incorrectly and are therefore labelled as valid or invalid cues respectively. The cue should elicit orienting towards its location and facilitate target detection or discrimination in valid trials compared to invalid trials. Observed differences between valid and invalid trials are referred to as "orienting effects".

Latencies to detect targets are typically faster to validly cued targets and slowest to invalidly cued targets. Original accounts of this effect proposed that attention functions as a spotlight, focusing limited processing capacity onto the cued location in space. With valid cues, attention would not need to shift elsewhere, as the target would appear at that location. Invalid cues would require two additional processes: the ability to disengage from the cued location and to shift towards the target location (Posner, 1980). The conceptualisation of attention as a spotlight has since been criticised (e.g., Desimone & Duncan, 1995; Pashler, 1998), and instead attention is understood as a mechanism functioning in parallel across the visual field, within the constraints of objects that segment such field in the environment. However, the notions that attentional capacity is captured by abrupt peripheral onsets and then suffers if required to process stimuli at another location remain (Yantis, 1998, 2000). The temporal dynamics of orienting effects depend on a number of factors. The initial effect of the sudden onset of a peripheral stimulus is the faster processing of stimuli at its location or nearby, presumably due to a reflexive attention shift towards the location of the sudden onset. This effect has been termed facilitation. However, when the onset is not task relevant and a variable period of time passes from the onset of the peripheral event, an inhibitory after-effect occurs, resulting in delayed responding to stimuli subsequently displayed at the originally cued location. This effect has been termed inhibition of return (Posner & Cohen, 1984). In sum, reaction times are faster to targets at the cued location when the interval between the cue and the target is short and slower when the cue-target interval is long. This inhibitory effect does not follow a shift of attention that was directed endogenously and only occurs when orienting is driven by peripheral cues. Importantly, the processes involved may

be developing at differential rates, stressing the need to follow changes over time. How do orienting effects and their temporal dynamics change over developmental time?

5.1.1. Typical development of exogenously-driven orienting

Cognitive processes: The effects of cue validity and cue-target interval

Children's ability to orient to relevant stimuli in the environment changes rapidly during the first year of life, but this ability displays protracted changes throughout childhood. As with adults, in its most basic form, the ability to visually co-orient with visual stimuli depends on the ability to orient attentional resources to stimuli occurring abruptly in the environment. This orienting facilitates the processing of information at the location of this orienting.

The different processes leading to performance on the orienting task have in the main been investigated with either typically developing infants or children older than 6. In the first study to investigate exogenous orienting in infancy, Clohessy et al. (1991) required infants to orient overtly towards a peripheral cue stimulus and then re-orient towards central fixation. Infants were then presented with bilateral targets and the experimenters measured the percentage of trials during which infants preferred the uncued target. Although groundbreaking, this initial study required overt orienting towards the cues, except for one condition in which 12-month-olds were presented with a cue while the central fixation stimulus was still present (covert condition). It therefore differed from tasks used with adults as it tapped mainly overt attention shifts, rather than covert ones.

Later studies investigated this ability in a manner that resembles adult tasks without eliciting orienting towards cues. This can be achieved by presenting the cues while the infants are still focusing on a central stimulus (Hood, 1993; Johnson & Tucker, 1996). The experimenter measures the effects of a covert cue on overt orienting towards a subsequent unilateral target (Hood, 1993) or, using bilateral targets, the percentage of orienting towards the cued target compared to the uncued one (Johnson & Tucker, 1996). Figure 5.1 illustrates differences and similarities between paradigms testing overt and covert attention.

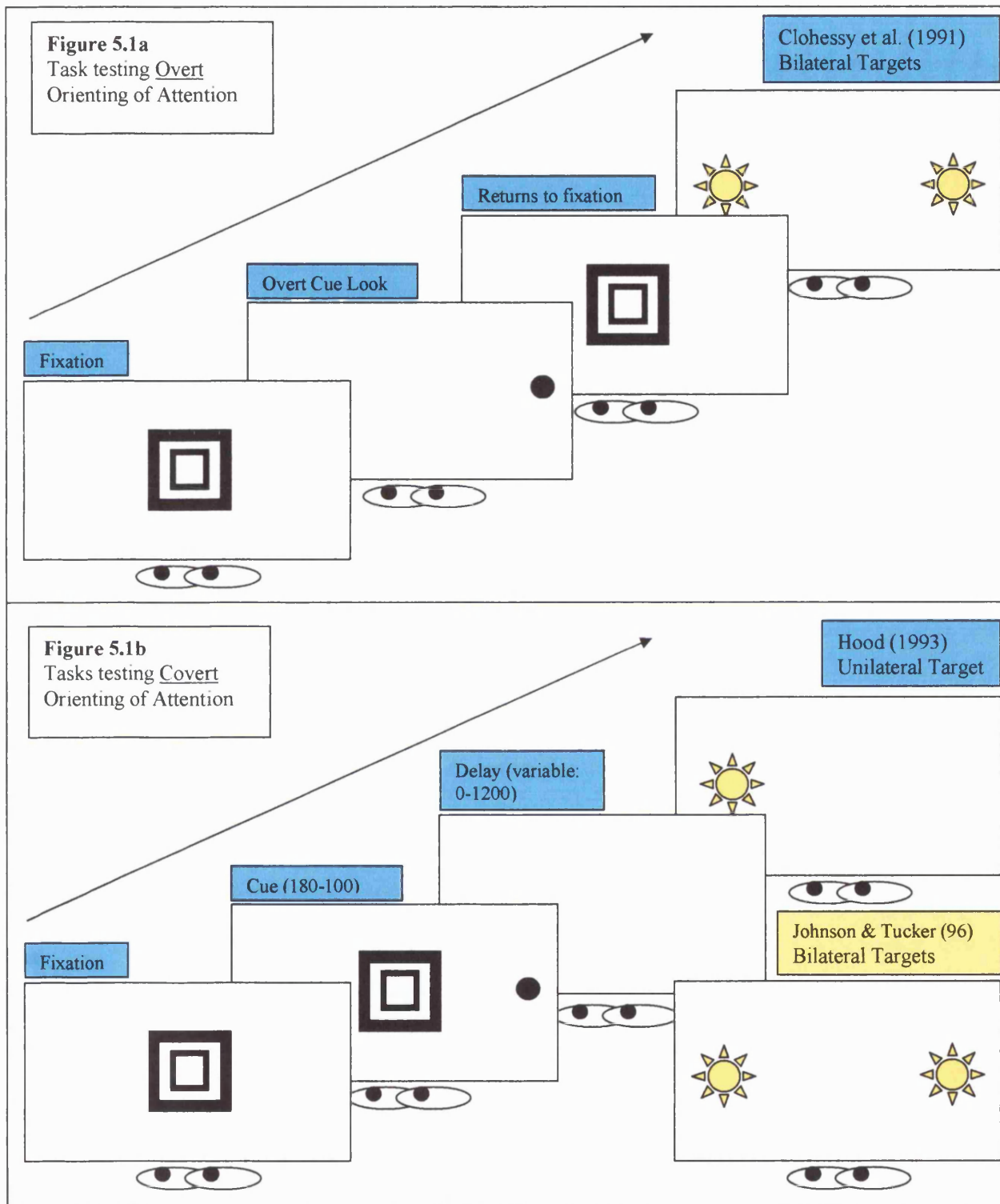


Figure 5.1. Paradigms used to test (a) Overt Orienting of Attention (Clohessy et al., 1991; most conditions except 1 covert, used with 12 month-olds), (b) Covert Orienting of Attention with unilateral target presentations (Hood, 1993) or bilateral targets (Johnson & Tucker, 1996; Clohessy et al., 1991, covert condition). Note that unilateral target presentation resembles the conditions used with adults. However, bilateral target presentations allow the researcher to measure both reaction time to targets and the preference for a cued vs. uncued target.

Focusing on covert orienting, Hood (1993) presented 6-month-old infants with a central fixation stimulus accompanied by a peripheral cue. Simultaneous presentation of the cue and fixation prevented overt orienting towards the cue, but it affected reaction times to targets appearing at the same or opposite location. Infants were faster at orienting towards the uncued location than towards the cued one, displaying an inhibition of return effect, even with a very brief cue-target interval. This experiment first investigated the effects of cue validity with a covert orienting paradigm, but it did not test the effects of variable cue-target intervals, as this was fixed at 180 ms.

In order to investigate early developmental changes in the temporal dynamics of orienting, Johnson and Tucker (1996) tested the effects of varying cue-to-target intervals in 2-, 4- and 6-month-old infants. The youngest infants showed only weak effects of the cue, whereas 4-month-olds showed the characteristic facilitation 200 ms after cue onset and the characteristic pattern of inhibition 700 ms after cue onset. In contrast, 6-month-old infants were not facilitated by cues with cue-to-target intervals of 200 ms but they showed clearer evidence of inhibition at the later cue-target interval, suggesting a progressive increase in the speed of orienting within the first few-months of life. Indeed, 7-month-old infants did not reveal facilitation at 200 ms but only at the shorter cue-target interval of 133 ms. These older infants also displayed evidence of inhibition at cue-target interval of 700 ms.

How can performance on these tasks be compared with those obtained with adults? Rather than measuring eye-movements, most of cueing experiments require responding manually to indicate target detection or discrimination. By six years of age children's orienting of attention in response to peripheral cues affects the speed of their manual responses in detection or discrimination tasks (Akhtar & Enns, 1989; Enns & Brodeur, 1989; Brodeur & Enns, 1997; Brodeur & Boden, 2000). Effects of having been validly vs invalidly cued, however, vary with development. Akhtar and Enns (1989) used cues that were not predictive of target location and tested exogenous orienting in 5-, 7- and 9-year-old children and adults, finding reliable cue validity effects at all ages. Furthermore, the size of the cue cost decreased with age, and in conditions in which the cue was rarely valid, adults were best at suppressing the effects of the peripheral cues. The authors speculated that adults may be better able to exploit the predictive value of the cue to orient attention adaptively. Similarly,

using cues that were valid on 80% of trials, Wainwright and Bryson (2002), showed that 6-year-olds displayed significantly larger costs of invalid cueing than 8-year-olds and older groups.

Enns and Brodeur (1989) tested this hypothesis directly by providing cues that were either randomly associated with the target location (unpredictive) or predictive of the target location on 80% of trials. Neutral trials were also included so that orienting effects (valid vs. invalid reaction times) could be interpreted in terms of costs (response times to targets preceded by invalid vs. neutral cues) or benefits (neutral vs. valid cues). When cues were unpredictable of target location, 6- and 8-year-olds showed larger costs than adults, suggesting a difficulty in disengaging attention from a previously cued location, when the cue is not a good predictor of where the target will appear. In contrast, there was no difference in the magnitude of benefits. In fact, cue benefits were only reliably measured when cues were predictive, but only for adults, suggesting that children were not capable of using the information value of the cue to enhance their performance. However, age effects were not present for orienting benefits at the shortest cue-target intervals. Brodeur and Boden (2000) recently tested the effects of cue predictability (33, 50, 67% validity) and cue-target interval in an orienting task with multiple possible target locations. When cues occurred more often at the location opposite to the target location (33% validity) and cue-target intervals were short (120 ms), younger children alone (6-year-olds) showed a cost of being invalidly cued. This is presumably because the older children and adults used the predictive value of the cue to orient attention to the opposite location. In contrast, at longer cue-target intervals, 6-year-olds behaved as the older groups, showing that given more time they could use cues' predictive value strategically. Within this task, children exhibit larger orienting effects than adults and under conditions of random cue-target predictability adults do not show any orienting effect at all.

In summary, adults may use stochastic cue information to strategically orient their attention, indicating that cue validity is an important factor to consider when designing studies comparing different age groups of typically developing individuals or atypical populations. The interval intervening between the onset of the cue and the onset of the target also seems to have an effect on target reactions times, although results from different studies across age

groups do not converge neatly. Furthermore, there is limited published information on developmental changes in orienting between the ages of 12 months and 6 years.

Neural systems requirements: developmental changes

Posner and Petersen (1990) first proposed that the operations underlying visual orienting each appear to be localised in discrete neural areas, comprising a network of cortical fronto-parietal (disengage), midbrain (shift), and thalamic structures (engage). This proposal, however, was intrinsically linked to the view of attention as a spotlight which has been subsequently criticised (e.g., Desimone & Duncan, 1995). Despite these (grounded) criticisms, a similar, but more integrated network of areas has been shown to exist for attention shifts in both covert and overt exogenously-driven attention shifts (Nobre et al., 2000). The large network of areas described in Chapter 3, section 3.1.1, is also thought to be involved in such covert shifts. In particular, parts of the posterior system, reaching the brainstem through the superior colliculus, modulated by inputs from visual cortex, middle temporal area, parietal cortex, substantia nigra and basal ganglia, play a role in exogenous covert orienting in adults (Nobre et al., 2000).

In infancy, early changes in the neural processes underlying covert orienting have been investigated using event-related potentials (Richards, 2000). This study examined the changes in event-related potentials during a cueing task in 14, 20 and 26 weeks-old infants. Older infants exhibited larger inhibition of return effects and an enhanced P1 component on valid versus invalid trials. ERPs preceding saccades to the target were also larger when it appeared at the cued vs uncued location. The author suggested that these changes reflect increasing cortical contributions in covert orienting over the first year of life, consistent with theoretical models of attention and attention-related eye movements (e.g., Johnson, 1990; Johnson et al., 1998; Richards & Hunter, 1998).

5.1.2. Atypical development of exogenous orienting

The effect of exogenous factors on covert orienting of attention has been investigated in a number of developmental disorders, notably ADHD. For example, Swanson, Posner, Potkin, Bonforte, and Youpa (1991) used a version of the cueing paradigm to test children who had been diagnosed with ADHD. They reported that these children had slower reaction times than controls. Furthermore, they were slower to orient to invalidly cued targets presented to the right than to the left of fixation for longer cue-target intervals, but not for shorter ones. However, the cues in the experiment were valid on 80% of trials and, as noted earlier, the use of peripheral cues plus the weighting towards valid trials with atypical populations could recruit both exogenous and endogenous mechanisms, the latter involved in the ability to detect and exploit cue-predictability. In contrast, Carter, Krener, Charjedian, Northcutt and Wolfe (1995) used non-predictive cues with another sample of children with ADHD. They found that the left-right asymmetry was only present at the shortest cue-target intervals, whereas at the longer cue-target intervals performance was indicative of the classical inhibition of return in both the ADHD and control samples. This in turn suggests that at least some of the effects associated with exogenous orienting appear to be (behaviourally) normal in children with attentional difficulties. However, the neural underpinnings of these apparently unimpaired behavioural indices may differ across patient and control populations. Perchet et al. (2001) examined performance on the orienting paradigm in typically developing children and children with ADHD. They found that ADHD children had a shortened interval between the N2 and P3 ERPs and the motor response. They proposed that, despite similar behavioural effects, such difference in neural markers of processing points to an atypical pattern of motor impulsivity, with the release of motor responses before stimulus processing is adequately completed.

Can behavioural performance on the orienting task reveal further details atypical attentional development and its neural underpinnings? Hines, Paul and Brown (2002) assessed orienting in individuals with agenesis of the corpus callosum, showing that the orienting of attention from one visual hemi-field to the other requires the functioning of callosal projections from one hemisphere to the other. As well as with developmental conditions affecting cortical development directly, atypical orienting effects are also found as a result of conditions

affecting the quality of peripheral inputs. The issue has been investigated in children who suffered from cataracts and therefore had binocular visual deprivation during the first few months of life (Goldberg, Maurer, Lewis, & Brent, 2001). Using central visual cues at various cue-to-target intervals, patients with congenital binocular cataracts showed atypical validity effects at the later cue-target intervals asynchronies (800 ms). When the peripheral task required not target detection but discrimination of a target amongst distractors, the interference exerted by incompatible distractors was larger and the effects of cue validity were larger for upper visual field targets.

Implications for fragile X syndrome: Empirical predictions

Part II demonstrated that infants and toddlers with fragile X syndrome already display deficits in the endogenous control of orienting and response selection. However, Chapter 1 detailed how a neurodevelopmental approach highlights the need to examine, in infancy, processes that do not exhibit deficits later in life. A strong form of this hypothesis will predict measurable, although perhaps more subtle effects of FXS on exogenously-driven orienting. In a weaker form, the nature of FXS as a neurodevelopmental condition characterised by ubiquitous effects on cortical function suggests that the influences of exogenous factors deserve at least as much investigation as endogenous control.

5.2. Experimental data

5.2.1. Experiment 3a. Typical effects of peripheral cues on visual orienting

In the review of the literature on the cueing paradigm, I identified two critical variables affecting orienting responses. First, cue-validity emerged as a crucial factor in determining orienting effects. Would orienting effects change across the toddler years, as they do in infants and older children? I chose to use totally unpredictable cues, in order to target truly exogenous orienting and avoid confounding changes in orienting with changes in the ability to interpret and exploit the predictive value of the cue. Moreover, with regards to cue validity effects, the literature suggests that orienting effects should vary with age. In particular, while benefits of valid cueing may remain relatively unchanged, costs of invalid

cueing should decrease over developmental time (Brodeur & Enns, 1989; Brodeur & Boden, 2000; Wainwright & Bryson, 2002). Secondly, the interval between the cue and the target plays an important role in determining facilitation (at short intervals) as opposed to inhibition of return (at longer intervals). I also decided to use a number of different stimulus onset asynchronies to investigate the temporal dynamics of visual orienting initially in typically developing infants, toddlers and young children. Indeed, as demonstrated elegantly by Johnson and Tucker (1996) for infants, orienting effects may be present across the toddler years, but vary in their latency and magnitude. As discussed in Chapter 2, delineating the typical developmental trajectory of exogenous cueing effects would be crucial to interpret performance within the group of infants and toddlers with fragile X syndrome. Critically, studies on typically developing individuals focus on comparing very narrow age ranges (e.g., 2-month-olds vs. 4-month-olds), but such a method is not appropriate to assess the sensitivity of a task that would need to be used with atypically developing children who are: (a) older and, (b) whose age and developmental level spans a wide age range.

The aims of Experiment 3a were therefore: (1) to develop a modification of the standard cueing task that could be used to test exogenously-driven covert orienting in typically developing infants as well as toddlers, given the paucity of data on children between 12 months and 6 years of age and, (2) to explore changes in the cueing effects over a wide, rather than narrow, age range and test whether age would account significantly for the variability in performance.

Method

Participants

Participants were 30 infants and toddlers from the age of eight to 34 months, all with no known birth or other complications. The data from 10 children (age range from 12 to 34 months) were discarded because they failed to register codable trials in all cells, according to the criteria described below. Five infants and toddlers failed to complete the experiment due to fussiness, leaving a final sample of 15 infants and toddlers (1 girl), whose age ranged

from 8 to 30 months (mean: 21.9 months, standard deviation: 5.6 months). This rate of subject attrition is not unusual in similar studies of infants' covert orienting (e.g., Johnson & Tucker, 1996).

Procedure

The methodology employed here aimed to closely replicate the stimulus conditions used previously to test covert orienting of attention in younger infants (Hood, 1993; Johnson & Tucker, 1996). Participants sat on their caregivers' lap, 70 cm from the centre of a large colour monitor. The display on this monitor was controlled by a Pentium III computer. Each trial began with the presentation of an attractive fixation display (a cartoon character) that served to ensure that the infant or toddler was looking at the centre of the screen at the start of each trial. Four different characters were employed, but they all subtended 16 degrees of visual angle from the viewing distance indicated above. The experimenter could see the infant by means of a video camera mounted above the display screen.

Acuity trials.

For each participant, the first four trials aimed at determining whether he could detect the cue, also providing a baseline measure of orienting speed. As soon as the experimenter judged that the infant was looking at the fixation display, he activated the computer mouse to initiate a trial. A trial started with a bleeping sound and the animation of the fixation stimulus, which rotated on itself quickly for 450 msec. After its offset, the cue stimulus for experimental trials - a green diamond (5.5 degrees angle) - was presented to the right or left of fixation (18 degrees to the right or left) until the child oriented towards it. Then the experimenter clicked on the mouse to make the (initially static) fixation stimulus re-appear in the centre of the screen and waited for the child to re-fixate to initiate a new trial. During video coding (see below), the amplitude of saccades during these initial trials was also used to calibrate individually for each child the relative positions of left- vs. right-appearing stimuli as well as the position of the fixation stimulus.

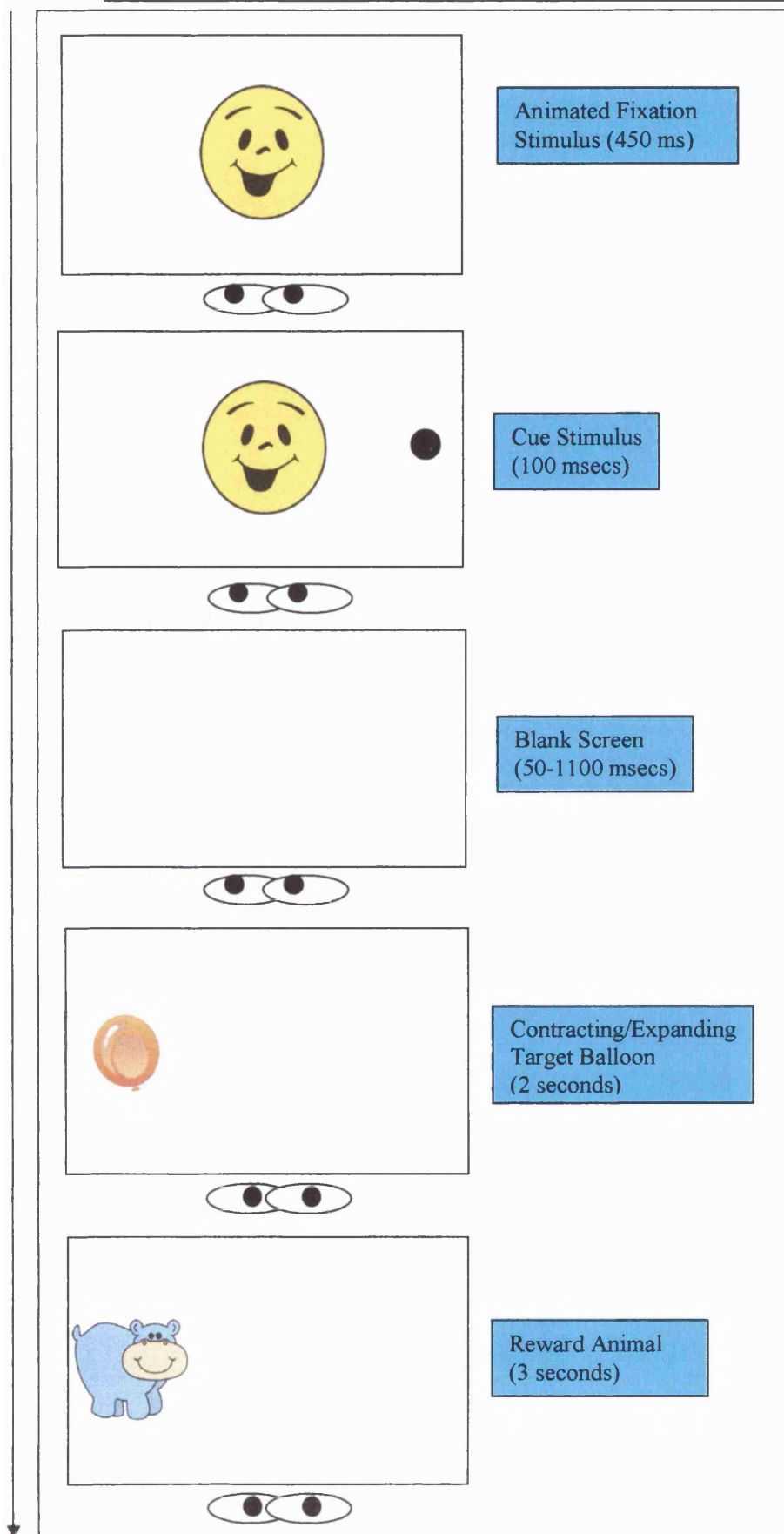


Figure 5.2. Sequence of events for experimental trials in Experiments 3a and 3b.

Experimental trials.

The sequence of events composing each experimental trial is depicted in Figure 5.2. While the fixation stimulus was still rotating at the centre of the screen, the cue stimulus - a green diamond (5.5 degrees angle) - was presented for 100 ms to the right or left of fixation (18 degrees to the right or left). The cue duration was selected as it has been shown to elicit the effects of interest both in infants younger than the age of choice here and in older children and adults (Clohessy et al., 1991). Simultaneous presentation of the cue and fixation stimuli helped prevent overt orienting towards the cue stimulus.

A blank screen was then presented for either 50, 300, 600 or 1100 ms before presentation of a target stimulus (an expanding and contracting balloon, subtending a maximum of 9.2 degrees angle), either in the same location as that in which the green diamond cue had appeared (validly cued targets) or in the opposite location (invalidly cued targets). After 2 seconds of successive expansions and contractions, the balloon was replaced by a cartoon animal of a group of eight different animals (approx. 20 degrees angle) that remained on screen for 3 seconds, to leave the child enough time to point to and/or name the animal. The (static) fixation stimulus re-appeared and the experimenter waited for the child to re-fixate in the middle before starting the following trial.

The side of presentation of the cue and target stimuli was determined by a pseudorandom computerised sequence, balanced within four blocks of trials, each lasting a maximum of 12 trials. Blocks differed only in the identity of the cartoon character acting as a fixation stimulus and could be interrupted if the child displayed signs of boredom to move onto the next cartoon character/fixation stimulus. For each block, targets were validly cued on 40% of trials, invalidly cued on 40% of trials and on the remaining 20% of trials the cue was absent. Cue validity was set at 50% because in this experiment, in contrast with the cues used in Chapter 3 (the antisaccade task), cues needed to be non-predictive of target location. Indeed, Wainwright and Bryson (2002) have shown that even the youngest children use the predictive value of cues to enhance their performance and I had already addressed whether children with FXS could use cue predictability in Chapter 3. To avoid confounding differences in attentional shifting with differences in the ability to exploit cue predictive value strategically, here cues did not have any predictive value. Indeed, in order to test

effects of exogenously-driven shift to the target, orienting could not be driven by the predictive value of the lateral cue. I also reasoned that the effects of interest (both facilitation and inhibition of return) have been successfully obtained with peripheral cues. As highlighted in Chapter 2, all analyses in the present thesis aim to test group differences in performance on attentional tasks of various nature. It therefore becomes extremely important to tease apart components of group differences that may not depend on the constructs of interest. In the case of the present experiment, differences in the speed of orienting may play a part in the group differences but carry no direct relevance to investigations of how attention functions in fragile X syndrome compared to controls. For these reasons, no-cue trials were introduced (cf. Johnson & Tucker, 1996). The asynchrony in the onset of the cue and target (cue-target interval) were randomly set at 150, 400, 700 and 1200 msec. The 150 ms interval was selected as this was the shortest interval that could be reliably presented with our equipment (allowing for blank screens of 50 ms) and the necessary cue duration to elicit orienting in infants and toddlers (at least 100 ms, Clohessy et al., 1991). The 1200 ms interval was chosen because it has been suggested to be the time at which the inhibitory effects of the cue decrease (Johnson & Tucker, 1996).

Video coding protocol and inter-rater reliability

Videotapes of children's eye movements during the task were coded off-line (using the Observer video coding equipment, after digitising the video tape material). A time code generator imprinted the time on each video frame and the auditory signal indicating the beginning of each trial was mixed onto the video tape to indicate the onset of the trial for coding. All trials were coded with the off-line coder being blind to the precise onset of the cue and target stimuli. The observer recorded the onset of the initial auditory signal (to the nearest frame, 40 ms), the direction (centre, left, right) and onset of saccades, as well as eye-blinks and frames spent looking elsewhere. Saccade direction was coded relative to left/right/centre positions on the video-screen established during the initial acuity trials individually for each child. Saccade onset (in ms) was recorded by selecting the first frame in which an eye movement to a discrete centre/left/right location was detected. Saccade onset was used as an indication of reaction time, only if the saccade went directly to the indicated centre/left/right locations. After blind coding, the coding record from the Observer

and the recorded sequence of events (E-Prime) were synchronised. Trials were most commonly rejected because the child was not looking at the fixation stimulus at the start of the trial, because he was not looking at the fixation stimulus at cue onset, because he oriented towards the cue overtly or because she looked elsewhere throughout the duration of the trial. Data from each toddler were only included in the final analysis if he completed at least one scorable trial for each Cue-target interval and cue validity condition. Reliability on 20% of videotapes between two trained coders blind to the children's identity, was 0.9 (Cohen's K) for whether trials should be rejected or scored and 1.0 for the direction of saccades. There was a mean correlation of .85 for saccade onsets. In 98% of scorable trials coders recorded reaction times within one frame difference (40 ms).

Statistical Analyses

Overall orienting effects.

Reaction times (ms) were analysed in three different ways to provide converging evidence for the effects of orienting. First, reaction times from all conditions were plotted to explore their distributions. They were then analysed using standard statistical packages (SPSS, G-Power). Dependent measures were checked for normality and homogeneity of variance before being entered in repeated measures parametric statistics, with Cue-target interval (150, 400, 700 and 1200 ms) and Cue Validity (Valid, Invalid) as the within-subject variable. Second, I calculated a difference score: Invalid-Valid cue conditions at the four cue-to-target intervals. This would give a simpler measure of the orienting effects, regardless of individual differences in orienting. Third, I calculated difference scores for orienting costs, i.e., slowing in reaction times to invalidly cued targets compared to the neutral condition, and orienting benefits, i.e., speeding of responses in validly cued trials compared to neutral ones.

Age-related changes in orienting.

After conducting all these analyses on the sample as a whole, I considered the issue of age-related changes in performance. Children in this sample spanned a relatively large age-range compared to previous research on infant orienting effects. I therefore investigated age effects by (a) plotting scattergrams of individual data-points depicting the relationships between age and RTs (and age and difference scores) which also made it possible to address the issue of

individual variability in the sample and, (b) entering Age as a co-variate in the analyses above.

Results

In summary, effects of the cues were not evident when infants and toddlers were considered as a homogeneous group. However, when age was introduced as a co-variate, the results suggested that developmental changes masked cueing effects. Older toddlers seemed less affected by invalid cues than did younger toddlers. By contrast, the benefits of valid cueing did not change significantly with age. However, scatterplots of individual data-points also highlighted considerable individual variability and the presence of an outlier. These results were supported statistically as follows.

Overall Cueing Effects

The variables were checked for normality and homogeneity of variance. Descriptive statistics suggested that the former of these assumptions was not met by the original reaction times (e.g., Kolmogorov-Smirnov test, p -levels from .2 to <.001) and therefore a natural logarithmic transform was used. Transformed variables largely met the assumptions of the ANOVA. The assumption of sphericity was not met by the variable cue-target interval. Therefore I adopted the Greenhouse-Geisser correction to the significance levels of the F values. When a 2 (validity: valid, invalid) X 4 (cue-target interval: 150, 400, 700, 1200) ANOVA was run on the reaction times to targets, there were no statistically significant effects of Validity, $F(1, 14) = 2.124$, $p = .167$ nor of cue-target interval, $F(3, 25.663) = .779$, $p = .459$ (Greenhouse-Geisser correction used). The interaction was also not statistically significant, $F(3, 42) = .440$, $p = .726$.

Furthermore, I analysed the effects of cue-target interval on the difference in reaction time between invalidly and validly cued targets (known as “orienting effects” in the literature, e.g., Wainright & Bryson, 2000). The effect of cue-target interval was not statistically significant, $F(3, 42) = 1.297$, $p = .280$. There were also no effects of cue-target-interval on cueing benefits (i.e., reaction time difference for the neutral minus valid conditions), $F(3,$

42) = 1.506, $p = .227$ and on cueing costs (i.e., reaction time difference for the invalid minus neutral conditions), $F(3, 42) = .510$, $p = .678$.

Differential age effects

Cue-target interval did not meet the assumption of sphericity and therefore a Greenhouse-Geisser correction was employed for this variable. There was a main effect of Validity, $F(1, 13) = 7.858$, $p = .015$. Furthermore, there was an interaction between validity and Age, $F(1, 13) = 6.086$, $p = .028$. None of the other effects nor interactions were significant (p levels between .395 and .334). I investigated the sources of this interaction by analysing the difference in reaction time to valid vs. invalidly cued targets, this time with age as a co-variate. The effect of cue-target interval was not significant, $F(3, 39) = .757$, $p = .525$. However, Age had a statistically significant effect, $F(1, 13) = 6.784$, $p = .022$.

Figure 5.3 illustrates that this effect depended on older children displaying smaller orienting effects than younger children. I explored this further by testing the age-related changes in cueing benefits (i.e., reaction time difference for the neutral minus valid conditions) and in cueing costs (i.e., reaction time difference for the invalid minus neutral conditions).

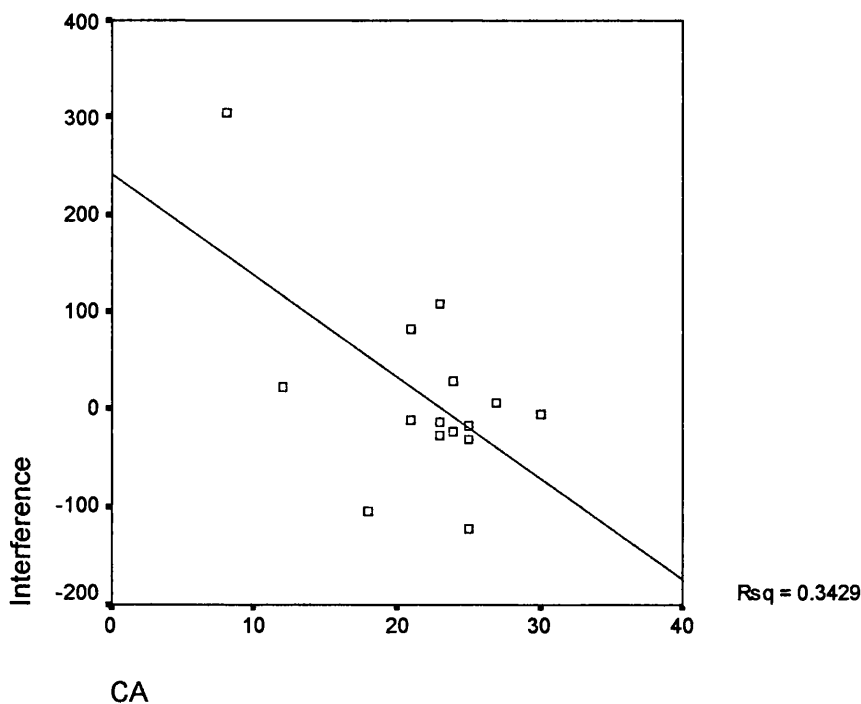


Figure 5.3. Interference Scores (Invalid-Valid reaction times) plotted against chronological age (months). The graph illustrates the general decrease in interference score across ages, as well as the large individual differences and the effect of the youngest child displaying a large interference effect.

Figure 5.4 illustrates that, while cueing benefits did not vary substantially with age, $F(1, 13) = .374$, $p = .551$, cueing costs exhibited a trend towards significance, $F(1, 13) = 3.682$, $p = .077$. This provides tentative evidence suggesting that older toddlers were less affected by invalid cues than younger ones.

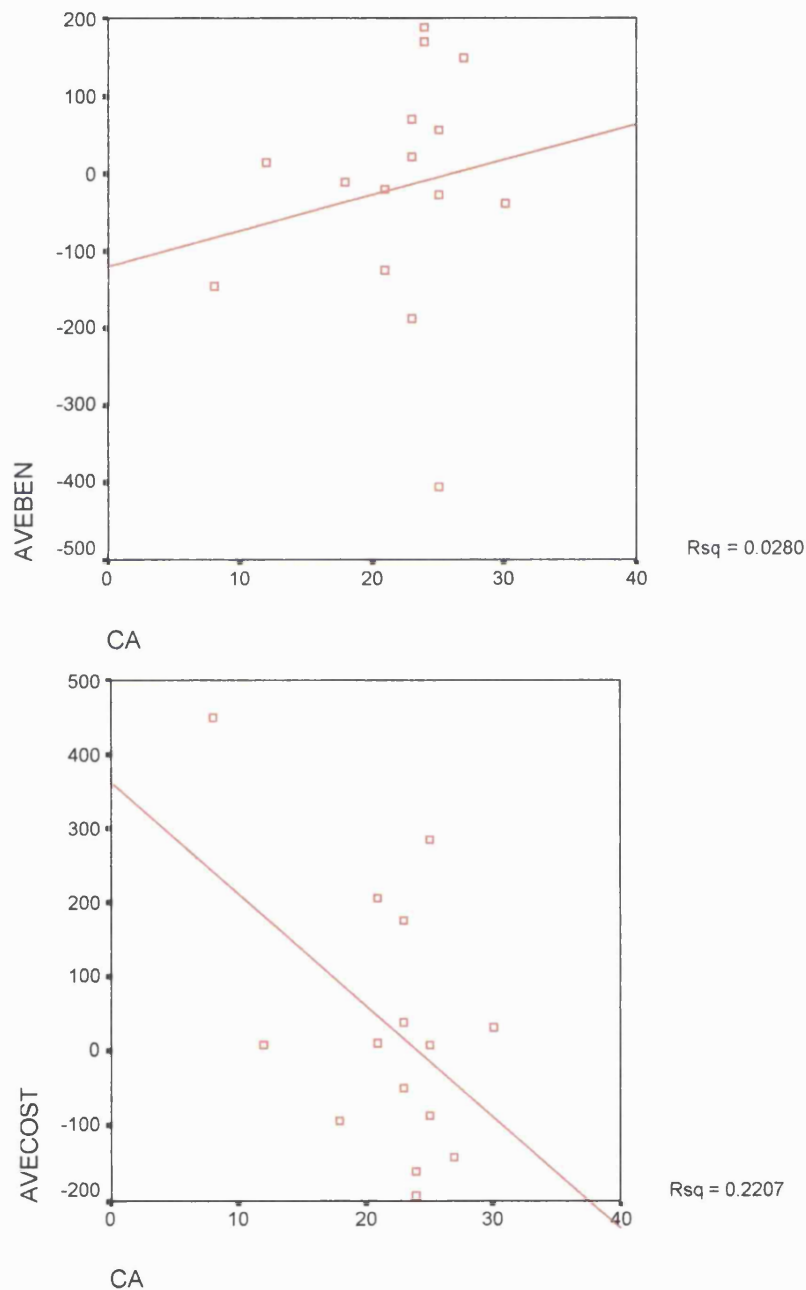


Figure 5.4. Relationship of Age (chronological age in months) and (a) Cueing benefits (i.e., neutral reaction time minus valid), (b) Cueing Costs (i.e. invalid minus neutral reaction time). The graph illustrates the general decrease in interference score across ages for cueing costs but not cueing benefits.

In general, although there were cueing effects, cue-target interval did not affect orienting times as expected, producing early facilitation and later inhibition of return. Splitting the group into two groups of older and younger toddlers provided suggestive (but only qualitative) evidence of a shift in the temporal dynamics of cueing effects, with younger children exhibiting inhibition of return later than older children (Fig. 5.5). However, the large individual variability may have masked these effects. I therefore turn to the issue of individual variability.

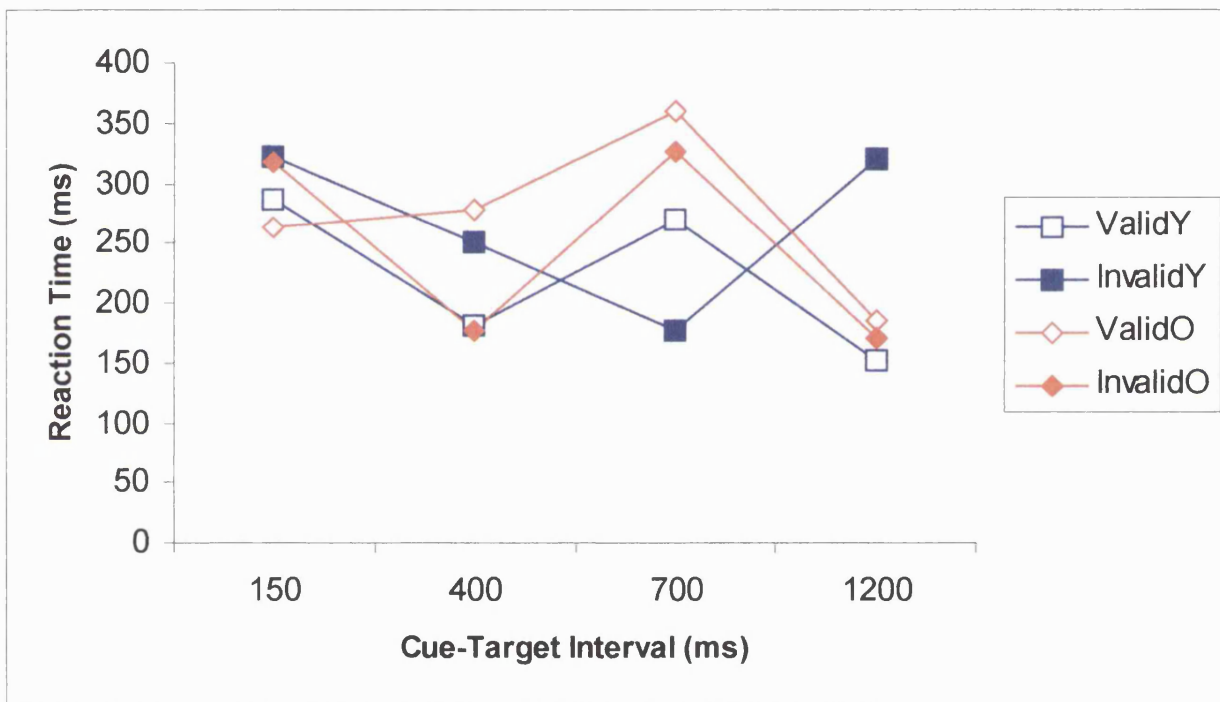


Figure 5.5. Reaction times to Validly (empty shapes) and Invalidly (filled shapes) cued targets for young toddlers (blue lines and squares) and older toddlers (red lines and diamonds). The graph illustrates a qualitative trend suggesting that older toddlers may exhibit faster orienting to cued targets (facilitation) earlier than younger toddlers, followed by earlier faster orienting towards uncued targets (inhibition of return). This trend should be tested within a larger sample.

The importance of examining individual toddlers' data

Often experiments on infants do not report individual data points, but here visual inspection of the scatterplots of Figures 5.3 and 5.4 reveals two important points that are often not evident in reports of group data. First of all, the youngest child in the group considerably skewed the data, suggesting caution in interpreting the age effects reported above. An alternative interpretation is indeed that the age effects above are spurious effects of this outlier. Secondly, there was a large amount of individual variability that was not accounted for by age. These points highlight the need for these results to be confirmed with a larger number of infants and toddlers and data are currently being collected to address this issue. In turn, this suggests that this paradigm may not be powerful enough to detect significant effects in a group of atypically developing children that is forcedly small due to difficulties with testing and recruiting.

Discussion

In summary, I predicted that (1) there should be effects of cue validity, with faster orienting towards validly cued targets, (2) cue-target interval should affect the speed of orienting and, (3) these effects should change with age. In this initial study, it was only when I included a measure of developmental change in the analyses (even if measured very roughly by age) that the cueing effects of interest were found. Orienting effects decreased with age and this was accompanied by a trend for orienting costs to decrease. Notably, there was also a considerable degree of individual variability that would need to be further investigated in a larger group of children, currently being tested.

The cueing effects converged with those found in the literature on older children (e.g., Brodeur & Enns, 1997; Brodeur & Boden, 2000). Toddlers in this sample oriented faster towards validly cued targets than towards invalidly cued ones. This suggests that this adaptation of the paradigm can be used to measure cueing effects in an age group that has scarcely been studied in the literature. Importantly, effects seem to vary with age, suggesting the importance of considering experimental effects within a developmental context. Orienting effects decreased and the costs of invalid cueing also seemed to decrease with age,

as has been found in the literature following the development of orienting in tasks requiring manual responses (Brodeur & Boden, 2000).

As well as revealing changes associated with age, these results point to a number of important notes of caution. Firstly, the cueing effects here were not very large and they were masked by developmental changes. This emphasises the problem of finding reliable large effects with a wide age range, as opposed to the narrow age range for which many of these experimental tasks were initially designed (e.g., with 6 month-olds, Hood, 1993; with multiple discrete groups of young infants, Johnson & Tucker, 1996). This in turn highlights a crucial methodological drawback in the use of these tasks with samples that necessarily cover a wide age range, as is the case for rare developmental disorders with a very variable (and as yet delayed) age of diagnosis. Secondly, the considerable individual variability and the effects of an outlier point to the need for these results to be confirmed with a larger number of infants and toddlers. In turn, they suggest that this paradigm may not be powerful enough to detect significant effects in a group of atypically developing children that is necessarily small due to difficulties with testing and recruiting.

Furthermore, the results here did not replicate the effects of changes in cue-target interval on orienting. The literature using this paradigm with younger infants (e.g., Johnson & Tucker, 1996; Hood, 1993) and adults (e.g., Posner & Cohen, 1984) points to a shift from early facilitation effects of valid cues to later inhibition of return, but I found no evidence of the latter with my adaptation of the paradigm. This could be due to the limited sensitivity of the measure I used, compounded by individual variability and a wide age range. I focused on reaction times only, in part following the procedure used Hood (1993) who, however, used a single cue-target interval. In contrast, by presenting bilateral targets Johnson and Tucker (1998) elegantly obtained a measure of preferences towards the cued vs. the uncued target. Although this manipulation differentiated their paradigm from that used traditionally with adults (with unilateral target presentation), they found this to be a more sensitive measure of the temporal dynamics of orienting. It is possible that it would have been preferable to present bilateral targets in the present study, but this would have compromised my attempt to mirror adult paradigms.

5.2.2. Experiment 3b. Covert visual attention in infants and toddlers with fragile X syndrome

This experiment aimed to employ the cueing task developed in Experiment 3a to test exogenous orienting in infants and toddlers with fragile X syndrome. Section 5.2.1 introducing Experiment 3a discussed the importance of two factors influencing the direction and temporal dynamics of orienting effects: cue-validity and cue-target interval.

With regard to cue-validity, section 5.1.1 also reviewed how children's ability to use cue validity to their advantage affects orienting. As shown in Chapter 3, infants and toddlers with fragile X syndrome may have particular difficulties in using cues to modify their behaviour, a difficulty that could confound differential effects of peripheral cues on the covert orienting of attention. This point was addressed here by using cues that were not predictive of target location, thereby assessing the effects of exogenous cue validity. If I had not done so, this task would have potentially measured differential abilities to use predictive information to exert (endogenous) control over exogenous orienting. I maintained the modifications of cue-target interval presented above. My reasoning was that differences between typically and atypically developing children would be more likely to vary subtly in their temporal dynamics than to differ in an all-or-nothing fashion.

Throughout Part III, I predicted subtle atypical effects of the fragile X syndrome on exogenous attentional processes, as well as the larger effects on endogenous attentional control. What would be more detailed predictions for orienting in infants and toddlers with FXS? This is the first study to investigate covert orienting of attention in fragile X syndrome, so I could not base my predictions on results obtained with older children. Results with older atypically developing children without fragile X syndrome attentional difficulties are mixed. On the one hand, some studies show difficulties in re-orienting attention towards invalidly cued targets (e.g., Swanson et al., 1991). Others find variable reaction time but typical inhibition of return effects (e.g., Carter et al., 1995), although these may be supported by atypical neural processes (e.g., Perchet et al., 2001).

On these grounds, I made the following predictions. Larger cueing effects would reveal whether toddlers in the FXS group are affected by cueing more than typically developing children. These effects would depend on difficulties in re-orienting attention towards away from an invalidly cued location in space. Furthermore, the temporal dynamics of their responses might vary compared to typically developing children. For example, they may exhibit longer lasting facilitation effects of valid cues and later onset of inhibition of return.

Method

Participants

Toddlers with FXS were recruited as discussed in Chapter 2. Fifteen boys and their families agreed to visit the Infant Testing Laboratory of the Neurocognitive Development Unit, in London. Of these, 1 boy fussed shortly after the beginning of the experiment and this had to be discontinued; 4 boys did not produce scorable trials on all cells. This left 9 boys who completed the task (chronological age: mean = 35.9 months, SD = 12.7 months, range = 14-55 months). Their developmental level as measured on the BSID-II, Mental subscale, was equivalent to 21.9 months on average (SD = 6.1 months, range = 12-30 months). These boys were individually matched by mental age equivalent within one month, to nine typically developing boys (mental age equivalent: 12-30, mean: 20.6 months, SD: 5.8 months), all of whom had contributed to Section 5.2.1., henceforth referred as MA controls. There was no statistically significant difference in mental age equivalent between toddlers with FXS and MA controls, $p = .349$.

Procedure

As for Experiment 3a.

Video coding protocol and inter-rater reliability

As for Experiment 3a. Trials were most commonly rejected because the child was not looking at the fixation stimulus at the start of the trial, because he was not looking at the fixation stimulus at cue onset, because he oriented towards the cue overtly or because he

looked elsewhere throughout the duration of the trial. Data from each toddler were only included in the final analysis if he completed at least one scorable trial for each cue-target interval and cue validity condition. Reliability on 20% of videotapes between the experimenter and a trained coder blind to the children's identity was 0.85 (Cohen's K) for whether trials should be rejected or scored and 1.0 for the direction of saccades. There was and a mean correlation of .80 for saccade onsets. In 92% of scorable trials coders recorded reaction times within one frame difference (40 ms).

Statistical Analyses

As in Experiment 3a. Due to the limited sample size, I conducted compromise power analyses (G-Power, Faul & Erdfelder, 1992) in order to establish whether the present sample size was too small to yield statistically significant results on the variables of interest. These power analyses are reported in Chapter 2, Table 2.4.

Results

Toddlers with FXS displayed faster orienting towards invalidly cued targets than towards validly cued targets, exhibiting large inhibition of return effects. These results were statistically supported as follows. Firstly, there were no statistically significant group differences in the accuracy and speed of orienting towards the cue during acuity trials.

Overall Cueing Effects

Figure 5.6 illustrates the reaction time to orient towards validly and invalidly cues targets for toddlers with FXS and MA controls. The variables were checked for normality and homogeneity of variance. Descriptive statistics suggested that the former of these assumptions was not met by the original reaction times (e.g., Kolmogorov-Smirnov test, p-levels from .2 to <.001) and therefore a natural logarithmic transform was used. Transformed variables largely met assumptions of the ANOVA. A 2 (group: FXS, MA controls) X 2 (validity: valid, invalid) X 4 (cue-target interval: 150, 400, 700, 1200)

ANOVA with group as the between-subject and validity and cue-target interval as the within-subject variables was run on the reaction times to targets. There were no statistically significant effects of Validity, $F(1, 16) = 1.372$, $p = .259$ nor of cue-target interval, $F(3, 48) = 1.549$, $p = .214$. Furthermore, the effect of Group was not statistically significant, $F(1, 16) = .071$, $p = .793$. The interaction between Group and Validity was statistically significant, $F(3, 48) = 5.203$, $p = .037$. None of the other interactions reached statistical significance, p -levels ranging from .667 to .936. I investigated the sources of this interaction by analysing the difference in reaction time to validly vs. invalidly cued targets for each group. Toddlers with FXS tended to be faster at orienting towards an invalidly cued target (on average, reaction time was 209.2 msec \pm 15.9) than towards a validly cued one (243.17 \pm 27.0 msec), $F(1, 8) = 4.302$, $p = .072$. In contrast, MA controls did not display this effect, $F(1, 8) = .114$, $p = .744$.

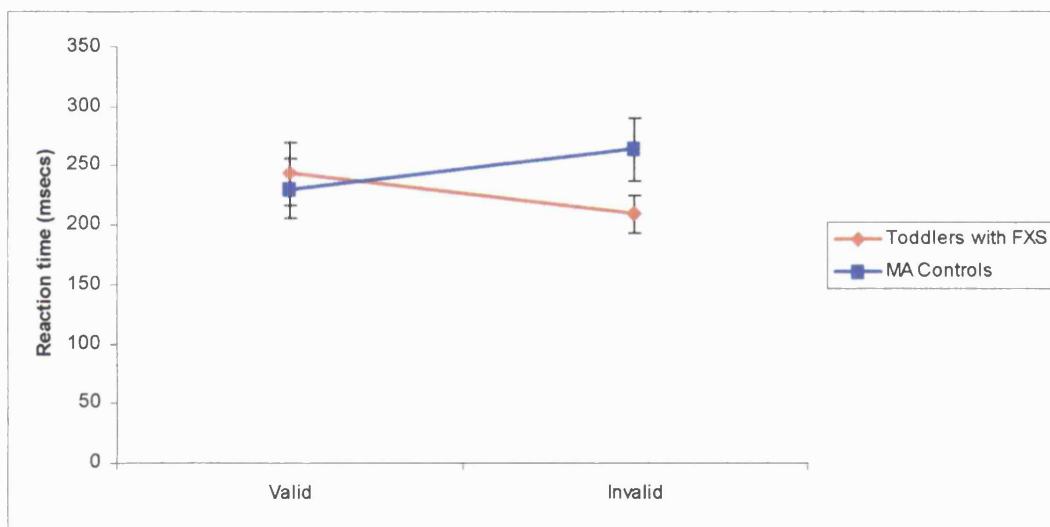


Figure 5.6. Reaction times (msecs) to Validly and Invalidly Cued Targets for toddlers with FXS (red line, diamonds) and MA controls (blue lines and squares). The graph illustrates the faster reaction times for uncued targets for toddlers with FXS but not MA controls.

Figure 5.7 illustrates the fact that 8 out of 9 infants and toddlers with FXS were faster at orienting towards the invalidly cued target, whereas this effect was much more variable in MA controls.

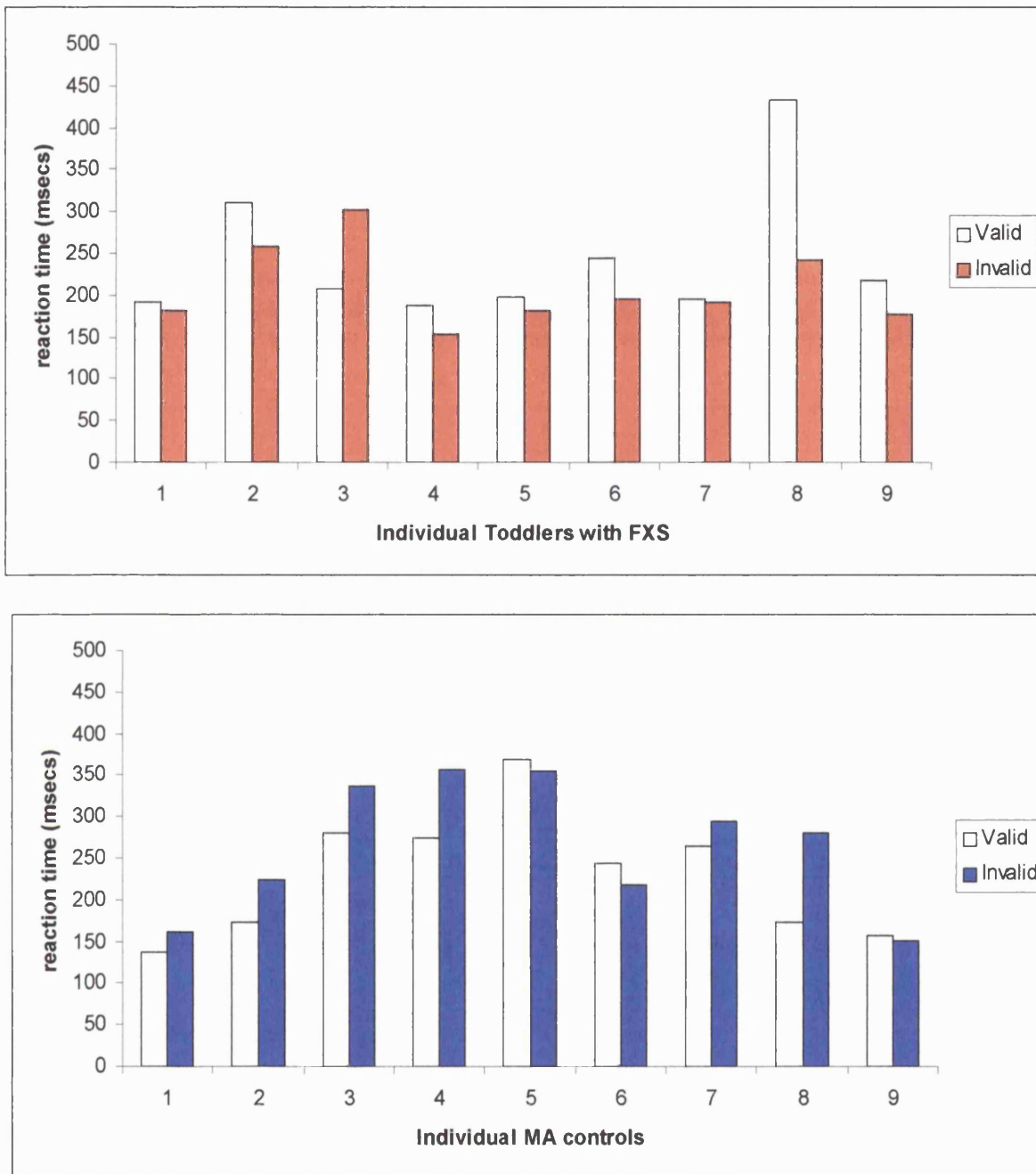


Figure 5.7. Individual toddlers' reaction times to valid (empty columns) and invalidly cued targets for (a) toddlers with FXS (red), (b) MA controls (blue). The graphs illustrate how 8 toddlers with FXS out of 9 exhibited faster reaction times to invalidly cued targets.

I also analysed the effects of cue-target interval on the difference in reaction time between invalidly and validly cued targets (“orienting effects” in the literature, e.g., Wainwright & Bryson, 2000). The effect of cue-target interval was not statistically significant, $F(1.931, 30.898) = .294$, $p = .740$ (Greenhouse-Geisser corrected). There were also no effects of cue-target-interval on cueing benefits (i.e., reaction time difference for the neutral minus valid conditions), $F(1.788, 28.612) = 1.489$, $p = .242$ (corrected) and in cueing costs (i.e., reaction time difference for the invalid minus neutral conditions), $F(3, 48) = .073$, $p = .974$. None of the related Group X Validity interactions were significant, $p = .740$, $.914$, and $.8$ respectively.

Differential effects of developmental level

I then examined the effect of developmental level as a co-variate in the above analyses. When Mental Age was entered as a covariate, there were no main effects of Validity, $F(1, 15) = 2.323$, $p = .148$, of Cue-target interval, $F(3, 45) = 1.595$, $p = .204$, nor of Group, $F(1, 15) = .024$, $p = .879$. However, the interaction between Validity and Group was still statistically significant, $F(1, 15) = 7.416$, $p = .016$. None of the other effects nor interactions were significant, including the main effect of age (p levels between $.862$ and $.375$). When orienting effects, cueing benefits and costs were analysed with Mental Age as a co-variate, none of the main effects nor interactions were statistically significant, p levels ranging from $.302$ to $.982$.

Discussion

In summary, I predicted atypical effects of exogenous cues on orienting by infants and toddlers with fragile X syndrome. This was indeed the case: infants and toddlers with FXS differed from typically developing controls in the effects of cue validity. However, the direction of the effect pointed in an unexpected direction. Toddlers with FXS were significantly faster at orienting attention towards an invalidly cued target than towards a validly cued one, exhibiting a larger inhibition of return than matched controls, across cue-target intervals. This effect was larger when the variability contributed by developmental level was taken into account.

How could this inhibition of return effect be interpreted? First, it could be that these effects result from a spurious effect of having developed a paradigm that simply did not elicit inhibition of return successfully in typically developing children. In the discussion of Experiment 3a, I addressed these concerns and the experimental paradigms that could test them in a larger group of typically developing children and replicate them in different samples. However, this would not be practical in the limited sample of children with FXS given its relatively rare prevalence in the normal population. Furthermore, variants of the task could not be run on the same subjects in the same session, as this would introduce spurious order effects. Secondly, it is possible that, with this paradigm, inhibition of return could reveal itself with older typically developing children, although there was no indication of this effect in the age-related changes in performance presented for Experiment 3a. If this were the case, toddlers with FXS could place themselves between MA and chronological age (CA) matched controls. This possibility can only be addressed by testing a sample of older typically developing toddlers and young children to extend the developmental trajectory of Experiment 3a.

If, however, one takes these results at face value, there are a number of interpretations and testable hypotheses that I can offer for them. It could be that these results are due to smaller effects of FMR1 silencing on subcortical circuits at least partly responsible for inhibition of return. Secondly, it may be that modulation of inhibition of return by cortical areas increases developmentally, and developmental deficits in these cortical projection (rather than lesions later in life) may result in paradoxical effects on inhibition of return.

Converging evidence suggests that the superior colliculus plays an important role in inhibition of return. Inhibition of return (IoR), indeed, occurs in infancy, prior to full cortical development, suggesting further that it depends on subcortical processing (Valenza, et al., 1994; Clohessy et al. 1991; Hood, 1993). Furthermore, patients with cortical lesions exhibit IoR, while localised subcortical damage results in the elimination of the effect (Posner et al., 1984). As I reviewed in Chapter 1, FMRP is expressed throughout cortex and subcortical areas. However, the glutamatergic system, affected in fragile X syndrome, is crucial for cortical, rather than subcortical projections (e.g., Kandel, Schwartz, & Jessell, 2000; Mountcastle, 1998). It is therefore possible that the inhibition of return measured here for

toddlers with FXS results from a lesser involvement of subcortical areas in the neuropathology associated with the condition.

However, this interpretation of the results does not explain why infants and toddlers with FXS should display enhanced inhibition of return compared to controls. Recent neurophysiological evidence may shed light on this puzzle. A number of single-cell recording studies in non-human primates suggest that neurons in the superior colliculus reflect inhibition of return (Dorris et al., 2002), but this may depend upon inputs from other brain systems representing a part of space. A likely source of these inputs is parietal cortex. These findings warn against attributing IoR exclusively to collicular activity. While IoR in neonates (Valenza et al., 1994) and infants (Hood, 1993) is predominantly under subcortical control, cortical modulations of the effect may augment with age. Increasing levels of cortical maturation would change the balance of control over this phenomenon. It should therefore be reflected in behavioural changes as well as changes in brain processing.

The cortical projections responsible for these developmental changes in modulation are affected in fragile X syndrome (as glutamate is the neurotransmitter mostly involved in cortico-subcortical projections). So, it could be that, although toddlers with FXS produce behavioural evidence for inhibition of return, the neural correlates of this behaviour vary compared to controls, because of the very developmental nature of the condition itself. This interpretation yields a testable prediction: electrophysiological measures of IoR in fragile X syndrome should reveal atypical waveforms compared to controls, and source analysis should indicate different dipoles associated with inhibition of return. However, the current paradigm did not elicit reliable IoR from typically developing children. It is therefore necessary to address these concerns by suggesting the design for future experiments. This will be part of the focus of the general discussion.

5.3. General Discussion

5.3.1. Exogenously-driven visual orienting: typical and atypical trajectories

This Chapter aimed to assess the effects of non-predictive peripheral cues on orienting in typically and atypically developing toddlers. In experiment 3a, I found that typically developing infants and toddlers were faster at orienting towards a validly cued target. Furthermore, this orienting effect decreased with age, with older toddlers also tending to display smaller costs of having been invalidly cued. This effect converged with the findings obtained with older children (e.g., Akthar & Enns, 1989; Brodeur & Boden, 2000; Brodeur & Enns, 1989; Wainwright & Bryson, 2002). However, in contrast with infant (e.g., Johnson & Tucker, 1996) and adult studies (e.g., Posner & Cohen, 1984), this paradigm did not elicit reliable effects of cue-target interval leading to early facilitation and later inhibition of return. As discussed in section 5.2.1, these may well have been too small to be detected with a relatively small sample and within a wide age range.

In experiment 3b, toddlers with FXS were differentially more affected by exogenous cues. However, they displayed an unexpected effect. In contrast with the typically developing toddlers of Experiment 3a, they oriented faster towards invalidly rather than validly cued targets. They therefore exhibited a larger inhibition of return than control children across cue-target intervals. This could depend on a number of factors and the current data do not allow us to discriminate between these possibilities, but I proposed a number of experiments that may address this issue. I shall now elaborate on these interpretations of the effect and on its implications for other attentional tasks, like visual search, the focus of Chapter 6.

5.3.2. Limitations and future research questions

It is important to note that the inhibition of return measured here is based on cueing of space, rather than delimited sections of space or objects. Tipper and colleagues have extensively investigated similarities and differences between object-based and space-based

inhibition of return (e.g., Tipper et al., 1991; 1994; 1996). Space-based and object-based inhibitions of return appear to be dependent, at least partially, on overlapping and distinct neural substrates. Indeed, inhibition of return in object co-ordinates depends on cortical structures being intact (Tipper et al., 1997). This has two implications for the current findings. First of all, object-based inhibition of return may be affected in FXS, even though the toddlers here seem to show enhanced (space-based) IoR. None of the published studies on IoR in infancy has addressed this issue, as most of them test space-based effects, rather than object-based ones. There is, however, a notable exception: Harman, Posner, Rothbart and Thomas-Thrapp (1994) investigated both and found that the object-based inhibition of return developed later than space-based IoR. It would therefore be critical to design matched tasks testing potentially different developmental trajectories for the two in infancy and toddlerhood and their potential interactions.

What implications would these experiments have for the study of fragile X syndrome? It could be that in this population inhibition of return is obtained, but supported by a predominantly sub-cortical mechanism even later than in infancy. This in turn would predict that object-based inhibition of return may be differentially more affected in the syndrome, but that both types of processes may result in atypical electrophysiological measures (ERPs and gamma activity). The distinction between space- and object-based inhibition of return has another important implication. As will become apparent in the next chapter, delaying with and disengaging from objects (and/or previously rewarded responses associated with objects) may be precisely what children with FXS may have difficulties with. So, the first future investigation that needs to be investigated would be the effects of cueing on object-based inhibition of return within this group.

Another future direction would be to modify the predictive nature of the cue and measure effects on covert orienting along the continuum of cues that are highly predictive and validly cue the target location, vs. truly un-predictive cues, vs. predictive but invalidly cueing cues. Typically developing older children may be differentially more able to use the information value of the cue to speed their orienting towards the target. In contrast, younger children may not be able to do so as efficiently. Furthermore, in the case of predictive cues that reliably appear on the side opposite to the target, younger children may not be able to orient

attention adaptively in the opposite direction as well as older children. This would show a similar effect to that obtained in Chapter 3, but for covert cueing of attention rather than overt visual orienting. One could focus in particular on the methodology used by Brodeur and Boden (2000). What would be the predictions for atypically developing children with attentional difficulties? Although children with FXS show effects of exogenous cueing, they may not be able to use cues to speed orienting towards the target location. Additional manipulations used by Brodeur and Boden (2000) were the distance between the cue and the target, as well as the length of the cue-target interval. This allowed the authors to investigate developmental changes in the size of the attentional focus (Castiello & Umiltà, 1990, 1992). These measures provide alternative ways of assessing difference in attentional control. Children with FXS may find it difficult to modulate the size of their attentional field effectively, as do children with ADHD (McDonald et al., 1999).

5.3.3. Implications for other attentional tasks

Atypical covert orienting and visual search

What are the relationships between covert orienting and the filtering of information? Klein (1988) was amongst the first researchers to suggest that mechanisms like inhibition of return, investigated in standard cueing tasks, would be the basis for foraging in standard search tasks that require searching for targets amongst distractors. Efficient foraging behaviour in standard search tasks involves not only voluntary control, but also use of the information stored in memory about previously searched locations.

It is indeed very important to understand how this type of phenomenon, inhibition of return, would affect performance on search tasks that require easier or more complex discriminations of targets from distractors. Inhibition of return has indeed been found with a number of non-spatial discrimination tasks, different from the ones used here (e.g., Lupianez et al., 1997; Pratt et al., 1997). It should function as a foraging facilitator (Klein, 1988, 2000; Klein & McInnes, 1999). Therefore, the results in this chapter make a strong (perhaps paradoxical) prediction. Toddlers with FXS exhibit larger inhibition of return than matched controls. Would they perhaps be better at performing the search task?

Although it may be tempting to suggest superiority in FXS search, it is important to remember that inhibition of return measured in cueing tasks like the ones used in this chapter is only a particular type of IoR. In this chapter I focused solely on space-based inhibition of return, but recent studies have suggested that IoR relevant for search environments is also, crucially, object-based (reviewed by Klein, 2000). Furthermore, there may be subtle differences between the mechanisms driving inhibition of return in cueing tasks, two-dimensional search and three-dimensional foraging. This underscores the possibility of intriguing similarities and differences in orienting and search results. Indeed, in Chapter 6 we now turn to examine the effects of target salience on typical and atypical search performance.

5.4. Chapter Summary

This Chapter emphasised the importance of investigating exogenous attention as well as endogenous control. I focused on the effects of non-predictive peripheral onsets on the speed of visual orienting because these have been studied extensively both in the adult and the infant literature. In Experiment 3a, I investigated the effects of cue validity in typically developing infants and toddlers, finding faster orienting towards validly vs invalidly cued targets. The cueing effect decreased with age and older toddlers tended to be less affected by invalid cues than younger infants. In Experiment 3b, toddlers with FXS exhibited the opposite effect of cue validity, displaying faster orienting to invalidly rather than validly cued targets. Chapter 6 assesses their performance in search tasks, for which inhibition of return is thought to function as a facilitator. Will toddlers with FXS paradoxically outperform typically developing children, as predicted?

Visual Search: The Effects of Target Perceptual Salience

Visual selective attention is crucial for dealing with our everyday, cluttered visual environment (e.g., Parasuraman, 1998; Pashler, 1998). What cognitive processes underlie this ability? How do they develop? Models of normal adult attention have relied heavily on how visual-search performance varies with the number of items in the display, and with the properties distinguishing targets from nontargets (e.g. Bundesen, 1990; Duncan & Humphreys, 1989; Treisman & Gelade, 1980; Wolfe, 1994). In a typical visual search task, observers respond as accurately and quickly as they can to indicate the presence/absence of a pre-specified target or singleton stimulus within a visual array.

Initial work suggested a dichotomy between preattentively discriminated properties (e.g., simple visual features), versus those requiring focal attention and leading to serial search (e.g., conjunctions of features: Treisman & Gelade, 1980). But this dichotomy is now

controversial in adult research, with some models (e.g., Duncan & Humphreys, 1989) suggesting a continuum of search efficiency, with increased efficiency as targets and distractors become more physically distinct, and as distractors become more homogenous. Performance is thought to be influenced both by goal-directed endogenous control, driven by the representation of task-relevant stimuli, and by stimulus-driven mechanisms that determine the perceptual salience of stimuli in the display. These in turn depend on both the perceptual similarity between the target and distractors and on the homogeneity of distractors (Duncan & Humphreys, 1989). Let us consider how these findings can inform investigations of the development of selective attention.

6.1.1. Typical development of selective visual attention

Much of the existing literature on the life-span development of visual search has also tended to dichotomise feature versus conjunction searches (e.g., Plude, Enns, & Brodeur, 1994; Trick & Enns, 1998). For example, Gerhardstein and Rovee-Collier (2002) contrasted feature and conjunction searches by using a computer touch-screen to obtain search reaction times for 12-, 18-, 24- and 36-month-olds. These experiments were methodologically groundbreaking, being the first to investigate search in young infants and toddlers using reaction times rather than novelty preference (e.g., Bhatt, Bertin, & Gilbert, 1999). Gerhardstein and Rovee-Collier found steep versus flat search functions against set-size for conjunctive and feature searches respectively, which did not change with the age of the toddlers. They suggested that the different cognitive mechanisms underlying performance in adults across conjunctive and feature searches also underlie performance in infants and toddlers, and do not change qualitatively with age. Similarly, Trick and Enns (1998) systematically manipulated components of search to tease apart the developmental processes underlying the greater vulnerability of performance by young children and elderly adults in conjunction versus feature searches in comparison to young adults. They asked 6-, 8-, 10-, 22- and 72- year-olds to search for single conjunctive and feature targets appearing at fixed and random locations, with and without distractors. Results suggested that young children were less able to search for conjunctive targets due to the need to integrate multiple features,

but that other factors also played a role, because children were less able to move their attention voluntarily across items in the search display.

However, the adult literature suggests caution against inferring qualitatively different feature versus conjunction mechanisms from search-slopes alone, because these can be influenced by factors other than the specific need to integrate features (e.g., see Duncan & Humphreys, 1989). Moreover, recent evidence indicates that target-distractor discriminability on even a single feature can determine the speed and accuracy of search for older children (O’Riordan & Plaisted, 2001). Furthermore, infants as young as 5 months can be sensitive to manipulations of featural target-distractor similarity (tested with tasks relying on kicks to mobiles for familiar visual patterns, Gerhardstein, Renner, & Rovee-Collier, 1999) and nontarget heterogeneity (tested with the novelty preference paradigm, Bertin & Bhatt, 2001). These studies provide evidence that a target’s featural salience can play a role in selection at as early as 3 months of age, even when feature integration is not required. All currently published investigations of early developmental changes in search processes have focused on contrasting feature and conjunction searches (Gerhadstein & Rovee-Collier, 2002). However, no research has thus far sought any early developmental changes in the effects upon search of featural discriminability alone. My first aim was therefore to design developmentally-appropriate tasks for studying any age-related changes in the effects of target featural salience, for visual search by typically developing toddlers (at 2-3 years of age). I therefore manipulated target featural salience by varying the similarity of targets and distractors in Experiment 4a.

6.1.2. Atypically developing visual selective attention

Further, I aimed to examine visual search and the role of target featural salience in toddlers with fragile X syndrome. As detailed in Chapter 1, Fragile X syndrome (FXS) has been associated with difficulties in executive control (e.g., Munir et al., 2000) accompanied by relative strengths in visuo-perceptual skills (Cornish, Munir & Cross, 1999). Visual search represents an interesting paradigm for assessing such relative strengths and weaknesses at even younger ages, since it involves both executive aspects (e.g., selectively attending to

targets while ignoring distractors) and visual-perceptual aspects (e.g., encoding the visual properties that distinguish relevant from irrelevant information).

Based on the previous work in adults and on the bases of the results of Part II, one might suggest that deficits in endogenous control would be found in FXS toddlers in the presence of normal effects of exogenous manipulations of the visual environment. As stressed throughout the present thesis, it should be noted that in fact adult end-states do not always predict infants' cognitive profiles (e.g., Paterson et al., 1999). Furthermore, behavioural strengths and weaknesses in developmental disorders have typically proven to be relative rather than absolute, with subtle patterns of atypical performance emerging even in domains of apparent proficiency, as for example in language or face processing in Williams syndrome (e.g., Karmiloff-Smith et al., 2003; Grice et al., 2001). Adult phenotypic differences should thus always be considered the outcome of a developmental process whose early trajectory cannot be simply inferred but must be empirically investigated (Karmiloff-Smith, 1998). In Experiment 4b, I therefore examined visual search in toddlers with FXS, compared to the typically developing toddlers matched for chronological or mental age. I opted to examine search for multiple targets with a computerised touch-screen method (c.f. Gerhardstein & Rovee-Collier, 2002), while manipulating the presence of intermingled nontargets and their physical salience relative to the targets. With this method one can assess not only search speed, and the distance between successively touched items, but also the nature of any errors (e.g. touching nontargets instead of targets; or perseverating on targets that have already been found).

6.2. Experimental Data

6.2.1. Experiment 4a. Effects of target-distractor similarity in typically developing toddlers.

My first aim was to test whether manipulations of target featural salience modulate the efficiency of toddlers' visual search, and whether this changes through early development. In Experiment 4a, I focused on salience as determined by target-distractor similarity, since

this has been extensively investigated in the adult literature as well as in young infants and older children (e.g., O’Riordan & Plaisted, 2001), but not in toddlers. Here I manipulated similarity by varying the distractors’ size: target stimuli surrounded by smaller distractors are salient (Braun, 1994) and can capture attention (Yantis & Egeth, 1999).

By presenting multiple targets within each array, I could examine the search path used by the observer to find successive targets and the type of any errors committed when searching. Search path can be operationalised in a number of ways. For example, one can record the distance between successive touches. Shorter distances suggest a more systematic search through the visual display than longer ones. Using this method, Wilding, Munir and Cornish (2001) found that typically developing 10-year-old children who were rated as more attentive by teachers produced a shorter distance per hit than children rated as less attentive. Short distance per hit was a good predictor of belonging to the “good attention” rather than the “poor attention” group, and in a principal components analysis it loaded on the same factor as other measures of cognitive control. In a subsequent re-analysis of the data correcting for the time and distance wasted in errors, error types proved to be even more informative of group differences than search speed and distance (Wilding, 2003). Error types during visual search have also been used as indicators of underlying difficulties in adult neuropsychological patients (e.g., see Manly et al., 2002).

Previous studies (O’Riordan & Plaisted, 2001) elegantly investigated the effects of target-distractor similarity in older children using classical reaction-time paradigms. Here I aimed to measure any developmental changes in the effects of target featural salience on search speed, path, accuracy and error types, for toddlers. To ensure that any age-differences depended on the requirement to search for targets amongst distractors, we also measured baseline performance on search displays that did not contain any distractors but only multiple targets, and then used these baseline measures as co-variates in our analyses. If toddlers develop in their ability to search for targets amongst distractors, this should result in age effects over and above those found in baseline trials. So, including nontargets may exert effects over and above individual differences in the systematicity with which different children explore a visual display containing multiple targets alone. In terms of search path, baseline performance alone may provide interesting information on age changes in the

systematicity of search. In contrast, baseline age differences in search speed are representative of age-related changes in, say, motor speed rather than in visual attention.

Given data from older children and adults, nontargets that were more similar to the targets (in size) were expected to disrupt search performance more than smaller nontargets that render the large target more salient. There exist, however, no data investigating any cross-sectional age changes for this, nor any investigation of the correlations between everyday attention and search performance.

Method

Participants

Fifty typically developing toddlers were recruited through local nurseries and came predominantly from middle-class Caucasian families. Parents and teachers reported children's vision as normal or corrected. Forty toddlers completed the task satisfying the criteria set below: 19 two year-olds (mean = 29 months, SD = 3.8 months, range = 24-35 months, 10 girls), 21 three year-olds (mean = 42, SD = 3.8 months, range = 36-48 months, 8 girls).

Materials

Pre-test acuity trials involved four laminated stimulus cards each displaying a single target circle and a single distractor circle (see below for dimensions). During the demonstration phase, as well as practice and test runs, participants viewed stimuli on a 15'' portable touch-screen (Elo AccuTouch) connected to a portable laptop computer. Large black target circles were randomly placed on an 8 x 4 light green grid. Viewed from a 30-cm distance, each target subtended 5.7 degrees angle. Distractors were also black circles, subtending either 2.8 degrees (small distractors, very dissimilar from the target) or 4.2 degrees (medium distractors, more similar to the target). All search displays contained 10 target circles and either no distractors (baseline condition), or 6 or 24 dissimilar (small) distractors in addition, or 6 or 24 similar (medium) distractors in addition (Fig. 6.1). Distractor type and number were thus used as within-subjects manipulations.

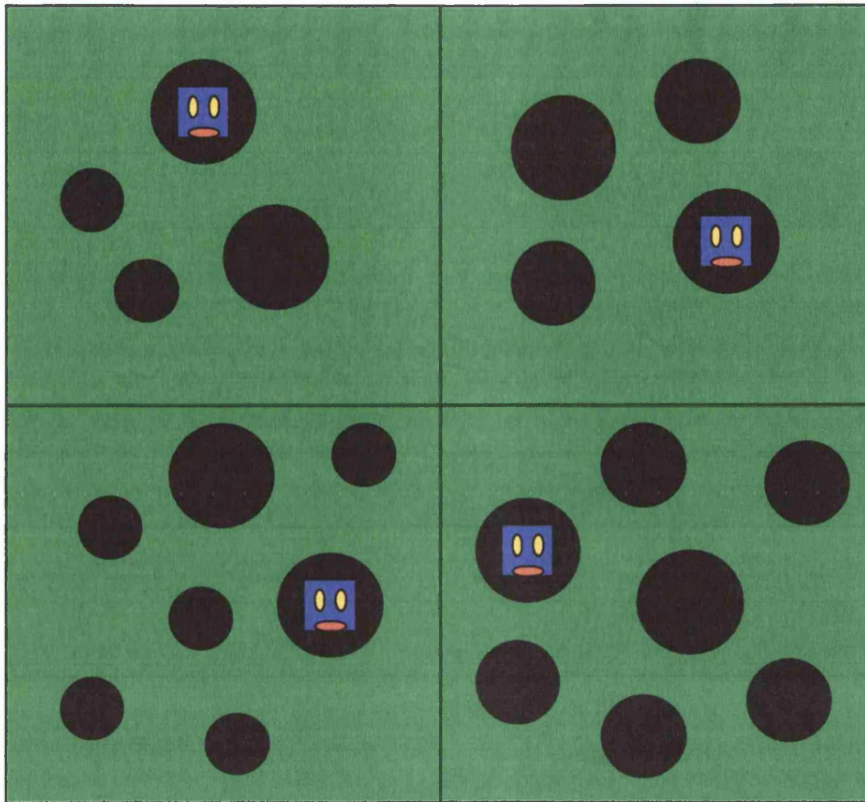


Figure 6.1. Sample test displays maintaining the target-distractor ratio in the original test displays. Top-left: few small distractors (dissimilar to targets); top-right: few medium distractors (similar to targets); bottom-left: many small distractors; bottom-right: many medium distractors

Procedure

Toddlers were tested in a quiet room either at their nursery, at home or in the Neurocognitive Development Unit infant testing lab. Toddlers sat at a little table approximately 30 cm from the touch-screen, either on their caregiver's lap or on an appropriately sized chair.

Pre-test acuity trials.

During four pre-test trials, toddlers were asked to “touch the big circle” on laminated cards displaying a single target and a distractor. Toddlers had to point to the large circle on the second acuity card for each distractor type to continue.

Demonstration, practice and test phases.

I introduced the search game, explaining that funny monsters were hiding under the big target circles, but not under the little circles. I then gave a demonstration, touching the target (big) circles with my index finger. When a target circle was touched, a coloured square-shaped face covering approximately half the area of the target appeared and remained on display for the duration of the trial. This eliminated the requirement of remembering which targets had been previously found and therefore isolated differences in search from (possibly independent) memory differences. When a non-target circle (small or medium) was touched instead, nothing happened. The search continued until the child had either found 8 targets or touched the screen twenty times. When the final target was touched or at the location of the twentieth touch, a large face appeared for a few seconds and the search was terminated. After the demonstration, toddlers undertook a practice run, during which they were verbally reinforced by both the experimenter and the parent for touching targets and encouraged to look for more monsters. Toddlers were presented first with the baseline run (10 targets alone, with no distractors) and then with the four experimental runs (with 6 or 24 small or medium nontargets in addition to the 10 targets) in randomised order across children. Each trial run was preceded by a practice run.

Data from 10 toddlers (7 two-year-olds) were discarded because they did not complete the pre-test phase successfully ($N = 2$) or they refused to complete the testing phase ($N = 8$). Two additional criteria determined inclusion in the final analyses, in order to ensure that all toddlers had understood the task and remembered it while performing the search:

1. The toddler touched more circles on the screen than empty space;
2. The toddler touched more targets than distractors.

Data from all toddlers satisfied these criteria.

Statistical Analyses

Mean search time per hit (speed measure), mean distance between successive touches (path measure), total number of errors (accuracy measure) and error types (touches on distractors, or repetitions on previously found targets) were calculated for each toddler. Time was measured in seconds, and distance in centimetres. These measures were corrected for the

time and distance spent while making errors, in order to obtain measures that would be independent of accuracy and error types. To correct time, I subtracted the time spent making any type of error and divided the remaining time by the total number of hits. To correct distance, I divided the total distance between successive touches (whether they were correct or not) by the total number of touches (excluding immediate repeats on targets, which did not accrue any distance). Additional corrections were used to remove near misses due to inaccurate pointing or touches with parts of the hand other than the index finger. Results were then analysed using standard statistical packages (SPSS, G-Power).

All analyses were preceded by an exploratory phase during which I plotted all variables of interest to explore distribution and variances. Dependent variables were checked for normality, homogeneity of variance and transformed where necessary before being entered in a 2x2x2 mixed factorial ANOVA with target-distractor similarity (dissimilar versus similar distractors) and distractor number (6 versus 24) as within-subject variables, and age (two year-olds versus three year-olds) as the between-subject variable. Children in the sample spanned a large age range, and they were split into two age groups, a convenient way of looking at age differences. However, this arbitrarily separates children who are, for example, 35 months, from those who are 36 months, and groups them with children who are likely to be much more different (24 or 48 months). As discussed in the general Methods section (Chapter 2) and in Chapter 5, I decided to investigate age effects by also using age as a covariate (ANCOVA using sums of squares of type II). This would provide converging evidence of robust age effects and would test whether splitting the group introduced any spurious effects. Bonferroni adjustments for multiple comparisons were used for post-hoc tests of all main effects. Variables measured during baseline runs (with no distractors) were then used as covariates to establish whether any age effects could be attributed specifically to the requirement for search amongst distractors.

Results

In summary, two-year-old toddlers were slower than three-year-olds when searching for targets among nontargets, even after accounting for variability in mean speed to touch targets in the condition without distractors. Search for targets was fastest when distractors

were more dissimilar from them (small rather than medium) and when displays contained fewer distractors, again regardless of baseline variability. In contrast, the overall effects of these display manipulations on search path (i.e. on the distance between successive touches upon items on the screen) disappeared once baseline variability was taken into account. However, the age differences in search path for displays with nontargets present still remained significant, with younger toddlers producing longer overall distances between successive touches than did older children. Two-year-olds produced longest distances for the displays containing many distractors that were similar to the targets, whereas three-year-olds' distances were longest with these similar distractors but were unaffected by their number. Furthermore, two-year-olds made more errors (including both repetitions on targets and touches on distractors) than the older group. These findings were supported statistically as detailed in the next section. Preliminary analyses with gender as a between-subject factor did not reveal any statistically significant difference between boys and girls on any of the dependent variables (p levels ranged from .103 and .902) and therefore gender was dropped from the further analyses described below.

Analyses of Search Speed

Mean time per hit was significantly affected by target-distractor similarity, $F(1, 38) = 16.288$, $p < .001$. Distractors that were similar (medium in size) to the large targets resulted in longer search times than dissimilar (small) distractors (2.06 v. 1.76 seconds per hit), and this effect remained statistically significant after co-varying performance on trials without distractors, $F(1, 37) = 6.741$, $p = .013$. Mean hit time was also affected by distractor number, $F(1, 38) = 12.863$, $p = .001$, with many distractors resulting in longer search time per hit than few distractors (2.1 v. 1.76 seconds per hit), even with baseline performance as a co-variate, $F(1, 37) = 5.236$, $p = 0.028$. None of the interactions was statistically significant (p levels from .11 to .47). Age had an overall effect on search time, $F(1, 38) = 14.951$, $p = .001$, with two year-olds being slower (2.21 seconds per hit) than three year-olds (1.63 seconds per hit). Analysing age as a continuous rather than as a dichotomous variable provided an equivalent effect of age, $F(1, 38) = 17.334$, $p < 0.001$. Furthermore, this age difference remained when baseline speed was co-varied, $F(1, 37) = 8.607$, $p = 0.006$, as well as when both age and baseline performance were analysed as covariates, $F(1, 37) =$

12.105, $p = 0.001$. This suggests that the age effect on search speed was not simply due to differences in motor speed between two- versus three-year-olds.

Analyses of Search Path

Figure 6.2 displays mean distance between successive touches as a function of target-distractor similarity, number of distractors and toddlers' age. Mean distance was affected by target-distractor similarity, $F(1, 38) = 5.048$, $p = .031$, due to similar (i.e., medium) distractors resulting in longer distance per hit than dissimilar distractors. Target-distractor similarity and distractor number interacted, $F(1, 38) = 4.910$, $p = .033$. However, these effects disappeared when baseline distance was co-varied, $p = .125$, and $.440$ respectively.

Age had a main effect on distance, $F(1, 38) = 12.737$, $p = .001$, with younger toddlers producing longer distances between successive touches (mean distance of 5.84) than older toddlers (5.0 cm). The effect was also statistically significant when age was treated as a continuous rather than as a dichotomous variable, $F(1, 38) = 7.709$, $p < 0.008$. This effect remained significant even with baseline distance per hit as a co-variate, $F(1, 37) = 11.485$, $p = .002$ as well as when both age and baseline distance were entered as covariates, $F(1, 37) = 6.232$, $p = 0.017$. Most importantly, the Similarity \times Distractor number \times Age interaction was significant, both when age was treated as a dichotomous variable, $F(1, 37) = 4.780$, $p = 0.035$ and as a continuous variable, $F(1, 38) = 4.067$, $p = 0.05$. This effect also reached significance when baseline performance was covaried, $F(3, 37) = 3.984$, $p = .05$. The data were entered into separate ANOVAs for each age group to investigate the source of this interaction. For two year-olds, the interaction between Similarity and Distractor Number was significant, $F(1, 18) = 6.721$, $p = .018$. This was due to longer distances on runs with many medium distractors than either few similar distractors ($t(18) = 2.437$, $p = .025$) or many dissimilar distractors ($t(18) = 2.132$, $p = .047$). For three year-olds, Similarity alone was statistically significant, $F(1, 20) = 4.477$, $p = .047$, due to these toddlers producing longer distances between successive touches with medium compared with small distractors.

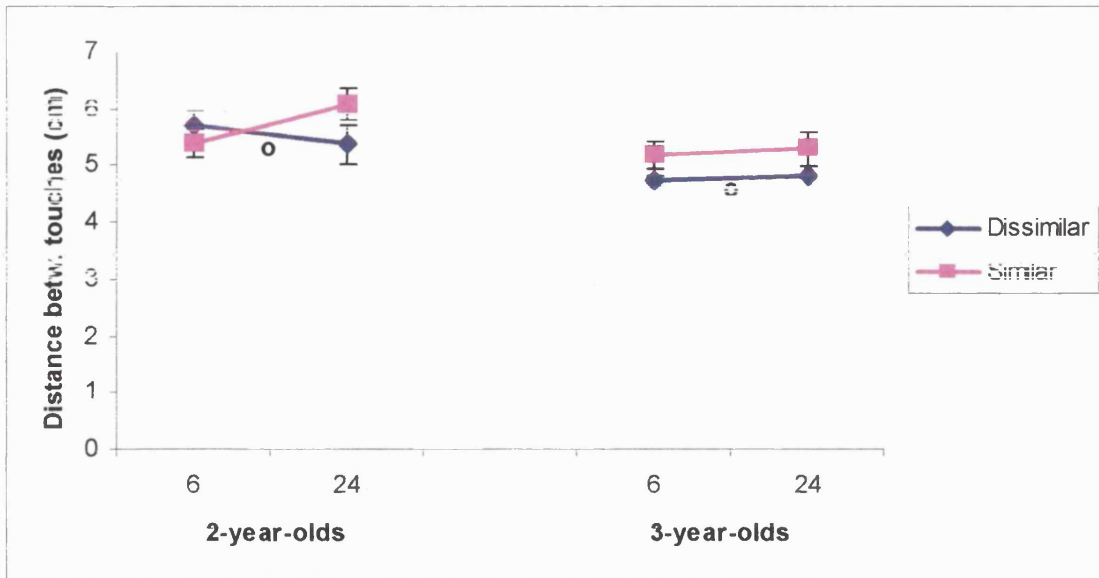


Figure 6.2. Mean corrected distance between successive touches (cm, \pm SEM) as a function of target-distractor similarity (similar and dissimilar sized distractors), distractor number (6, 24) and age (two- and three-year-olds) for typically developing toddlers. o = Distance between successive touches in target-only displays.

Search Accuracy and Error Types

Two year-olds produced more incorrect touches (on average 3.52 errors) than three year-olds (.89 errors), $F(1, 38) = 22.185$, $p < .001$. The effect of age was also significant when age was considered as a covariate, $F(1, 38) = 27.133$, $p < 0.001$. Furthermore, the effect of age remained significant when total baseline errors were taken into account, $F(1, 35) = 10.115$, $p = .003$ as well as when both age and baseline errors were treated as covariates, $F(1, 37) = 25.810$, $p < 0.001$. When the overall number of hits was calculated and errors were categorised into touches on distractors or repetitions on previously found targets, the data were not normally distributed and transformations did not succeed in fully normalising the data. Non-parametric tests were therefore used and age was considered only as a dichotomous variable. Younger and older toddlers produced equivalent numbers of hits both across the experimental conditions (overall means of 7.54 v. 7.99 hits) and for the baseline condition (7.89 v. 7.91 hits), Mann-Whitney U, p levels from .107 to .533. Two-year-old toddlers produced more errors of both types than three-year-olds. Younger toddlers touched

more nontargets than three-year-olds across conditions (overall means of 1.63 versus .5, Wilcoxon test, p-levels from .05 to < .001), and they repeated touches on previously touched targets more often (1.22 versus .131, Wilcoxon tests, p-levels from .06 to < .001). However, this group difference did not occur for repetitions in the baseline data, independent t-test, $t(38) = 1.463$, $p = .152$.

Discussion

Experiment 4a sought to investigate whether a manipulation of target featural salience would affect toddlers' search for multiple targets among nontargets, and how this ability may change between 2 and 3 years of age. It provides the first investigation of the effects of target featural salience on toddlers' performance, with speeded responses, that does not focus on the feature versus conjunction dichotomy (cf., Gerhardstein & Rovee-Collier, 2002). It also provides the first study in toddlers integrating speed measures with search path measures, extending a rationale previously employed only with older children (e.g., Wilding et al., 2001). Target featural salience had a strong effect on search speed, suggesting that featural salience should perhaps be investigated as extensively as the requirement for conjunction versus feature searches. The findings showed that manipulations of perceptual salience for targets can affect toddlers' search speed, even when search does not involve conjunctive search but is limited to search for a feature within a single dimension (here, size).

How do these effects change across early development? The effects of display manipulations on search speed were stable across age groups, as found by Gerhardstein and Rovee-Collier (2002) using a different reaction time paradigm (concerned with feature versus conjunction tasks). Nevertheless, the age difference (for 2- versus 3-year-olds) found in the present experiment for search speed could not be explained by simple differences in motor speed. It remained significant even when I accounted for age differences in baseline performance on target-only trials, suggesting an increased ability to deal with search amongst distractors. Similarly, the age difference in search path suggests an increase in the systematicity with which children search for targets amongst distractors, regardless of

individual variability with target-only displays. While younger toddlers' search paths appear sensitive to both the saliency and the number of distractors, older toddlers' paths appear mostly sensitive to the saliency of distractors. This interaction of display manipulations with age for search path suggests that this path measure may be more sensitive to some age-related changes in the sensitivity to target saliency than is search speed (c.f., Gerhardstein & Rovee-Collier, 2002). The typical developmental trajectory observed here was also characterised by a decrease in the number of errors of both types with age (repetitions on particular targets, or touches on distractors). This suggests that older children are better able to discriminate targets from distractors and that they can inhibit repetitions on previously found targets better than younger toddlers.

In the next section, I examine performance on the same search task in toddlers with Fragile X syndrome in comparison to the typically developing toddlers from Experiment 4a. Control children were individually matched with the atypically developing children either by chronological age (to control for the level of experience) or on the bases of overall cognitive functioning (to isolate attentional difficulties over and above that expected given general delay).

6.2.2. Experiment 4b. Effects of target-distractor similarity in toddlers with fragile X syndrome

As detailed in Chapter 1, the attentional profile of individuals with FXS has been relatively well-studied in late childhood or adulthood, but not for the toddler age-group studied here. Visuo-spatial deficits appear to affect particularly skills requiring visuo-spatial and visuo-constructional abilities, with visuo-perceptual skills functioning within the range expected from the overall developmental level (Cornish, Munir & Cross, 1999). Moreover, adults (Cornish, Munir & Cross, 2001) and older children with the syndrome (Munir, Wilding, & Cornish, 2000) differ from typically developing and other atypically developing control groups in their inability to inhibit task-irrelevant repetitive responses.

Of particular relevance to search performance, Munir, Wilding and Cornish (2000) used a conjunctive search task for multiple targets with older children with FXS. They found that 10-year-olds with the syndrome (range: 7 to 15 years of age) produced equivalent search times but longer distance per hit compared to both typically developing children matched for verbal mental age and than children with Down's syndrome (DS). Subsequently, Wilding, Cornish and Munir (2002) also found that children with FXS, and to a lesser extent children with DS, produced a very large number of repetitive errors on previously found targets. The authors suggest that these repetitive errors may result from a weakness in inhibiting repetition of successful responses, an important component of top-down executive control. Indeed, the number of repetitions was pervasive across conditions, but most apparent when the children were required to switch successively between two target types, a manipulation of executive load (but one that may be hard to implement in toddlers). It is unknown, however, whether manipulations of the perceptual characteristics of the display would also affect error numbers and types in FXS. Moreover, search by toddlers with the syndrome has not been investigated previously.

Predictions for the visual-search performance of toddlers with FXS might be derived from the attentional profiles of adults with the syndrome, although as noted earlier, due to the developmental nature of the disorder (Karmiloff-Smith, 1998, Paterson et al., 1999), the adult and toddler profiles might in fact differ. If toddlers with FXS display early difficulties analogous to those in older children with the syndrome (see Wilding et al., 2002), their search performance should be characterised by repetitive errors and longer mean distances between touches, i.e., by decreased systematicity of their search path relative to typically developing toddlers. If their visuo-perceptual abilities are relatively unaffected, we do not expect differential effects of the target-distractor similarity manipulation compared to mental age controls.

Method

Participants

Fourteen boys with FXS completed the present search task (chronological age: range = 34 to 55 months, mean = 43.5 months, SD = 4.9 months). Their developmental level was assessed

using the Bayley Scale of Development II – Mental Subscale (BSDM-II; Bayley, 1993), which revealed a mean mental-age equivalent of 29.1 months (SD = 4.9 months, range = 23 to 36). They were individually matched, by mental age equivalent (within one month), to fourteen typically developing toddlers, all of whom had participated in Experiment 1 and had been also been assessed with the BSMD-II (mean = 29.1 months, SD = 4.7 months, range = 24 to 36 months), henceforth referred to as the MA controls. They were also matched by chronological age (within one month) to fourteen typically developing children (mean = 43.3 months, SD = 5.0 months, range = 34 - 55), seven of whom had participated in Experiment 4a, henceforth referred to as CA controls. There were no significant differences in CA between the CA controls and the toddlers with FXS (paired t-test, $p = .9$), nor in MA between the MA controls and the toddlers with FXS ($p = .95$).

Apparatus and procedure

As in Experiment 4a.

Statistical Analyses

As in Experiment 4a, except that the occurrence of more errors in the search task led to further division into subtypes. Errors were classified into three mutually exclusive categories: repetitive touches (due to toddlers touching again a previously found target); touches on distractors; and any other erroneous touches (due to toddlers touching the background, rather than any of the targets or distractors). The third category was then dropped from further analyses as these errors most likely reflect inaccuracies in motor control rather than any of the attentional constructs of interest. Repetitive touches were further divided into immediate repetitions (i.e., a touch on target directly following a preceding correct touch that a particular target) versus later returns to targets (with at least one touch elsewhere intervening). As discussed in Chapter 2, I conducted compromise power analyses (G-Power, Faul & Erdfelder, 1992) in order to establish whether the present sample size was too small to yield statistically significant results on the variables of interest. These are reported in Chapter 2, Table 2.4.

Results

In summary, toddlers with FXS made more errors in the search task than the control toddlers. Toddlers with FXS differed from the other groups in repeatedly touching targets that had already been found, on both experimental (nontargets present) and baseline (targets only) trials. When such repetitions were further divided into immediate repetitions versus later returns to previously touched targets, toddlers with FXS produced more of both types of repetitive errors per hit than the other groups. Immediate repetitions per hit for this group were not affected by the presence or appearance of distractors, but later returns per hit were, suggesting that the latter but not the former type of repetitions depended on the requirement to search amongst distractors. Performance by FXS toddlers was also influenced by targets' perceptual salience. Indeed, increasing the number of distractors did not increase touches upon them by toddlers with FXS, but they nevertheless touched similar (medium) more than those dissimilar (small) distractors to the large targets, a pattern not found in control toddlers. Despite these striking differences in error patterns, the toddlers with FXS did not produce longer search speed and path than expected given their developmental level, i.e., their performance resembled the much younger MA controls.

All these empirical conclusions were supported statistically, as follows.

Analyses of Accuracy

Non-parametric statistics were used to test differences in the number of hits, due to heterogeneous variance (mainly caused by low numbers of errors in the controls). Toddlers with FXS did not make significantly fewer correct touches than MA controls (Mann-Whitney U, p levels ranging from .102 to .074) across all conditions, including the baseline all-target displays ($p = .074$), except for the condition with few medium distractors ($p = .05$), in which they made fewer correct touches.

Overall errors were transformed using a square root transform because variances were not homogeneous (and positively skewed). The transform succeeded in not violating the assumptions of ANOVA. An analysis of overall errors revealed main effects of target-distractor similarity, $F(1, 39) = 4.991$, $p = .031$ and group, $F(2, 39) = 29.411$, $p < .001$.

Toddlers with FXS made significantly more errors than both MA controls (means of 2.95 errors versus 1.87, $p = .001$) and CA controls (mean = 1.25, $p < .001$). When baseline errors were co-varied, the effect of Group remained significant, $F(2, 38) = 7.237$, $p = .002$ and the same pattern of differences across groups was maintained. Similarly, target-distractor similarity continued to have an effect on the number of errors, $F(1, 38) = 7.552$, $p = .009$. Furthermore, ANCOVA revealed an interaction between Similarity and Group, $F(1, 38) = 6.731$, $p = .003$. Separate ANOVAs were conducted for each group to ascertain the source of this interaction. It originated from a larger main effect of target-distractor similarity on total errors for toddlers with FXS ($F(1, 12) = 11.310$, $p = .006$) than for MA controls ($F(1, 12) = 5.626$, $p = .035$) once the variability in baseline errors was accounted for. No other main effects or interactions reached significance (p levels between .428 and .951).

Erroneous Touches on distractors.

Figure 6.3a displays mean touches on distractors as a function of group, target-distractor similarity and number. Distractor number had a main effect for touches on distractors, $F(1, 39) = 6.721$, $p = .013$, with more errors of this type being produced when the display contained a larger amount of distractors. Target-distractor similarity also had a main effect on this error type, $F(1, 39) = 11.048$, $p < .002$, showing that many more distractor touches occurred with similar rather than dissimilar distractors. Group had a main effect on the number of touches on distractor circles, $F(2, 39) = 10.117$, $p < .001$. Importantly, toddlers with FXS did not differ significantly from MA controls on this measure ($p = 0.663$). CA controls produced fewer errors than toddlers with FXS (.63 distractor touches, $p < .001$). Noteworthy is the fact that Similarity and Group interacted, $F(2, 39) = 3.820$, $p = .031$. Touches on distractors were then entered into separate ANOVAs for each group to determine the source of this interaction. The analysis of simple effects revealed that toddlers with FXS made significantly more errors of this type when distractors were more similar to the targets $F(1, 13) = 6.663$ $p = .023$ and when there were many distractors, $F(1, 13) = 12.530$, $p = .004$. These effects did not hold for MA and CA controls (for distractors size and number, p -levels respectively .452, .219 for MA controls and 286, .614 for CA controls).

Repetitions on previously touched targets.

Figure 6.3b displays mean repetitions per hit on previously found targets as a function of group, target-distractor similarity and distractor number. The total number of repeats was divided by the number of hits to account for the difference between groups in the overall number of hits. Group had a significant effect on the number of such repetitions, $F(2, 39) = 18.201$, $p < .001$. Critically, toddlers with FXS produced significantly more repetitions on targets that they had already touched (on average, .68 repetitions per hit, even though these were now clearly marked by a monster face), than MA controls (.15 repeats per hit, $p < .001$) and CA controls (.04 repeats per hit, $p < .001$). Other main effects and interactions were not significant.

The effect of Group remained significant when the variability in repetitions for baseline (targets only) trials was taken into account, $F(2, 38) = 10.980$, $p < .001$. The difference between toddlers with FXS versus MA and CA controls remained significant ($p = .001$ and $p < .001$ respectively). A high number of repetitions for toddlers with FXS was found even when all items were targets (though note that a previously touched target in effect then becomes a nontarget for correct search, being marked visibly with a monster face), $F(2, 39) = 7.146$, $p = .002$. Indeed, toddlers with FXS produced on average .93 (+/- SEM = .38) repetitive errors per hit on such baseline trials, in contrast with an average of only .22 (+/- .09) for MA controls ($p = .035$) and .02 (+/- .01) for CA controls. However, the difference with MA controls on trials containing distractors remained significant after covarying baseline, suggesting that the presence of the distractors influenced repetitions by toddlers with FXS over and above what might be expected given their developmental level.

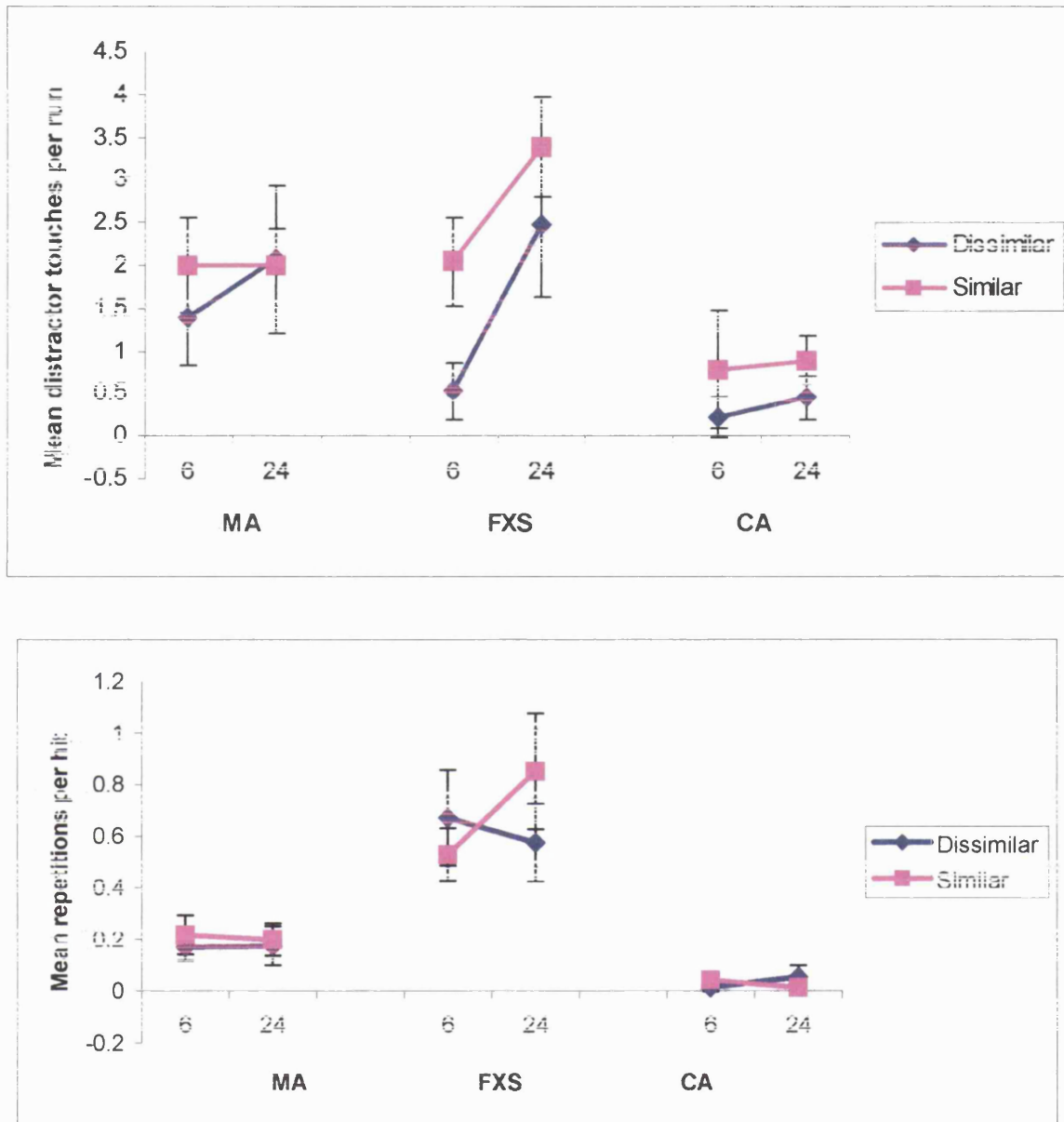


Figure 6.3. Effects of target-distractor similarity (similar and dissimilar sized distractors), distractor number (6, 24) and group on a) mean touches on distractors and b) mean repetitions per hit on previously found targets (+ SEM) for toddlers with FXS, MA and CA controls.

To investigate repetition errors further, these were subdivided into immediate repetitions versus later returns to previously touched targets (with the latter errors requiring at least one intervening touch on another item before returning to a particular target). These are illustrated in Figures 6.4a and b. Because many children in the control groups committed few immediate repetitions per hit, these data were not normally distributed and so non-parametric statistics were used for group comparisons. Toddlers with FXS produced significantly more immediate repetitive errors than MA controls ($Z = 2.675$ to 1.817 , $p = .007$ to $.069$) in the conditions containing distractors. In the baseline condition, FXS toddlers produced more immediate repeats than toddlers with MA controls ($Z = 2.124$, $p = .034$) in this condition as well. The high number of immediate repeats in toddlers with FXS appears consistent with a dysexecutive perseverative tendency (Shallice, 1988). FXS toddlers' immediate repetitions were not affected by target-distractor similarity, $F(1,13) = .445$, $p = .516$, or number $F(1, 13) = .545$, $p = .473$.

Most of the toddlers in the control groups did not produce any later returns to previously touched targets, so these were analysed parametrically only for toddlers with FXS, and group comparisons were tested non-parametrically. Toddlers with FXS produced more such returns with similar than with dissimilar distractors, $F(1, 13) = 6.182$, $p = .027$, suggesting that this type of repetitive error by toddlers with FXS was influenced by the display properties, unlike their immediate repeats. They did not differ from the other groups in the number of returns per hit on baseline trials ($p = .137$ compared to MA Controls), but they did differ from the MA controls on the number of returns per hit in displays containing distractors (many similar distractors, $Z = 2.359$, $p = .018$).

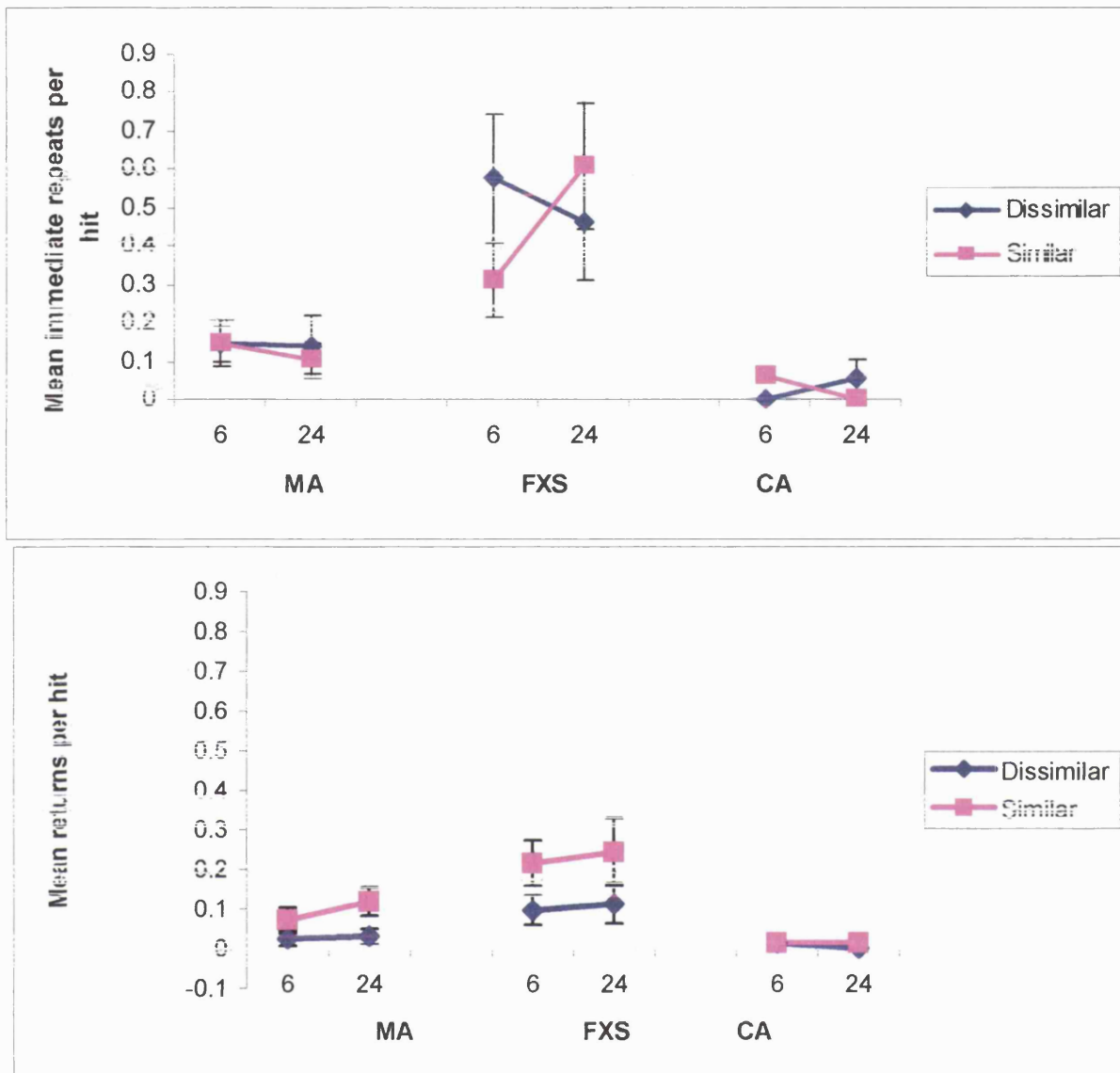


Figure 6.4. Effects of target-distractor similarity (medium and small sized distractors), distractor number (6, 24) and group on a) mean immediate repeats per hit on previously touched targets and b) mean returns per hit on previously found targets (+ SEM) for toddlers with FXS, MA and CA controls.

Analyses of Search Speed and Search Path

Group did not have an effect on overall time per hit, $F(2, 39) = 2.711$, $p = .065$ (and the trend depended on MA controls tending to be slower than CA controls ($p = .063$), suggesting that once total search time was corrected for the time spent in incorrect touches, toddlers with FXS found targets in the same amount of time as controls. The effect of distractor number reached statistical significance, with larger displays resulting in longer search times per hit, $F(1, 28) = 4.885$, $p = .033$. None of the other main effects or interactions was significant (p levels from .119 - .859).

In terms of search path, there was a main effect of Group, $F(2, 39) = 9.195$, due to toddlers with FXS producing longer search paths than CA controls ($p < .001$) and tending towards a similar difference with MA ($p = .071$). The effects of group and distractor number on distance between successive touches interacted, $F(1, 39) = 4.316$, $p = .020$, but this effect was not significant when the variability in baseline distance was taken into account, $F(2, 38) = 2.178$, $p = .127$. None of the other main effects or interactions was statistically significant (p levels between .183 and .510).

Discussion

Experiment 4b investigated any differences in search performance for toddlers with FXS, comparing them to typically developing controls. The current findings reveal some differences between the clinical and the control groups (especially in the types of errors made), as well as some similarities on other measures. In terms of search speed and search-path, the FXS group displayed a similar level of performance, with no difference from that expected given their developmental level (and only a trend for the search path measure). As for data in Chapter 4 for the control of conflict, there are important reasons not to dismiss the absence of a difference between a clinical group and younger typically developing controls, as this “simple delay” may later predict deviance. This argument against the dismissal of similar performance will be further articulated within a longitudinal context, in Chapter 7. For now, I shall focus primarily on group differences. The notable differences related instead to the number and types of errors produced. Toddlers with FXS produced

more repetitive errors (touching a previously found target again, even though it was now already marked by a monster-face) than the other groups. Furthermore, toddlers with FXS also produced more distractor errors in conditions of low target perceptual salience.

The pattern of repetitive errors by toddlers with FXS, which included both a high level of immediate repetitions and some later returns to previously rewarded responses, is similar to that reported by Wilding et al. (2002) for older FXS children (aged on average 11 years), and provides new evidence for an early core deficit in inhibition in FXS. These errors cannot be explained in terms of poor memory of visited locations, since previously touched targets were clearly marked throughout trials. They are better accounted for by the difficulty to suppress a previously correct but now inappropriate response, a hall-mark of inhibitory problems (Shallice, 1988). A non-executive interpretation of these perseverations could suggest that, for example, children with FXS like the appearance of the monsters more than the other groups and are therefore more motivated to touch them repeatedly. I believe that these are not mutually exclusive interpretations; in general, rather than in this task alone, perseverations can be explained by either difficulties in inhibiting prepotent responses, by a higher reward value of a previously correct response, or by a combination of the two processes. The repetitive errors in FXS also revealed a vulnerability to the manipulation of target salience, with FXS toddlers returning more frequently to previously touched targets when the display included similar rather than dissimilar distracters. The high level of immediate repetitions in FXS indicate executive dysfunction in inhibitory processes, while later returns may reflect an interaction of executive dysfunction with perceptual processes, with returns to old targets becoming more likely when a new target is perceptually harder to locate.

6.3. General Discussion

6.3.1. Typical and atypical effects of target salience on visual search

Taken together, search results for typically and atypically developing toddlers indicate that target featural salience affects several aspects of search in this age group, including speed, search path, accuracy, and the type and frequency of errors. Younger typically developing

toddlers were in general slower, less systematic and less accurate than older toddlers, but search path proved the most sensitive measure for detecting differential age effects of target salience in the typically developing groups. In contrast with older toddlers', younger toddlers' search path (but not their speed) was affected by both target salience and display size. By contrast, it was primarily error patterns, rather than search speed or path, that clearly differentiated the group of toddlers with fragile X syndrome, supporting my earlier suggestion that differences in the typical developmental trajectory may not overlay neatly on atypical development. Toddlers with FXS produced more repeats on previously touched targets than both the other groups.

In Experiment 4a, the use of multiple measures during computerized search on a touch-screen allowed me to reveal age differences between younger and older toddlers that would not have been detected had I merely focused upon more traditional search measures. Younger toddlers' search was slower than older toddlers', but this effect could not be attributed solely to age differences in motor speed alone (c.f. Gerhardstein & Rovee-Collier, 2002), because it did not disappear when accounting for any differences in speed on baseline trials (where all items were targets). Younger toddlers also produced less systematic search-paths in conditions of both low target salience and large display size; by contrast, older toddlers' search paths were only affected by target salience, suggesting distinct developmental changes in the ability to deal with manipulations of display properties during search tasks.

In Experiment 4b, the pattern of errors suggested striking qualitative differences in search performance between toddlers with FXS and typically developing toddlers, but also some similarities in their vulnerability to manipulations of target featural salience. Toddlers with FXS produced more errors than both age-matched and younger controls, suggesting overall delay in their ability to search. More importantly, over and above this general pattern of delay, the FXS group showed different types of errors. Toddlers with FXS repeated previously successful responses, thus producing many repetitive errors, as older children with FXS also do (Wilding et al., 2002). These perseverative errors in FXS toddlers are consistent with performance by older children and adults with the syndrome, both in search tasks and on other executive tasks (e.g. Munir et al., 2000; Cornish et al., 2000). Here I

provide evidence for difficulties with executive control in the syndrome arising as early as in toddlerhood. However, the FXS toddlers also showed some vulnerability to manipulations of target featural salience, which might appear surprising given their reported later proficiency with standardised visuo-perceptual tasks (e.g. Cornish et al., 1999), but could potentially relate to the attentional nature of the present task.

6.3.2. Limitations and future research questions

A number of issues for future investigation emerge from the new data presented here plus extant hypotheses about other age groups. First, there were some differences in the deficits observed here for FXS toddlers as compared with older children with the syndrome, in addition to the similarities such as more repetitive errors in FXS. For example, the FXS toddlers did not differ from controls in terms of search path (there was only a trend in this direction; cf., Munir et al., 2000). Given these differences, it would be useful to examine these aspects of performance in an extended longitudinal study, rather than the cross-sectional approach taken here. This is indeed the focus of Chapter 7. It could also be useful to manipulate target salience during search tasks in additional ways to manipulating target-distractor similarity or distractor heterogeneity (Duncan & Humphreys, 1989). For example, one could do so by looking at other featural dimensions in addition to size. Finally, there have been many recent suggestions that executive function may itself consist of several separable components (e.g., see Baddeley 1996; Shallice & Burgess, 1998), such as the ability to inhibit prepotent responses, to switch attention from one dimension or concept to another, and to maintain in working memory the task in hand (Miyake et al., 2000). It might therefore be useful to compare search tasks against other tasks with different executive components in future studies of FXS toddlers, to test the specificity of the present deficits found during search. The difficulty observed here in preventing response repetitions during search by FXS toddlers might conceivably relate to other characteristic behaviours seen in FXS groups at later age (e.g., repetition in speech, problems with sequences, difficulty with the WALK task of the TEACH reported by Munir et al., 2000; reflexive saccades towards the cue in Chapter 3). Chapter 7 indeed addresses this issue by investigating cross-task correlations at both Time 1 and Time 2.

6.4. Chapter Summary

I began this Chapter by asking how the featural salience of a target may influence the typical developmental trajectory of visual search, and whether selective attention in atypically developing toddlers may break down in a manner that resembles the pattern obtained in later childhood and adulthood. I found that both typical and atypical toddlers' search performance is influenced by target featural salience. In particular, search path indicated age-related changes in the effects of salience in typically developing toddlers. In contrast, the type of errors distinguished differential effects of salience on search by toddlers with FXS. The distinctive patterns of errors for the toddlers with FXS highlight similarities to the adult phenotype, as well as some subtle differences. Notably, toddlers with FXS produced more repetitive errors than the other groups, but they were also differentially more affected by target salience. This in turn suggests the need to investigate empirically the developmental processes leading to the clearer dissociations found in adulthood, rather than simply inferring early selective impairments from the adult phenotype. Indeed, Chapter 7 focuses on longitudinal changes in performance.

Part III – Concluding Remarks

Part III examined whether the early attentional profile in fragile X syndrome is associated with atypical exogenous attention, as well as with difficulties in endogenous control addressed in Part II. I hypothesised that the low-level neural changes associated with the syndrome may influence more substantially the functioning of systems involved in endogenous control. However, I argued that the ubiquitous nature of these changes across cortex, as well as the neurodevelopmental nature of the condition, highlighted the need to investigate exogenous as well as endogenous attention, despite the seemingly normal perceptual processing on older children and adults with FXS.

In Chapter 5, I investigated the effects of non-predictive cues on the speed of orienting towards peripheral targets in typical infants and toddlers as well as infants and toddlers with FXS. Typically developing toddlers exhibited faster responses to validly cued targets, but this effect decreased with age and seemed to depend on an increased ability to deal with the cost of having been cued invalidly. In contrast, infants and toddlers with FXS displayed faster reaction times to invalidly cued targets, a phenomenon that is known in the literature as inhibition of return and has been suggested as a foraging facilitator in visual search tasks. Intriguingly, these results lead to the counterintuitive prediction of relatively good search performance by infants and toddlers with FXS.

Chapter 6 investigated this directly, by testing visual search for targets amongst distractors. I manipulated the perceptual salience of the targets and relate these changes to measures of temperament designed to load on perceptual sensitivity as well as on inhibitory control. In spite of larger inhibition of return measured in Chapter 5, I found that search by toddlers with FXS turned out not to be better than expected given their developmental level. A striking pattern of errors differentiated their performance from that of typically developing toddlers. Their search was characterised by a large number of perseverative behaviours, a hallmark of difficulties with endogenous control. Furthermore, errors were also differentially affected by perceptual salience.

Despite important notes of caution on the inferences that can be drawn from the different methodologies used in Chapters 5 and 6, the results of Part III point to atypical development of exogenous attention. They therefore highlight that, in neurodevelopmental conditions like fragile X syndrome, it is crucial to focus in depth not only on the areas of largest impairment, but also on areas that in adulthood appear proficient. This in turn highlights the importance of investigating developmental change directly, preferably using longitudinal designs. This is my focus in Part IV, to which we now turn.

Part **IV**

Longitudinal Predictors of Atypical Selection

Part IV – Introductory Synopsis

Part III addressed the issue of whether the early attentional profile in fragile X syndrome is associated not solely with large difficulties with endogenous attention, but also with atypical influences of stimulus-driven processes. However, all the studies discussed thus far could only indirectly capture changes in performance through development, because of the exclusively cross-sectional designs employed. Part IV therefore attempts to trace developmental trajectories in performance by using a longitudinal design.

First, Chapter 7 investigates developmental changes in visual search by collecting longitudinal measures on the task used in Chapter 6 of this thesis. I predicted both similarities and differences in performance by toddlers with FXS when first tested (Time 1) and when re-tested a year later (Time 2). If difficulties in endogenous attention are a stable deficit of toddlers and young children with FXS, they should exhibit the perseverative behaviours that differentiated them from control children in the studies reported in Chapter 6, both at Time 1 and at Time 2. Furthermore, given the relative strengths in visual processing that characterise older children with the syndrome, erroneous touches on distractors may decrease at Time 2 compared to Time 1. Thirdly, older children produce longer distances between successive touches than typically developing controls (Munir et al., 2000), a finding that did not obtain for the toddlers with FXS tested in Experiment 4b. These differences in search path may or may not begin to emerge later in development.

Secondly, I asked whether performance measures at Time 1 predicted performance at Time 2. In particular, the following question was of interest: do processes that at an earlier time-point simply revealed “delay” (i.e., performance at the level of MA controls) predict later deviant performance? The independence of measures that appear initially unrelated should be empirically tested longitudinally, rather than assumed *a priori*.

In summary, this section explores developmental changes in visual search as well as relationships between early and later measures of selection. It therefore tests the role of developmental change in attentional performance in both toddlers with FXS and matched typically developing MA controls.

Longitudinal Changes in Visual Selection

Following longitudinal changes in cognitive processes is a powerful tool for the study of development. First, repeated measurements allow an assessment of the early predictors of variability within a group. This becomes crucial when investigating development in atypical populations. Indeed, large individual variability means that group scores can mask subgroups of children whose performance deviates from the norm across developmental time. Therefore, while it is informative to assess group differences globally between atypical populations and control groups, tracing the precise developmental trajectories of performance for children within groups is equally important. Secondly, while cross-sectional measurements provide information about differences in performance across age groups, collecting multiple data-points on a number of measures allows an assessment of their independence, not only at a particular point in developmental time, but also later/earlier through development. This is critical when studying processes that may mutually influence

each other, both in the adult and in the developing system. For example, studies of grammatical production and comprehension in aphasic patients show that various, apparently distinct, deficits interact in determining performance (Dick, Bates, Wulfeck, Utman, Dronkers & Gernsbacher, 2001). When considering the developing system, studies of early word production and comprehension suggest that, although these may appear independent at some points in development, there are strong developmental correlations between them across time (e.g., Bates, 1993). This reasoning also extends to later linguistic development. For example, longitudinal assessments of a group of young adults who were first assessed as toddlers for language impairments showed that concurrent individual differences in variables like naming speed for digits, non-verbal IQ and executive function all contributed unique variance to language achievement (Young et al., 2002). Can such an approach provide novel insights into domains other than language? Assessing empirically whether attentional measures in typically and atypically developing toddlers are independent or related will be the focus of this Chapter.

7.1.1. Investigating the typical development of attention longitudinally

Theoretical Issues

Different attentional measures may be uncorrelated at particular points in development. Indeed, a number of researchers have proposed the existence of distinct attentional networks and processes involved in endogenous control, spatial orienting and alerting, both in the adult (e.g., Posner & Petersen, 1990; Fan, McCandliss, Sommer, Raz, & Posner, 2001) and in the developing infant (e.g., Colombo, 2001). In the present thesis, I have adopted a broader, but still dichotomising distinction between endogenously and exogenously-driven influences on selection. Results suggest that, at least within the age range of interest for this thesis, performance may vary on tasks that load differentially on the two. For example, Chapter 3 showed that older typically developing children differed from younger toddlers in their ability to control saccades according to informative cues. In contrast, in Chapter 5 the effects of uninformative cues did not vary significantly with age. Measuring differences between attentional measures at each point in development, however, leaves the following question unanswered: are indices of attentional performance neatly segregated across the

entire span of development? It is possible that measures of endogenous control and exogenously-driven effects do not relate at a particular time in development, but that either predicts performance on the other at a later time-point. Cross-sectional designs cannot address questions about the independence of measures across age groups, an empirical issue to be investigated longitudinally here.

Despite the wealth of research on the development of attention in typically developing infants and young children, most studies have focused on cross-sectional comparisons between groups of children of various ages. In some cases, this is motivated by the results of cross-sectional studies themselves. For example, there appear to be few changes in exogenously-driven orienting (Enns et al., 1998), and this is why such processes tend not to be investigated longitudinally. In contrast, longitudinal changes in endogenous control have been examined in more detail. Diamond and colleagues (e.g., Diamond & Doar, 1989; Diamond, 1996; Diamond, Prevor, Callender, & Druin, 1997), for example, report steady improvements on tasks measuring executive functions in typically and atypically developing infants tested longitudinally. Studies by Kochanska and colleagues (e.g., Kochanska, Murray & Harlan, 2000; Kochanska, Coy & Murray, 2001) also found that effortful control on a number of tasks improved steadily during the first four years of age and that greater effortful control predicted concurrent improvements in social development.

But what, if any, are the interactions between endogenous and exogenous influences on children's attention? Oakes, Kannass and Shaddy (2002) addressed this question by assessing the role of object familiarity (i.e., of toys that they had previously seen or not) on distraction latencies during object exploration in infants tested longitudinally at 6.5 and 9 months. When they were older, but not younger, infants took longer to be distracted when they investigated novel, compared to familiar toys. The authors concluded that increasing endogenous control (driven by higher interest in novel objects) interacted with exogenously-driven distractions in the allocation of infants' developing attention. These findings suggest interactions across early attentional development but they beg the question of whether these are correlated to neural changes in specific and independent neural substrates, or whether they reflect interactions across brain circuits.

Neural systems: Developmental changes and their theoretical implications

Diverging views of brain development make distinct predictions with regard to the neural processes underlying changes in attentional selection. If neural networks underlying selection develop independently through maturation, then it is possible that performance supported by their functioning remains independent throughout development. Under this view, the maturation of discrete circuits involved in distinct attentional processes would underlie specific improvements in behavioural performance. Conversely, the damage of specific circuits involved in this maturation would lead to selective deficits in attentional control. Support for this view comes from the study of selective deficits on tasks tapping the functioning of dorsolateral prefrontal cortex (DLPFC) in infants and young children with phenylketonuria (Diamond, 1996; Diamond et al., 1997). The authors argue that selective damage to dopaminergic pathways innervating prefrontal cortex leads to selective deficit on tasks that are known to be dependent on the functioning of DLPFC in human and non-human primates (Diamond & Goldman-Rakic, 1989; Diamond, 1985), but not to other tasks.

There are, however, alternatives to these maturational accounts. For example, Johnson and colleagues (e.g., Johnson, 1998, 2001; de Haan, Humphreys, & Johnson, 2002) have proposed that changes across neural circuits supporting cognitive processing drive and in turn are influenced by changes in others as well as by experience with the environment. Electrophysiological measures of face processing development support the interactive specialisation of function across brain areas and attentional biases guiding developing systems' interactions with the environment (e.g., Halit, de Haan, & Johnson, 2003). Similar biases would also shape and constrain the development of the ability of human infants to detect and follow the direction of gaze of other humans (Farroni, Mansfield, Lai, & Johnson, 2003). These contrasting views on the neural bases of brain development have both been fertile ground for experimenters interested in neurocognitive development. However, as I shall argue henceforth, discriminating between these positions and their predictions requires following developmental change longitudinally. Indeed, this strategy allows one to ask whether performance measures associated with the functioning of particular brain circuits are independent within the same individuals.

7.1.2. Tracing longitudinal trajectories in atypical development

A number of recent studies have investigated the issue of longitudinal interactions between endogenous control processes and other domains of cognition, especially in atypically developing populations. For example, Hughes, Cutting and Dunn (2001) examined longitudinal changes in behaviour by “hard-to-manage” children tested at ages 5 and 7. Children whose pretend play at 4 years of age had shown a preoccupation with violence were more likely to respond negatively in a competitive situation at age 5 and at age 7. Furthermore, 4-year-old children who had performed poorly on tests of theory of mind and executive function showed higher rates of negative behaviour at age 5 but not at age 7. These findings illustrate “just a few of the multiple paths leading to peer problems among children with disruptive behaviour problems” (Hughes et al., 2001, p. 403). Furthermore, longitudinal interactions extend beyond relationships amongst cognitive and behavioural measures of control and extend to the social domain. Moore, Oates, Hobson and Goodwin (2002) have documented even earlier interactions between attentional processes in infants with Down syndrome, the quality of their interactions with their mothers and later effects on joint attention. They found that infants with DS did not differ from typically developing toddlers in the quality of their interactions with their mother. In contrast, the mothers adopted a warmer but more forceful style of interaction, which later predicted reduced focus on triadic interactions. These results highlight the importance of considering interactions between systems and processes, even when these initially appear independent. Furthermore, they illustrate how longitudinal studies of developmental disorders of known genetic origin can provide unique information on the cascade of events leading from underlying neurological causes of early attentional difficulties to later interacting effects of cognitive and social processes.

These empirical findings point to a need to consider carefully the implications of apparently typical performance (as, for example, the responses of infants with DS when tested with the still-face paradigm) on later performance. Moreover, there are theoretical and logical reasons for examining possible interactions between attentional processes, without assuming a priori their independence. Karmiloff-Smith, Scerif and Ansari (2003) addressed some of them. If atypically developing individuals perform at the level of younger typically

developing controls, should this equivalent performance be dismissed as “simple delay”? Careful considerations warn against this. At each particular developmental time-point, a process A may result in equal performance for FXS and MA controls (as was the case, for example, for search speed and path in Experiment 4b). Now hypothesise that, at a later time-point, performance on a second process B deviates from that of the (younger) control population. If processes A and B are related across time-points, variability on process A at Time 1 may predict atypical performance on process B at Time 2. This would in turn render so-called “simple delay” on process A a complex predictor of later deviance on process B. Dismissing delay amounts to implying that processes A and B are developmentally independent, an issue for empirical investigation, rather than a priori assumptions.

Implications for fragile X syndrome: Research questions

Parts II and III showed that infants and toddlers with fragile X syndrome display deficits in the endogenous control of orienting and response selection, as well as delay and atypical performance on tasks that load more on exogenously-driven processes. Chapter 1, however, detailed how a neurodevelopmental approach would highlight the need to investigate the developmental changes associated with each of these processes and the potential interactions between them. This is indeed the focus of the present chapter.

First, Experiment 5a investigates developmental changes in visual search by collecting longitudinal measures on the task used in Chapter 6 of this thesis. Do group differences and similarities in performance remain “static” across developmental time? The studies by Paterson et al. (1999) discussed in Chapter 1 already warned against making this assumption. Secondly, I asked whether performance measures at Time 1 predicted performance at Time 2. In particular, I was interested in the following questions: 1) Do processes that at an earlier time-point simply revealed “delay” (i.e., performance at the level of MA controls) predict later deviant performance? 2) Is variability across measures of performance correlated?

7.2. Experimental data

7.2.1. Experiment 5a. Longitudinal changes in search performance

As I discussed in section 7.1, longitudinal designs allow researchers to ask the following question: do performance markers for certain cognitive processes change across developmental time? Earlier comparisons between groups of infants and adults with Williams and Down syndromes warned against this static view of atypical cognitive development (Paterson, et al., 1999), but the extent to which infant and adult performance can be compared has been questioned. Differences in performance could at least in part depend on infant and adult paradigms measuring distinct constructs. In contrast, using identical tasks, validated across the age range of interest, makes it possible to compare performance directly. The aim of this experiment was therefore to investigate longitudinal changes in search performance in a sample of toddlers with FXS and individually matched controls. The typically developing toddlers were selected to match the developmental level of toddlers with FXS at Time 1 and were then re-tested when they reached the developmental level of FXS toddlers at Time 2. This would test whether changes in their performance were smaller or larger than expected, given their overall slower rate of development.

Predictions on both longitudinal changes and stable differences derive from comparing the results discussed in Experiment 4b and data from older children with fragile X syndrome (Cornish et al., 1999; Munir et al., 2000). The results of Experiment 4b suggest that, like older children with the syndrome, toddlers with FXS exhibit difficulties in inhibiting previously correct, but now inappropriate responses. I predict that these difficulties will remain evident at Time 2, as they characterise performance of older children with the syndrome (Munir et al., 2000). Furthermore, given the relative strengths in visual processing that characterise older children and adults with the syndrome (Cornish et al., 1999), erroneous touches on distractors will decrease at Time 2 compared to Time 1. Finally, older children with FXS produced longer search paths than controls, a finding that did not obtain for the toddlers of Exp. 4b. If equivalent search path to MA controls eventually changes into group differences may reveal initial changes in this direction.

Method

Participants

Participants were a sub-sample of the children whose data were presented in Experiment 4b. The included toddlers with FXS were the only children in the group who successfully completed the search task at both Times 1 and 2. I investigated the development of their performance within a 12 month interval to provide two data points for each boy (age range: 34-50 months at Time 1; 46-62 months at Time 2; developmental level measured using the BSID-M: 23-36 months at Time 1; 24-42 months at Time 2). Eight typically developing toddlers were also tested longitudinally (henceforth, “MA controls”), matching them individually to the boys with FXS by their general developmental level at Times 1 and 2. This meant that: a) MA controls were selected to match individually the developmental level of toddlers with FXS at Time 1; b) they were then tested for the second time at variable intervals of time (range: 1-6 months), in order to match the developmental level of their individual FXS match. I chose this matching procedure because the mental age equivalents of toddlers with FXS, both at Time 1 and 2, were sufficiently varied that it would not have been appropriate to test a group of younger typically developing toddlers within a restricted age range at Time 1 and 2. Thus, children with FXS were matched individually to MA controls. This would make it possible to test whether the pattern of errors by children with FXS changed over time more than expected given their overall changes in developmental level. Toddlers with FXS did not differ from their individually matched controls in developmental level measured on the BSID-M either at Time 1, $t(14) = 0.048$, $p = 0.963$, or at Time 2, $t(14) = 0.119$, $p = 0.907$.

Procedure

As in Experiments 4a and 4b (Chapter 6).

Statistical Analyses

The average number of correct and erroneous touches (accuracy measures), the average time to find targets corrected for false alarms (search speed measure) and the average distance between successive touches (search path measure) were calculated for each toddler at Time

1 and 2, as described in Chapter 6. All these dependent variables were tested for normality and homogeneity of variance before being entered in mixed factor ANOVAs with Time (time 1, time 2), Target-distractor similarity (similar, dissimilar) and Distractor number (6, 24) as the within-subject variables and Group (FXS, MA) as the between-subject variable. Changes in baseline performance were measured separately in 2 (time: 1 and 2) x Group (FXS, MA) mixed factor ANOVAs.

Results

In summary, as for the cross-sectional sample in Chapter 6, toddlers with FXS made more errors in the search task than the control toddlers. Toddlers with FXS differed from the other group in repeatedly touching targets that had already been found, on both experimental (nontargets present) and baseline (targets only) trials. When such repetitions were further divided into immediate repetitions versus later returns to previously touched targets, toddlers with FXS produced more of both types of repetitive errors per hit than the other group. Immediate repetitions per hit for this group were not affected by the presence or appearance of distractors, but later returns per hit were, suggesting that the latter but not the former type of repetitions depended on the requirement to search amongst distractors. Performance by FXS toddlers was also influenced by the perceptual salience of the targets. Indeed, toddlers with FXS touched significantly more distractors than typically developing children when there were many distractors and when they were similar to the targets, a pattern that was less marked in the typically developing controls. Despite differences in error patterns, the toddlers with FXS did not produce overall longer search speed and path than expected given their developmental level. However, there were interesting changes in performance over time. All children, both with and without FXS, decreased the number of perseverative behaviours, although children with FXS continued to produce more perseverative errors than typically developing younger controls. The similarity between targets and distractors also affected longitudinal changes in the time to find targets: toddlers with FXS took differentially longer to find targets amongst similar distractors at time 2 than at time 1. Moreover, toddlers with FXS were more systematic in searching for targets amongst many distractors, rather than few distractors. All these empirical findings were supported statistically as follows.

Analyses of Accuracy

Toddlers with FXS made fewer correct touches than MA controls, $F(1, 14) = 14.164$, $p = .002$. Fewer correct touches were made for targets amongst similar distractors, $F(1, 14) = 8.080$, $p = .013$, and numerous distractors, $F(1, 14) = 6.661$, $p = .022$. Toddlers made more correct touches at Time 2 than at Time 1, $F(1, 14) = 10.378$, $p = .006$, but this effect of time interacted with Group, $F(1, 14) = 9.421$, $p = .008$. Indeed, toddlers with FXS significantly improved their accuracy at Time 2 (6.9 hits on average) compared to Time 1 (5.67 hits), $F(1, 7) = 10.223$, $p = .015$. In contrast, MA controls did not improve the number of accurate touches, $F(1, 7) = .179$, $p = .685$, because they produced few errors both at Time 1 and 2 (7.9 hits on average at Time 1 and 2, with the maximum number of hits being 8). Furthermore, toddlers with FXS produced more hits with distractors that were dissimilar rather than similar to targets, $F(1, 7) = 5.877$, $p = .046$ and with displays containing fewer distractors, $F(1, 7) = 6.830$, $p = .035$. In controls, by contrast, accuracy was not affected by manipulations of target salience, lowest $p = .095$ for distractor similarity. Toddlers with FXS made less correct touches than MA controls on baseline runs ($F(1, 14) = 9.610$, $p = .008$), but this effect did not change across developmental time ($p = .176$), nor was there a significant interaction. Non-parametric statistics were also used to test differences in the number of hits, due to heterogeneous variances (mainly caused by low numbers of errors in the controls). At Time 1, toddlers with FXS made significantly fewer correct touches than MA controls (Mann-Whitney U, p levels ranging from .038 to .002, Exact significance to control for the small sample size) across all experimental conditions, except for the all-target displays ($p = .234$). At Time 2, toddlers with FXS did not differ from MA controls in terms of accurate touches, except for the condition with few medium distractors ($p = .038$).

Overall errors were transformed using a square root transform because variances were not homogeneous (and positively skewed, lowest $p = .004$). The transform succeeded in not violating assumptions of ANOVA (lowest $p = .06$). Group had a main effect, $F(1, 14) = 14.431$, $p = .002$. Toddlers with FXS made 7.24 errors on average, whereas MA controls made 2.34 errors. The errors decreased with Time, $F(1, 14) = 11.706$, $p = .004$. Toddlers made more errors at Time 1 than Time 2 (6.0 errors on average, as opposed to 3.58). Distractor similarity affected the number of errors, $F(1, 14) = 14.074$, $p = .002$. More errors were made when distractors were very similar to targets (5.57 errors on average), as opposed

to dissimilar (4.0 on average). There was also a trend for distractor similarity and number to interact, $F(1, 14) = 4.129$, $p = .062$. More errors were made when there were many distractors that were similar to targets (6.19 errors on average) than when there were few (4.95 errors on average). This was not the case for few and many dissimilar distractors (4.06 and 3.97 errors on average). None of the other main effects nor interactions were statistically significant.

Erroneous Touches on distractors.

Figure 7.1 displays mean touches on distractors as a function of target-distractor similarity, distractor number, time and group. Variances were not homogeneous (Kolmogorov-Smirnov test, lowest $p < .001$), and a square root transformation did not succeed in obtaining homogeneous variances for the data (lowest $p = .001$), suggesting caution in interpreting statistically significant effects from the following parametric statistics. There was a main effect of Group, $F(1, 14) = 7.728$, $p = .015$. Toddlers with FXS made more errors of this kind than typically developing toddlers (1.915 touches on distractors vs. .781 on average). The similarity of targets and distractors affected the number of touches on distractors, $F(1, 14) = 31.831$, $p < .001$. Distractors that were very similar to targets yielded more errors on distractors (on average, 1.98 touches on distractors) than those that were dissimilar to the targets (.719 +/- .17). There was a main effect of distractor number, $F(1, 14) = 10.104$, $p = .007$. Many distractors resulted in more touches on them than few (1.01 vs. 1.69 touches on distractors). Distractor similarity and Group interacted, $F(1, 14) = 6.560$, $p = .023$. Analyses of simple effects revealed that this interaction originated in relatively more distractor touches by children with FXS for distractors that were similar (2.8 errors) than dissimilar (1 on average), $F(1, 7) = 27.549$, $p = .001$. This difference was not as large for typically developing toddlers (1.12 Vs .44), $F(1, 7) = 6.094$, $p = .043$. Number of distractors and Group interacted, $F(1, 14) = 6.712$, $p = .021$. The sources of this interaction depended on toddlers with FXS producing more distractor touches with many than few distractors (2.53 Vs. 1.3 on average), $F(1, 7) = 12.255$, $p = .01$. This difference was not statistically significant for MA controls (.84 vs. .72 on average), $F(1, 7) < 1$, $p = .620$.

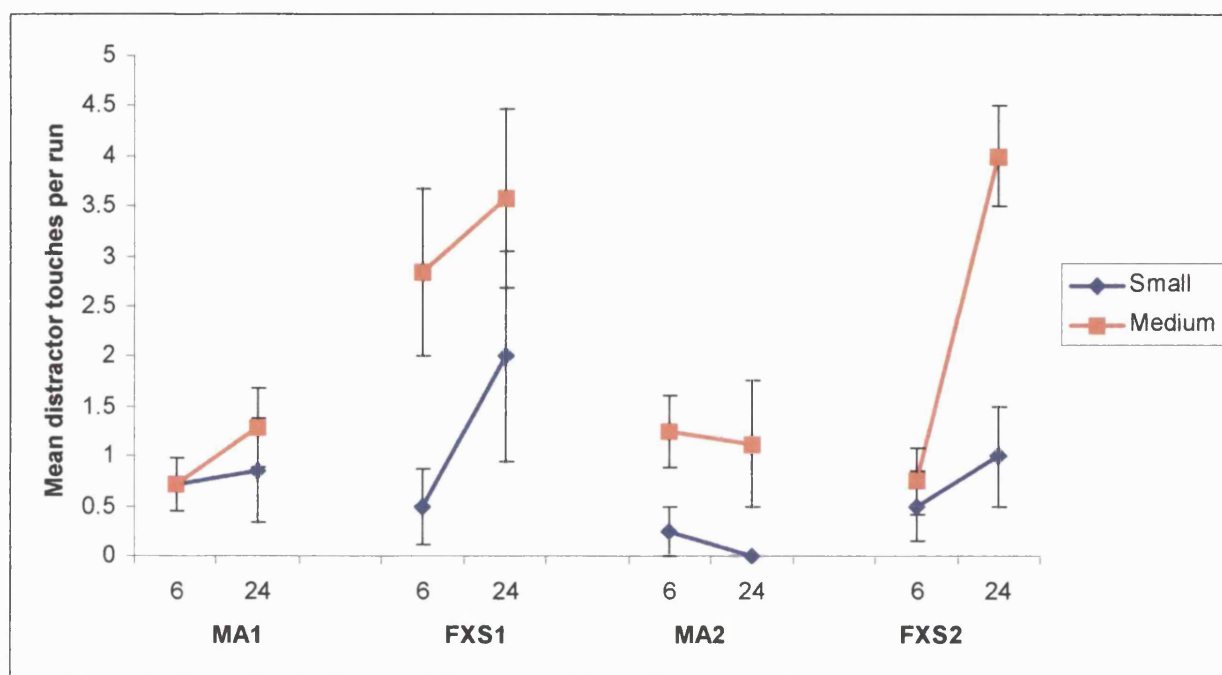


Figure 7.1. Average number of erroneous touches on distractors at Time 1 and 2 as a function of group, target-distractor similarity and number for toddlers with FXS at Time 1 (FXS1) and 2 (FXS2) and individually matched controls (MA1 and MA2). Red lines are for similar (medium) distractors and blue lines are for dissimilar (small) distractors.

Furthermore, these errors showed a tendency to change with time, $F(1, 14) = 4.022$, $p = .065$. There tended to be more touches on distractors at Time 1 than at Time 2 (1.57 vs. 1.13 touches on distractors). None of the other main effects nor interactions were statistically significant. In order to address concerns about the violation of homogeneity of variance, the differences between groups across conditions were also tested non-parametrically. At Time 1, toddlers with FXS produced significantly more erroneous touches on distractors than controls when distractors were similar to targets (few: $Z = 2.017$, $p = 0.05$, exact significance; many: $Z = 2.039$, $p = 0.05$, exact significance). At Time 2, toddlers with FXS produced more erroneous distractor touches than controls when distractors were many and similar to targets, $Z = 2.254$, $p = 0.028$, exact significance. Also, toddlers with FXS produced more errors of this kind when there were many distractors and these were similar to targets (Wilcoxon Signed Ranks Test, $Z = 1.973$, $p = .049$, exact significance).

Repetitions on previously touched targets.

Figure 7.2 displays mean repetitions per hit on previously found targets as a function of time and group. The total number of repeats was divided by the number of hits to account for the difference between groups in the overall number of hits. Homogeneity of variance was violated (lowest $p = .009$) and a square root transform did not succeed in meeting this assumption of ANOVA. Group had a main effect, $F(1, 14) = 14.942$, $p = .002$. Toddlers with FXS made on average .62 repeats per hit, whereas, MA controls only made .13. These effects changed with time, $F(1, 14) = 13.260$, $p = .003$. More repeats occurred at Time 1 (.54 repeats per hit on average) than Time 2 (.26). Time and Group interacted, $F(1, 14) = 5.176$; $p = .039$. An analyses of this interaction effect, split by group, revealed that toddlers with FXS produced more repeats per hit at Time 1 than at Time 2, $F(1, 7) = 11.065$, $p = .013$. This change was not statistically significant for MA controls, $F(1, 7) = 2.232$, $p = .179$. For displays that contained targets only, toddlers with FXS produced more repeats than MA controls, $F(1, 14) = 10.364$, $p < .001$ at Time 1 and at Time 2 there was a trend in a similar direction, $F(1, 14) = 3.529$, $p = .09$. Non-parametric statistics showed that toddlers with FXS produced significantly more repeats per hit than MA controls for all conditions at Time 1 and 2 (Mann-Whitney U, p ranging from .003 to .05, exact significance). Exceptions were the condition with few dissimilar distractors ($p = .105$, exact) and the all-target displays ($p = .065$, exact) at Time 2 only.

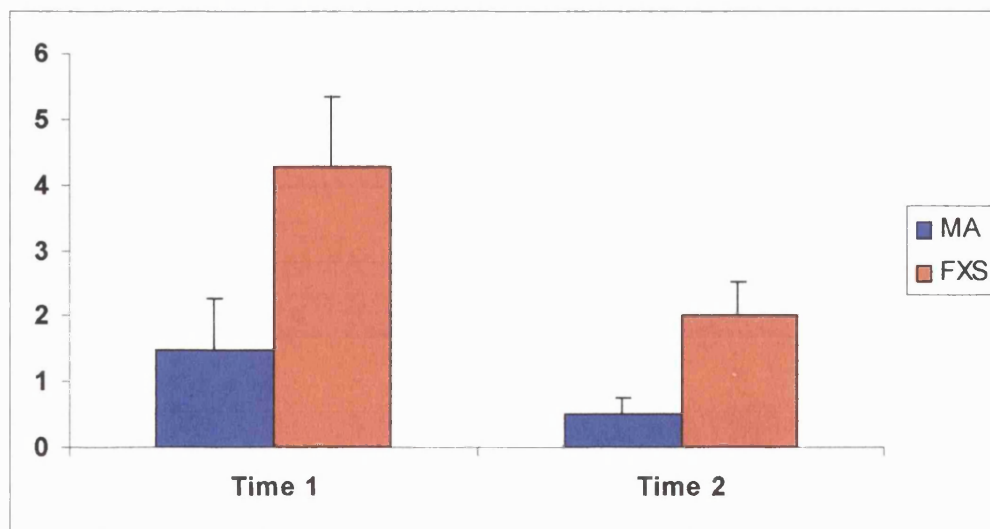


Figure 7.2. Average number of erroneous touches on distractors at Time 1 and 2 as a function of group and time. Red bars are for toddlers with FXS, blue bars are for control toddlers.

To investigate repetition errors further, these were subdivided into immediate repetitions versus later returns to previously touched targets (with the latter errors requiring at least one intervening touch on another item before returning to a particular target). Because many children in the control group committed few immediate repetitions per hit, these data were not normally distributed and transformations did not succeed in meeting the assumptions of ANOVA, (lowest $p = .003$). Thus, non-parametric statistics were also used for group comparisons. Toddlers with FXS produced significantly more immediate repetitive errors than MA controls (on average, .47 immediate repeats per hit, whereas MA controls made .096 repeats per hit) in the conditions containing distractors, $F(1, 14) = 12.664$, $p = .003$. In the baseline condition, FXS toddlers also produced more immediate repeats than MA controls, $F(1, 14) = 8.063$, $p = .016$, both at Time 1 and 2 ($p = .06$ and $.128$ for the effects of time and the interaction of time and group, respectively). The high number of immediate repeats in toddlers with FXS appears consistent with the dysexecutive perseverative tendency (Shallice, 1988) documented in Chapter 6. All toddlers made more immediate repeats per hit when distractors were dissimilar, rather than similar to targets (.30 vs. .26 immediate repeats per hit respectively), $F(1, 14) = 14.380$, $p = .002$. Furthermore, the number of immediate repeats per hit changed with time, $F(1, 14) = 11.852$, $p = .004$. At time 1, toddlers made .42 immediate repeats per hit, whereas at Time 2, they made .14 repeats of this kind. Time and group interacted, $F(1, 14) = 5.052$, $p = .041$. At Time 1, toddlers with FXS made .69 immediate repeats per hit whereas MA controls made .23 errors of this type on average. At Time 2, toddlers with FXS made .14 immediate repeats per hit, whereas MA controls made .05 errors of this kind. Toddlers with FXS produced more immediate repeats per hit at Time 1 than at Time 2, $F(1, 7) = 10.140$, $p = .015$, whereas MA controls did not significantly decrease the number of this type of errors, $F(1, 7) = 1.771$, $p = .225$, probably because these were low at both times. In spite of their improvement, toddlers with FXS continued to differ from MA controls in the immediate repeats per hit at Time 2, $F(1, 14) = 21.361$, $p < .001$. When these group differences were tested non-parametrically, toddlers with FXS produced significantly more immediate repeats per hit than MA controls in all conditions both at Time 1 and 2, (Mann-Whitney U, p ranging from .034 to .004, exact significance), except for the conditions with few similar distractors, ($p = .161$ and $.234$ at Time 1 and 2 respectively). None of the other main effects or interactions were statistically significant.

Most of the toddlers in the control group produced few returns to previously touched targets, so that variances were not homogeneous, lowest $p = .001$. Therefore the data were analysed both parametrically and non-parametrically. Toddlers with FXS made .15 return per hit, whereas MA controls made .031 errors of this type, a statistically significant difference, $F(1, 14) = 7.229$, $p = .018$. In general, more returns were made when distractors were similar than dissimilar to the targets (.13 Vs. .05 returns per hit on average), $F(1, 14) = 21.792$, $p < .001$. Group and distractor similarity interacted, $F(1, 14) = 11.598$, $p = .004$. Toddlers with FXS made .23 returns per hit when distractors were similar to the targets, in contrast with .08 such errors when the two were dissimilar. In contrast, MA controls made .04 errors of this type for similar distractors, and .02 for dissimilar ones. Toddlers with FXS produced more such returns with similar than with dissimilar distractors, suggesting that this type of repetitive error by toddlers with FXS was influenced by the display properties, whereas this was not the case for MA controls. Indeed, there was a statistically significant effect of distractor similarity for toddlers with FXS, $F(1, 7) = 19.422$, $p = .003$, but not for MA controls, $F(1, 7) = 2.177$, $p = .16$. On baseline runs, toddlers with FXS and MA controls did not differ in the number of returns to targets per hit, $p = .10$. Furthermore, there were changes in these types of error over time. The number of returns per hit decreased, $F(1, 14) = 4.574$, $p = .051$. More returns were made at Time 1 than at Time 2 (.12 vs. .06 returns per hit). Analyses of simple effects revealed that FXS toddlers produced more returns per hit than MA controls for distractors that were dissimilar to targets at Time 1 ($p = .04$, equal variances not assumed). They also produced more of these returns when distractors were similar to targets, both at Time 1 ($p = .07$, equal variances not assumed) and at Time 2 ($p = .026$, equal variances not assumed). None of the other main effects nor interaction reached significance, lowest $p = .071$ for the interaction between time and distractor similarity. Non-parametric tests revealed that toddlers with FXS produced significantly more returns per hit when distractors were similar to targets, at Time 1 ($p = .025$ and .06 for few and many distractors respectively) and at Time 2 ($p = .09$ and .025 for few and many distractors respectively).

Analyses of Search Speed and Search Path

Figure 7.3a and b represent search speed and path for typically developing toddlers and toddlers with FXS at Times 1 and 2, as a function of target-distractor similarity and number of distractors. Time per hit (corresponding to time taken to find targets, corrected for errors) and distance between successive touches (the measure of search path) were tested for normality (Kolmogorov-Smirnov test) and homogeneity of variance (Levene's test). These variables were not all normally distributed (lowest $p = 0.001$) and I therefore applied a natural logarithmic transformation to the data. The transformation did not succeed in normalising the data for the speed variable, lowest $p = .003$, but it was successful for the distance measure, lowest $p = .07$.

Toddlers were faster to find targets when there were few vs. many distractors (1.76 vs. 2.16 seconds on average), $F(1, 14) = 5.489$, $p = .034$. Distractor similarity also had a main effect on time to find targets, $F(1, 14) = 4.334$, $p = .056$. Toddlers found targets faster amongst dissimilar distractors (1.75 seconds) than amongst similar distractors (2.17 seconds). Group did not have an effect on overall time per hit, $F(1, 14) = 2.711$, $p = .071$, suggesting that once total search time was corrected for the time spent in incorrect touches, toddlers with FXS found targets in the same amount of time as controls. However, distractor similarity and number interacted with group, $F(1, 14) = 6.743$, $p = .026$. Indeed, there was a main effect of distractor similarity for toddlers with FXS, $F(1, 7) = 8.877$, $p = .021$, but not for MA controls. Search speed did not change across testing sessions, $F(1, 14) = .217$, $p = .649$. However, there was a statistically significant interaction between time, distractor similarity and group, $F(1, 14) = 6.225$, $p = .026$. Analyses of simple effects revealed that the two groups of toddlers did not differ in the time taken to find targets at Time 1 and Time 2 (independent t-tests, lowest $p = .11$; Mann-Whitney U, lowest $p = .195$). Nonetheless, toddlers with FXS were slowest with distractors that were similar to targets (2.5 seconds) than those that were dissimilar to targets (1.6 seconds) at Time 2 (paired t-test: $t(7) =$; Wilcoxon Signed Ranks test: $Z = 2.521$, $p = .012$), but not at Time 1 ($p =$ and $.484$ for parametric and non-parametric tests respectively). There were no differences between the two groups in time to find targets during baseline runs, $p = .928$. None of the other main effects or interactions was significant (p levels from $.119 - .859$).

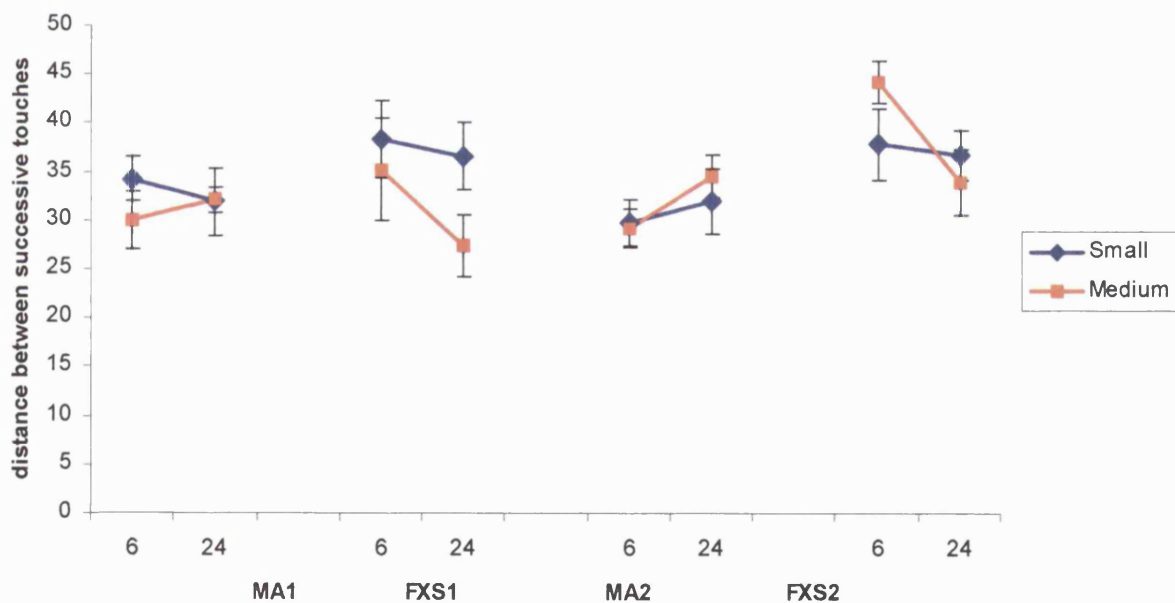
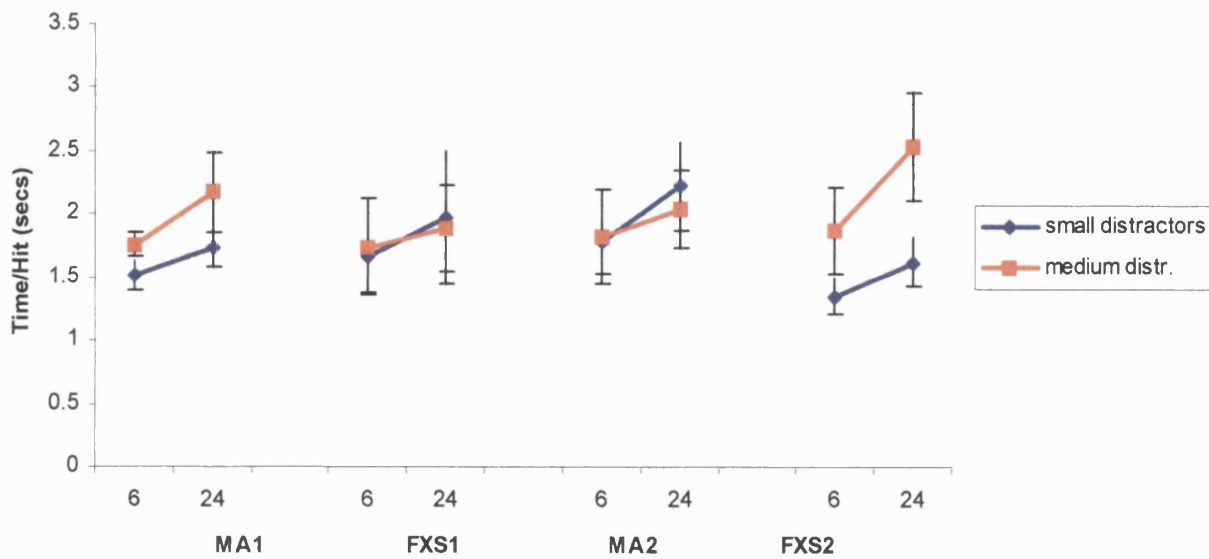


Figure 7.3. a) Mean search speed corrected for false alarms as a function of group, time, distractor number (6 and 24), similarity between targets and distractors (blue, dissimilar; red similar distractors to targets). Groups are MA controls at Time 1 and 2 (MA1 and MA2), and FXS toddlers at Time 1 and 2 (FXS1 and 2).

In terms of the search path, there was a trend towards a main effect of Group, $F(1, 14) = 3.834$, $p = .070$, with toddlers with FXS tending to produce longer distances between successive touches than controls (36.22 twips on average, whereas MA controls produced distances of 31.6 twips)². The effects of Group and the similarity of targets and distractors on search path interacted, $F(1, 14) = 9.636$, $p = .008$. Toddlers with FXS, but not MA controls ($p = .827$), produced longer distances when distractors were dissimilar, rather than similar to targets (39.18 vs. 33.26 twips on average), $F(1, 7) = 7.871$, $p = .026$. There were no differences in distance between successive touches on baseline runs, $F < 1$, $p = .430$ and this did not change with time ($F = 1.795$, $p = .202$). All other effects and interactions did not reach significance, $F < 1$, $p > .05$.

Discussion

The results of Experiment 4b and those obtained with older children with FXS led me to generate the following predictions: (1) Perseverative errors, characterising both younger toddlers and older children with the syndrome, should remain a prominent feature of their performance. (2) The difficulties in discriminating correctly between targets and distractors would decrease with time, leading to relatively unimpaired target-distractor discriminations in the tasks used by Munir et al. (2000), as well as on standardised visuo-perceptual tasks (Cornish et al., 1999). (3) After correcting for the time spent making erroneous touches, there would not be any group differences in search speed, but differences in search path may emerge at Time 2. The current findings met some of these predictions, but they also documented some unexpected similarities and differences compared to Time 1.

Let us first examine the similarities in performance across testing sessions. Children with FXS continued to produce more perseverative errors than typically developing younger controls, although they decreased the overall number of these errors. These findings support earlier results and they suggest that the ability to inhibit previously rewarded but later incorrect responses, a hallmark of executive attention, remains a stable area of difficulty in FXS throughout the toddler years. This suggestion is corroborated by the difficulties in

² Here distance measures are reported in twips (a Visual Basic measure, with 1 twip corresponding to 1/1440 of an inch), following Munir et al. (2000) and Wilding et al. (2002). The conversion to cm in Chapter 6 was requested by one of the co-authors in Scerif et al. (in press). However, all analyses were run on twips across Chapters 6 and 7.

controlling reflexive looks towards peripheral stimuli independently of children's mental age (Chapter 3) and by the larger number of switching errors (Chapter 4). Unexpectedly, toddlers with FXS continued to produce more erroneous touches on distractors than controls, pointing to difficulties in discriminating targets whose perceptual salience is reduced by the size characteristics of the distractors. Moreover, their average distance between successive touches, indexing the systematicity of the search path, was also differentially affected by the similarity of targets and distractors. Contrary to the effects found for typically developing toddlers in Experiment 4a, toddlers with FXS were less systematic in their search amongst dissimilar rather than similar distractors. This atypical effect of target salience could be explained in a number of ways. In typically developing toddlers, the search path measure seems primarily influenced by the ability to organising systematic search amongst distractors, as is suggested by the age-related improvements on this measure. In contrast, search path in toddlers with FXS may be dominated by other factors, unrelated to systematicity, like for example differences in the density of the search displays. Indeed, the denser the stimulus display, the faster the speed of target detection (Motter & Holsapple, 2000), suggesting that the passive constraints of stimulus density combine with the active selection for a stimulus attribute (in this case, distractor size) in order to orient towards and find a target. Displays containing similar distractors are denser than those containing dissimilar ones and toddlers with FXS may differentially rely on this perceptual aspect of the visual display to find targets, rather than on systematic search. This counters, and questions at least in part, reports of spared perceptual processing in older children with the syndrome. Indeed, these findings are supported by effects on the functioning of the magnocellular pathway in primates lacking FMRP and has stimulated renewed interest in more detailed investigations of visual processing difficulties in fragile X syndrome (Cornish, pers. comm.). Secondly, new group differences emerged at Time 2. Although search speed by toddlers with FXS was equivalent to that of controls, at Time 2 speed was differentially more influenced by target perceptual salience.

Taken together, these results highlight the importance of following performance longitudinally, rather than assuming a static view of cognitive strengths and weaknesses at each point in development (see discussions in Karmiloff-Smith, 1998; Paterson et al., 1999).

7.2.2. Experiment 5b. Early Predictors of Visual Search Performance.

Experiment 5a addressed the following question: does performance on multiple attentional measures change over and above what is expected given overall changes in FXS toddlers' developmental level? The results suggested differences and similarities in performance on each measure, compared to controls. However, the type of analyses conducted did not address the second question raised in section 7.1: Are measures of attentional performance independent across development? Experiment 5b consisted of a re-analysis of the results, exploring the predictive value of early measures of search performance.

A factor analytic approach incorporating multiple measures from all tasks used at Time 1 would have addressed elegantly the questions set above. It would have best investigated the complexities of attentional development in a neurodevelopmental condition like fragile X syndrome. However, practical issues did not make it possible to use such an approach. Too small a number of children successfully completed tasks other than the search task. This meant that the data-points available for analyses of, for example, the predictive power of antisaccade measures at Time 1 on search performance at Time 2 were limited. Therefore, the focus remained primarily on the results from the visual search task.

Method

Participants

Same as above.

Statistical Analyses

The aim of these analyses was the following: were measures revealing strengths and weaknesses at Time 1 independent of each other? Would measures showing "simple delay" at Time 1 predict later atypical performance? In particular, I aimed to examine the predictive power of early measures of endogenous control that best differentiated MA controls from

toddlers with FXS (e.g., erroneous touches on previously touched targets) and of the early effects of the manipulation of target-distractor similarity. A linear regression design was used to examine the predictive power of Time 1 performance on search at Time 2. Due to the limited sample size (and therefore low statistical power), the number of variables of interest was reduced by firstly calculating an average of search path, speed and error measures across the four experimental runs ("Average effects"). Secondly, a difference score was calculated for search path, speed and error types with similar and dissimilar distractors ("Similarity effects"). This second set of variables would allow me to investigate whether differential effects of target perceptual salience at Time 1 predicted later search performance.

When performing linear regression analyses, it is crucial to identify whether multiple predictor variables are highly correlated (Howell, 1996; Miles & Shevlin, 1992). In order to eliminate highly collinear variables, preliminary correlational analyses were run to isolate independent predictors to be entered in the regression analyses. These initial analyses revealed that all types of errors at Time 1 (total false alarms, coded as AVEFA1; total repeats per hit, coded as AVEREP1; total touches on distractors, coded as AVETODIS1) correlated with each other, lowest $r(16) = .615$, $p = .011$, 2-tailed. Therefore, the average number of false alarms (AVEFA1) was chosen as a predictor variable that would subsume the other two. However, average distance between successive touches (AVEDIS1), search speed (AVETI1) and all similarity effects did not correlate with each other, lowest $p = .07$, 2-tailed. The latter were computed as the difference between arrays containing similar and dissimilar distractors in terms of distance, SIMDIS1; speed, SIMTI1; repeats per hit, SIMREP1; and touches on distractors, SIMSICO1. Therefore, they were all considered as potential predictors of performance at Time 2. Having isolated potential predictors of performance at Time 2, I entered these variables into multiple regression, using Group as a predictor variable (coded as a dummy variable, FXS = 0, MA = 1). When Group resulted to as a statistically significant predictor of later performance, it was re-entered in the regression equation with the interaction of group and the other predictor variables as an additional predictor. Furthermore, linearity of the relationships, normality and equality of variance for the distributions of variables were evaluated by plotting all variables.

Results

In summary, various patterns of relations across variables at Time 1 and 2 emerged. As expected, variability within some measures predicted later performance on those same measures: the average number of false alarms at Time 1 predicted errors at Time 2 and the average search speed at Time 1 predicted speed at Time 2. The larger the number of false alarms and the slower the speed at Time 1, the larger and slower respectively these measures were at Time 2. Furthermore, some variables at Time 1 predicted later performance on earlier unrelated variables at Time 2. The size of the effect of target-distractor similarity on erroneous touches on distractors at Time 1 predicted its effect on search speed at Time 2. Indeed, the larger the effect of similarity, the slower the effect on speed later. Finally, the average number of false alarms at Time 1 predicted the distance between successive touches at Time 2, with longer distances predicted by more errors at Time 1. These empirical findings were statistically supported as follows.

Preliminary correlational analyses between measures at Time 1 and Time 2 were conducted to reduce the number of multiple regression analyses and hence the probability of Type II errors. These correlations are reported in Table 7.1. These relationships amongst variables were always plotted to determine whether they were linear or whether they were driven by outliers. This was the case for one of the statistically significant correlations, the correlation between the effect of similarity on search speed at Time 1 and the similarity effect on repetitions per hit at Time 2. Therefore, this was dropped from further analyses as it would violate the assumption of linear relationships amongst predictors and dependent variables in multiple regression. On the bases of these exploratory correlations, I ran separate multiple regression analyses on search speed, path and errors at Time 2.

Time 2

<i>Time 1</i>		<i>AveDis2</i>	<i>AveTi2</i>	<i>AveFa2</i>	<i>SimDis2</i>	<i>SimTi2</i>	<i>SimFA2</i>	<i>SimSiCo2</i>	<i>SimRep2</i>
	<i>AveDis1</i>	.358	.261	.290	-.442	.041	-.040	-.011	.350
	<i>AveTi1</i>	.044	.613*	-.147	-.078	.513*	-.133	-.181	.116
	<i>AveFa1</i>	.650**	.102	.772**	-.353	.297	.041	.480	.286
	<i>SimDis1</i>	-.284	-.081	-.524*	-.024	-.123	.015	-.028	-.035
	<i>SimTi1</i>	-.108	.376	-.277	-.025	-.097	-.453	-.428	-.658**
	<i>SimFA1</i>	.087	.272	.293	-.139	.407	.147	.111	.391
	<i>SimSiCo1</i>	.101	.353	.118	.485	.607*	.442	-.341	.243
	<i>SimRep1</i>	-.056	.157	.202	-.452	.088	-.343	.174	.292

Table 7.1. Correlations between measures at Time 1 and measures at Time 2. Abbreviations terminating in 1 refer to Time 1, those abbreviations terminating in 2 refer to Time 2. * marks significance levels below 0.05, ** marks a significance level below 0.01. Furthermore, as discussed in the text, the following abbreviations apply: AVEDIS = average distance between successive touches (search path measure). AVETI = average time per hit (search speed measure). AVEFA = average false alarms per run (accuracy measure). SIMDIS = similarity effect on distance (= distance between successive touches for similar distractor displays minus distance for dissimilar distractor displays). SIMTI = similarity effect on time (= time per hit for similar distractor displays minus distance for dissimilar distractor displays). SIMFA = similarity effect on false alarms per run (= false alarms for similar distractor displays – distance for dissimilar distractor displays). SIMSICO = similarity effect on size confusions, i.e., touches on distractors (= distractor touches for similar distractor displays minus distance for dissimilar distractor displays). SIMREP = similarity effect on repeats per hit (= repeats per hit for similar distractor displays minus distance for dissimilar distractor displays).

Predictors of Search Accuracy

A regression model including Group, Average errors (AVEFA1) and the effects of target-distractor similarity on search path at Time 1 (SIMDIS1) significantly predicted 70% of the variance for the number of errors at Time 2 (AVEFA2), $F(3, 15) = 9.757$, $p = .002$. Out of the three predictors, the average number of errors at Time 1 significantly predicted AVEFA2. The larger the number of false alarms at Time 1, the larger at Time 2, $\beta = .551$, $t = 2.563$, $p = .025$, whereas group membership and similarity effects on search path did not predict significantly variability in errors at Time 2 ($p = .083$ and $.392$ respectively). The relationship between errors at Time 1 and 2 is illustrated in Figure 7.4.

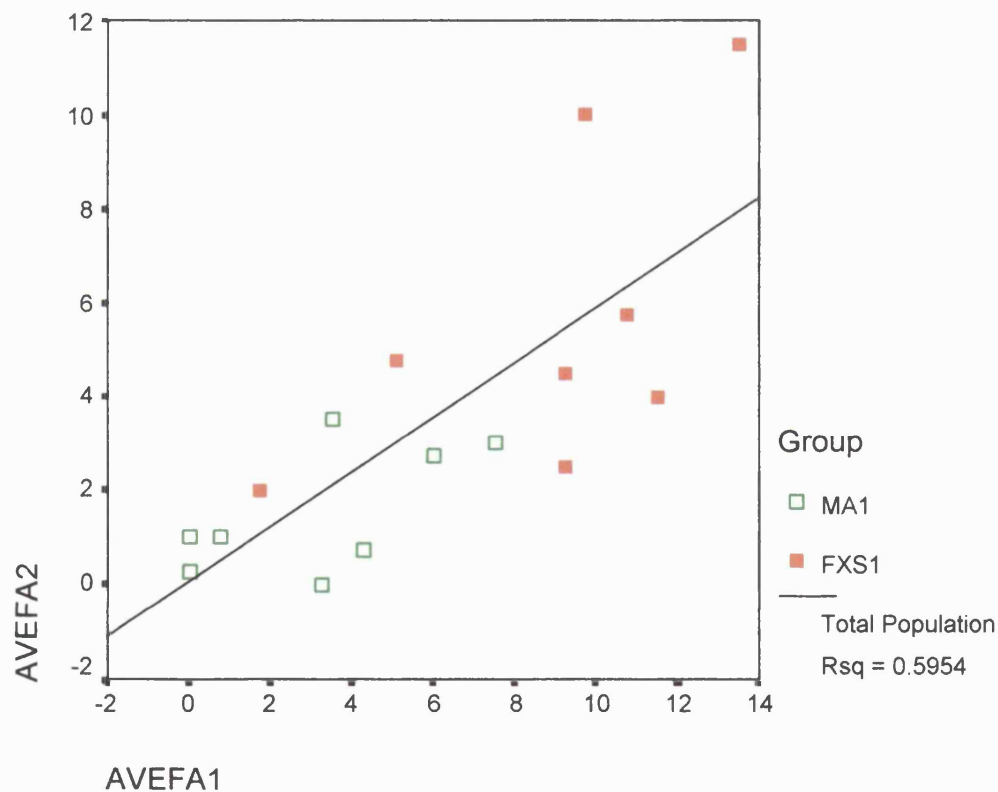


Figure 7.4. Average number of search errors at Time 2 as a function of the average number of errors at Time 1. Red full squares indicated toddlers with FXS, green empty circles indicate MA controls.

Predictors of Search Speed and Path

A linear regression model including Group and search speed at Time 1 (AVETI1) significantly predicted 39% of the variance in search speed at Time 2, $F(2, 13) = 4.165$, $p = .04$. The slower the search speed at Time 1, the slower it was at Time 2, $\beta = .627$, $t = 2.877$, $p = .013$. However, group membership was not a significant predictor of time per hit at Time 2, $p = .586$. Furthermore, a combined regression model including Group membership and the effect of similarity between targets and distractors on the number of erroneous distractor touches (SIMSICO1) significantly predicted 43% of the variance in the effect of similarity on search speed at Time 2, $F(2, 15) = 4.896$, $p = .026$. The larger the effect on distractor touches at Time 1, the larger the difference in search speed between similar and dissimilar distractor displays at Time 2, $\beta = .500$, $t = 2.193$, $p = .047$. This relationship is illustrated in Figure 7.5 below.

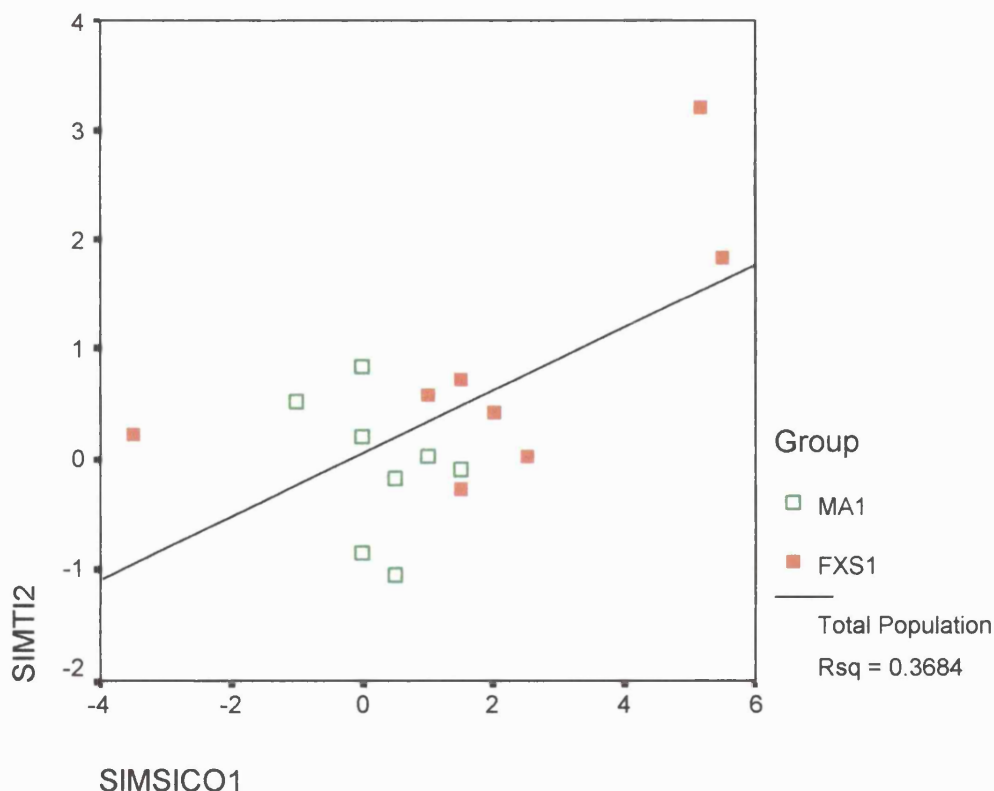


Figure 7.5. The effect of target-distractor similarity on search speed at Time 2 as a function of the size of the target-distractor similarity effect at Time 1 (SIMSICO1). Red full squares indicated toddlers with FXS, green empty circles indicate MA controls.

A multiple regression model including the average number of false alarms at Time 1 (AVEFA1) and Group significantly predicted the average distance between successive touches at Time 2 (AVEDIS2), $F(2, 15) = 5.493$, $p = .019$. False alarms at both Time 1 and Time 2 (AVEFA1 and AVEFA2) correlated with search path at Time 2, Pearson's $r(16) = .650$ and $.796$, $p = .006$ and $< .001$ respectively, 2-tailed. In turn, false alarms at Time 1 correlated with false alarms at Time 2, $r(16) = .772$, $p = < .001$. However, false alarms and search path at Time 1 did not correlate with each other, $r(16) = .368$, $p = .161$. The relationship between search path at Time 2 and false alarms at Time 1 is represented in figure 7.6 below.

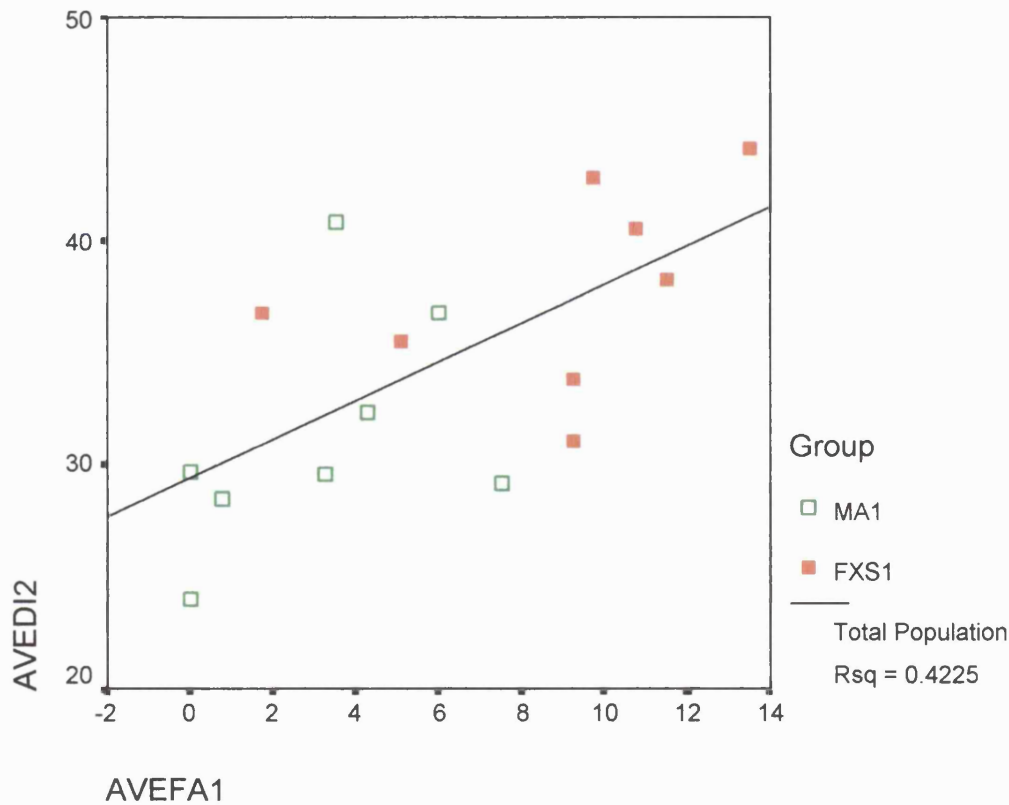


Figure 7.6. The average distance between successive touches at Time 2 (AVEDI2) as a function of the average number of false alarms at Time 1 (AVEFA1). Red full squares indicated toddlers with FXS, green empty circles indicate MA controls.

Discussion

In summary, I predicted that variability in performance at Time 1 would predict variability at Time 2, and was particularly interested in testing whether earlier unrelated variables predicted later performance. Indeed, different types of relations emerged between predictor and dependent variables. First of all, some variables predicted variability on their later counterpart. For example, the average number of false alarms at Time 1 predicted scores on this measure at Time 2. Secondly, in some cases average scores on variables at Time 1 predicted variance on different measures at Time 2, as in the case of average errors, combined with group membership, predicting later search path. This is probably mediated by their relationship to false alarms at Time 2. This was in the absence of significant correlations between errors and distance at Time 1, illustrating changes in concurrent predictive power of measures over time. Finally, the size of the effect of target-distractor similarity on erroneous distractors touches predicted later search speed, so toddlers whose errors of this type were most affected by similarity, later were also slowest at finding targets amongst similar distractors. These exploratory analyses would need to be followed by larger scale longitudinal studies, but they already suggest complex interactions amongst measures of search performance over developmental time.

7.3. General Discussion

7.3.1. Selective attention: typical and atypical longitudinal changes

This Chapter aimed to examine changes in search performance longitudinally and to explore early predictors of later search performance. Experiment 5a highlighted the importance of following atypical changes in performance longitudinally. While stable group differences in perseverative behaviours were predicted, difficulties in discriminating targets from distractors were surprising given the relative strengths in perceptual processing in older children with the syndrome (even in the context of search tasks, Munir et al., 2000). Changes in search speed and path also revealed that toddlers with FXS were differentially affected by target perceptual salience, in ways that could not always be predicted by the

typical developmental trajectory of performance. For example, their search speed was slower than controls for targets amongst similar distractors. Furthermore, and surprisingly, their search path was more systematic when distractors were similar to the targets, a pattern that was not found for typically developing toddlers. Different factors determining developmental change in typically developing toddlers compared to toddlers with FXS might drive these differences in performance. Changes in search path by typical toddlers may be driven by improvements in their ability to search systematically, whereas toddlers with FXS may rely on different aspects, like the differential density of search arrays. This would lead to the prediction of further group differences for dense arrays that would or would not ease systematic search through them. For example, search path for ordered arrays could be compared with arrays in which targets' location are random, but the overall density of displays is matched. If shorter search path for toddlers with FXS is driven by density, there should not be differences across search displays, but typically developing toddlers may benefit from ordered arrays that facilitate systematic search.

Experiment 5b investigated Time 1 predictors of later search performance. Although the results were tentative and the power of the analyses limited, the findings illustrated how initially unrelated variables can predict later performance. In and of itself, independently of the detailed relationships amongst variables, these findings warn against assuming the independence of variables across developmental time, at least in terms of search performance. For example, although the size of the effect of target-distractor similarity on touches on distractors at Time 1 did not correlate with search speed at the same time-point, it predicted search speed at Time 2. Similarly, the average number of false alarms and the average distance between successive touches (search path) did not correlate at Time 1, but Time 1 false alarms predicted search path at Time 2, perhaps mediated by their correlation with false alarms at Time 2. These relationships across measures support the need for determining possible relations across variables in time, rather than considering them as independent a priori if they were not initially correlated.

7.3.2. Limitations and future research questions

The number of children who completed the task of interest at both time points limited the statistical power of the analyses that I could carry out. For example, this did not allow me to test whether performance across multiple tasks at each time point loaded on distinct factors, consistent with a distinction between endogenous and exogenous attentional influences. For example, it would have been interesting to test whether antisaccade measures and perseverative errors loaded on a common factor on the one hand (corresponding to endogenous control), in contrast with effects of target perceptual salience and sensitivity to exogenous cueing (exogenous influences). These results would have rendered the correlations across measures even more interesting. However, beyond the results in themselves, this Chapter represented an attempt to lay out theoretical considerations and a methodological approach to be used with larger scale longitudinal investigations. Crucially, the Chapter aimed to highlight the importance of following developmental trajectories of performance across processes of relative strengths and weaknesses, without assuming their independence a priori. Further studies are obviously necessary, using where possible a larger sample and multiple meaningful measures from all children.

Finally, it would be of interest to extend the focus on longitudinal interactions in the development of cognitive attentional processes to their implications for other cognitive domains, such as early language development and social interaction. For example, Moore and colleagues (e.g., Moore et al., 2002) investigated both the development of attention and the quality of mother-infant interaction in infants with Down Syndrome. They found intriguing relationships between early difficulties in endogenous attention and the characteristics of interactions between mothers and infants. Indeed, mothers of infants with Down Syndrome tended to compensate for their infants slower orienting and responding with a warmer, but more forceful, style of interaction. This in turn seems to lead to atypical interactions of the dyad with objects of interest in the outside world (triadic interactions), one of the cornerstones of early word learning and therefore language development.

These findings have implications for future research on attention in FXS. For instance, they pinpoint the need to investigate the extent to which multiple measures of selective attention

are predicted and predict everyday behaviour, given the strong clinical and parental concerns about their everyday attention (Turk, 1998). This is one of the approaches that I am currently undertaking, using a well-validated measure developed by Rothbart and colleagues, the Early Childhood Behavior Questionnaire (Rothbart, 2001; Putnam et al., 2003). This scale was developed to assess constructs of temperament clustering around three main factors: effortful control (e.g., attentional focusing and shifting), negative affectivity (e.g., responses to emotional stimuli), and surgency (e.g., responses to high-intensity pleasurable stimuli). Testing correlations with attentional measures would assess the ecological validity of the experimental measures in terms of everyday behaviour. Another implication of complex longitudinal relationships between early attention and social cognition (Moore et al., 2002) is the importance of extending investigations beyond attentional processes alone. The current study focused on cognitive attentional processes outside the normal social context in which they operate. A future development of these results could be to investigate these early attentional measures as predictors of later attention in a social context, as for example joint attention abilities. As a prelude to this, I collected longitudinal parental ratings of early word comprehension and production in this sample of toddlers with FXS using the MacArthur Communicative Development Inventory (CDI – Infant Form, Fenson et al., 1993). Preliminary analyses of these data suggest that early attentional measures from the antisaccade and cueing tasks may correlate with later measures of early word comprehension and production (Scerif & Guerrini, in preparation). If confirmed through more detailed analyses, these findings would support the proposal of interactions between attentional processes and other cognitive domains (Moore et al., 2002) as well as highlight the need to investigate interactions through typical and atypical development, rather than merely focusing on single domains and processes.

7.3.3. Implications for neurocognitive theories of attention development

In spite of the limitations given by the necessarily small sample size tested here, the results of Experiments 5a and 5b yield some general implications for theory and research on the development of attention. They highlight the need to investigate performance in a truly developmental context, complementing cross-sectional studies with the unique information

that longitudinal studies can provide. Furthermore, these findings offer tentative evidence for correlations across measures through developmental time, even for measures that were not originally correlated. They therefore argue against assuming a priori the independence of seemingly unrelated measures.

What are the implications of these findings for neurocognitive theories of attentional selection and control? Section 7.1 juxtaposed different theories on cognitive processes and brain development. On the one hand, maturational accounts propose that maturation of independent circuits and of the neurotransmitter systems involved, for example, in endogenous control would account for developmental improvements in endogenous attention (e.g., Diamond, 1996). On the other hand, interactive specialisation models propose that multiple circuits, combined with evolutionarily selected biases and interactions with the perceptual environment, drive developmental change (e.g., Johnson, 2001). The current preliminary results point to interactions across variables and time, lending support to the latter, rather than the former, view of the neurocognitive development of attention.

More recent empirical evidence has stressed the importance of focusing on interactions across processes, both within and outside attention alone. For example, Oakes et al. (2002) collected longitudinal data on younger typically developing infants and found interactions between endogenous and exogenous influences on distractibility. The current results with toddlers lend support to those findings. However, it is necessary for the distinction between measures of endogenous and exogenous attention to be further operationalised so that their potential interactions can be measured adequately. This criticism applies to both the study by Oakes et al. (2002) and the current project. Factor analyses and structural equation modelling using data from larger samples, as well as data from a number of tasks would test more rigorously whether these measures are independent and whether the interactions generalise to larger samples of both typically and atypically developing toddlers. In the meantime, the results demonstrate the value of longitudinal studies in addressing questions about change and about the independence of processes through development.

7.4. Chapter Summary

This Chapter began by emphasising the importance of investigating attentional processes in a longitudinal context. Empirical data and theoretical arguments were presented to suggest that researchers should not assume a priori static strengths and weaknesses in performance in atypically developing populations. I also argued that seemingly independent variables may relate in complex ways through developmental time.

Experiment 5a analysed longitudinal changes in search performance comparing toddlers with FXS and typically developing toddlers selected to match their developmental level at both Time 1 and 2. The experiment could therefore address the following question: do multiple measures of performance by toddlers with FXS change more than would be expected given their rate of development? Stable differences between them and controls emerged in terms of perseverative behaviour. However, toddlers with FXS continued to erroneously touch more distractors than controls and their search speed and path were differentially affected by target perceptual salience in ways that could not always be predicted given the typical developmental trajectory. In Experiment 5b, the data above was re-analysed, asking whether distinct measures of performance at Time 1 remained independent at Time 2. The results highlighted the complex relationships that obtain across measures in time.

Collectively, these results point to the importance of taking a truly developmental approach by following changes and interactions longitudinally.

Part V

General Discussion

Summary and Implications

“What can we learn about attention from studying its development? [...] Developmental studies can perform a function in theory evaluation in the same way that studies of neurological patients, studies of people in different cultures [...] can shed light on theoretical issues. [...] What is unique about development is the necessity of the changes from childhood to adulthood.” (Enns, 1993, p. 273).

In the quotation above, James Enns argued that, when examining the component processes of adult attention, often multiple potential models can account for behavioural performance and studying typical development can inform attentional theories by constraining models to provide plausible trajectories of change. The present thesis aimed to extend this argument to the study of atypical development as a tool to inform cognitive neuroscientists investigating genotype-phenotype correlations. It illustrated the empirical questions, gathered the data and discussed the implications of a neuroconstructivist approach to developmental disorders of known genetic origin. The introduction treated the need for an understanding of multiple

levels of descriptions of such syndromes. In particular, it was argued that, for genetic disorders, it is unlikely that single high-level abilities, such as syntax or executive functions, can be selectively intact or spared, as may be the case of adult neuropsychological patients. Genetic defects are much more likely to impact low-level molecular and cellular mechanisms, that need to be analysed in depth and investigated in terms of their effects on the developing system as a whole.

Within this context, fragile X syndrome, associated with the silencing of a single gene, represented a powerful case study to examine the following hypotheses:

- a) Even with disorders whose aetiologies can be traced to single genes, understanding the associated neuropathology at multiple levels is crucial to evaluate the neural plausibility of “selective” deficits and “intact” processes.
- b) In developmental disorders, cognitive functioning in infancy and early childhood cannot be inferred from phenotypes in late childhood and adulthood, as these may result from multiple atypical developmental trajectories. Thus, not only should weaknesses be examined, but also, and critically, relative strengths need to be empirically investigated from early infancy through to adulthood.
- c) Single snapshots of performance, at any developmental time-point, are not sufficient to capture the complexity of developmental trajectories, because the paradigms used to test early and later cognitive functioning differ, sometimes radically. Within this context, longitudinal designs employing identical, validated tasks across testing sessions provide richer sources of information that can lead to mechanistic, rather than merely descriptive, accounts of developmental change.

Thus, the studies presented here were designed to investigate the early attentional profile of boys with fragile X syndrome, focusing on areas of both later relative strength and weakness, as well as longitudinal changes in performance. The following sections summarise results and their implications for future research.

8.1. Early Selective Attention in Fragile X Syndrome: Principal Results and Future Directions

The empirical chapters (Chapters 3-7) treated in detail results, limitations and outstanding questions that are pertinent to each of the independent experimental paradigms. Here, I shall discuss broader links across sets of experimental results and potential ways in which outstanding empirical questions could be addressed.

8.1.1. Early endogenous control difficulties

Part II examined early precursors of the difficulties with the endogenous control of attention that are characteristic of the late childhood and adulthood profile of fragile X syndrome. I hypothesised that, if the neural processes affected in fragile X syndrome are relevant to the early development of endogenous attention, multiple measures should provide converging evidence for difficulties with endogenous control from infancy and toddlerhood.

Chapter 3 examined adaptive changes in eye-movements to peripheral cues that predicted the location at which interesting stimuli would appear. In contrast to the typical case, infants and toddlers with fragile X syndrome did not change their reactions to informative peripheral onsets. Importantly, the atypical pattern of performance was also evident in the lack of a correlation with mental or chronological age in the FXS group, in contrast to controls, for whom this ability improved dramatically with age. Taken together, these findings suggested that eye-movement control is impaired in infants and toddlers with the syndrome. Chapter 4 investigated whether these control difficulties are also characteristic of manual responses, a finding that would be predicted from the literature on older children and adults with the syndrome (e.g., Munir et al., 2000; Cornish et al., 1999). The focus was on the ability to control conflict between the location of a target stimulus and its appropriate manual response, also monitoring the effects of previous responses on this ability. Typically developing toddlers revealed changes in the effects of context set by previous responses on conflict in each trial of interest. Toddlers with fragile X syndrome did not show

differentially greater difficulties in the ability to deal with conflict, but they displayed deficits in identifying accurately peripheral target identity and in switching responses sides effectively. These findings converged with those of Chapter 3. Infants and toddlers with fragile X syndrome, like older children and adults with the condition, displayed difficulties in the ability to inhibit inappropriate responses. However, a number of outstanding questions emerged from similarities and differences in results across tasks.

In particular, the contrast between the strikingly atypical eye-movement control and the relatively slower but “normal” effects on manual responses to spatial conflict need to be addressed further. In Chapter 4, I emphasised the crucial role of the timing of manual responses in response compatibility effects. Indeed, the slower the responses required by a conflict task, the smaller the size of conflict effects (e.g., Hommel, 2000). This suggested that the overall slower manual responses by toddlers with FXS could have masked the real size of response conflict effects for this group. In contrast with their slower manual responses, toddlers with FXS did not differ from controls in the speed of eye-movement responses (for both the antisaccade and the cueing tasks), suggesting that eye-movement measures would be better suited to investigate group differences in response compatibility effects than manual responses. The constructs addressed in Chapters 3 and 4 could be modified to design an oculomotor control task that would investigate both the control of reflexive saccades (as in Experiment 1) and the effects of both response conflict and previous response context (as in Experiment 2). Designing such a task would also allow one to test younger children than those who could perform the button presses required in Experiment 2.

Although they need to be further developed, the current results already demonstrate striking difficulties in the ability to modify behaviour adaptively on the bases of previous events and/or responses, a hallmark of endogenously-driven selection and action control. The general introduction discussed how the neurobiology of the syndrome would predict such an outcome, even at an early stage in development. However, the ubiquitous nature of the neural changes associated with the condition, as well as its neurodevelopmental nature, emphasised the need to investigate exogenous as well as endogenous attention. This was the focus of Part III.

8.1.2. Exploring early exogenous effects, as well as endogenous difficulties

Part III examined whether the early attentional profile in fragile X syndrome is characterised not solely by severe difficulties with endogenous attention, but also the extent to which it is associated with atypical influences of stimulus-driven processes.

In Chapter 5, I investigated the temporal dynamics of exogenously-driven shifts of visual orienting, by testing the effects of non-predictive peripheral onsets on the speed of eye-movements. These measures are thought to be, at least in part, independent of endogenous attentional control. I predicted that, if fragile X syndrome is not solely characterised by selective attention deficits, subtle but measurable atypical responses would emerge to peripheral stimuli that are thought to attract visual orienting automatically. Typically developing infants and toddlers oriented faster towards validly than invalidly cued targets. The cueing effect decreased with age and older toddlers tended to be less affected by invalid cues than younger infants. By contrast, toddlers with FXS exhibited the opposite effect of cue validity, displaying faster orienting to invalidly rather than validly cued targets, a phenomenon that is known in the literature as inhibition of return and has been suggested to be a foraging facilitator in visual search tasks. Intriguingly, these results lead to the counterintuitive prediction of relatively good search performance by infants and toddlers with FXS. Thus, Chapter 6 investigated search for targets amongst distractors, testing the hypothesis that performance in toddlers with fragile X syndrome is not only characterised by perseverative behaviours, a hallmark of difficulties with endogenous control, but also by atypical effects of target perceptual salience. Despite larger inhibition of return measured in Chapter 5, search by toddlers with FXS was not better than expected given their developmental level. Most importantly, a striking pattern of errors differentiated their performance from that of typically developing toddlers. Notably, toddlers with FXS produced more repetitive errors than the other groups, and they were also differentially more affected by target salience. This in turn highlights the need to investigate empirically the developmental processes leading to the clearer dissociation between perseverative behaviours and perceptual processes found in later childhood and adulthood, rather than simply inferring early selective impairments from the adult phenotype.

The current results raise a number of intriguing questions to be addressed. In particular, the relationship between inhibition of return in tasks testing the detection of objects appearing suddenly in the visual periphery and inhibition of return to previously searched objects and locations in search tasks remains to be explored developmentally, both in the typical and the atypical case. Many years ago, inhibition of return was proposed as a foraging mechanism facilitating search (Klein, 1988) and, despite being hotly debated, this view is supported by recent theoretical reviews and empirical evidence (e.g., Klein, 2000; Klein & McInnes, 1999; Paul & Tipper, 2003). However, multiple processes differentiate cueing tasks from visual search tasks. In Chapters 5 and 6, I pointed to numerous common and distinct mechanisms that can be recruited differentially in either task. For instance, these differ in terms of their requirements, in that cueing requires target detection as opposed to target discrimination being involved in search. However, both tasks have location-based and object-based processing components. The discrepancy in results for the cueing and search task may depend on toddlers with fragile X syndrome relying differentially on one of these processes for both tasks, leading to an advantage in cueing but not in search. Furthermore, differences in the speed of stimuli and required responses may account for some of the differences across tasks. For example, if toddlers with FXS are slower at orienting attention and mark previously visited locations less than controls, they may paradoxically be less influenced by invalid cues in an exogenous cueing task than controls. This is because, in a cueing task, typically developing toddlers may orient faster towards a cued location and retain a stronger memory trace for having visited it. In contrast, in a search task slower orienting and reduced memory traces for searched locations would be counterproductive and could lead to some of the errors produced differentially more by toddlers with FXS. This account raises the intriguing possibility that certain atypical mechanisms could lead to advantages on a particular attentional task and difficulties on another. To tease apart these possibilities, each of the component processes differentiating search and cueing should be manipulated by contrasting cueing tasks that require, in turn, detection or discrimination in location-based or object-based co-ordinates with search tasks that provide or not markers of searched locations or objects. All these mechanisms are candidates for differential developmental changes in typically developing populations, but also in fragile X syndrome.

Similarly, data from foraging tasks in three-dimensional space highlight subtle similarities and differences between classical visual search tasks in two-dimensional space and foraging (Gilchrist, North, & Hood, 2001). Gilchrist et al. (2001) measured markers of foraging performance compared to visual search and they found subtle performance differences across tasks. These, in turn, resulted in clearer mechanistic explanations of the processes driving both search and foraging. For instance, it seems that the costs of foraging reduce the rate of location re-checking that characterises classical visual search, suggesting that cost plays an important modulatory role across tasks. However, the extent to which this depends on the marking of previously visited locations, inhibition of return towards them, improvements in strategic search through the display, or a combination thereof, remains unclear. For example, in foraging tasks that are demanding, previously searched locations may be marked more effectively and/or more efficient strategies through the search display may be employed. The current results suggest that toddlers with FXS would find a foraging task differentially more difficult, but this could be modulated by providing them with alternative strategies for marking locations (e.g., visible and nameable markers) or implementing search paths (e.g., arrows). Moreover, modifying foraging tasks to measure inhibition of return from one search display to the next would test whether differences in this particular mechanism in fragile X syndrome are beneficial, detrimental or whether they simply do not play a part in foraging. Subtle differences between foraging and search performance also offer a further avenue of research into atypical selective attention. Indeed, foraging requires participants to represent one's own body in space, a demand that is not an integral part of classical visual search tasks. Difficulties in spatial cognition tasks that tap these representational abilities in two dimensions in adults with the syndrome (Cornish et al., 1999) suggest additional impairments in foraging compared to search. Would these simply add to the atypical mechanisms pinpointed here for cueing and search? Or would their contributions interact developmentally?

In summary, Part III suggests that atypical exogenously-driven effects of sudden peripheral onsets and of perceptual salience accompany the apparent difficulties in the endogenous control of attention. They therefore highlight that, in neurodevelopmental conditions like fragile X syndrome, it is crucial to focus in depth not only on the areas of largest impairment, but also on areas that in adulthood appear proficient. This in turn underlines the

importance of investigating developmental change directly using longitudinal designs, the focus of Part IV.

8.1.3. Investigating the atypical development of attention longitudinally

Part IV explored developmental changes in visual search as well as relationships between early and later measures of selection, discussing empirical data and theoretical arguments against assuming a priori static strengths and weaknesses in performance in atypically developing populations and the absence of complex relationships between variables across developmental time. Chapter 7 first investigated developmental changes in visual search by collecting longitudinal measures on the task used in Chapter 6. I predicted both similarities and differences in search by toddlers with FXS compared to matched controls tested longitudinally, when performance was first assessed (at Time 1) and a year later (Time 2). Stable differences in terms of perseverative behaviour obtained at both Time 1 and Time 2. Furthermore, toddlers with FXS continued to touch distractors erroneously more than controls and their search speed and path were differentially affected by target perceptual salience in ways that could not always be predicted given the typical developmental trajectory. Secondly, the experiment assessed whether performance measures at Time 1 predicted performance at Time 2. Re-analysing later performance in terms of the variables predicting it at Time 1 suggested complex temporal relationships in within-group variability across measures.

Besides providing novel information on the trajectory of performance within a relatively short time-frame, the current results raised at least two outstanding questions on the later attention difficulties documented in fragile X syndrome. First, a factor analytic analysis of changes in search performance in a much larger longitudinal sample would test whether aspects of change in search performance clustered differentially for toddlers with FXS and controls. How would this contribute further information on attentional trajectories? It is possible that, not only do children with FXS differ from controls in how their performance on a number of single measures changes, but also that performance on these measures may cluster differently for FXS compared to controls one or both time-points in development.

For example, if the length of search path and repetitive errors are both a measure of endogenous control, they may load on a single factor in typically developing toddlers. However, these may be unrelated in toddlers with FXS, especially at time 1, when search path does not characterise group differences but errors do, suggesting that different cognitive processes may underlie the two measures of performance in toddlers with FXS but not typically developing toddlers. Although the current sample size was the largest obtainable within the time constraints of a PhD thesis, I intend to pursue this further by following changes in performance by the toddlers who completed the task at Time 2 (but not at Time 1). Secondly, longitudinal measures of performance across multiple tasks tapping developmental trajectories in attentional processes across measures like eye-movements and manual responses, would have addressed whether particular markers of search performance can be predicted by early, simpler, eye-movement control mechanisms. Addressing this possibility rigorously would also require a larger sample. Unfortunately thus far few children in the group have contributed data-points to both the studies testing the endogenous control of saccades and the exogenous effects of cues at Time 1 and on search at Time 2. Assessing these changes further will be particularly informative to define early predictors of good or poor outcome within the group of toddlers with fragile X syndrome.

Collectively, the current results already illustrate how longitudinal investigations of performance in fragile X syndrome significantly enrich the understanding of developmental trajectories leading to both their relative strengths and weaknesses, in ways that would not have been achieved focusing on single snapshots of development.

8.2. Implications: Theory, Research, and Practice

Section 8.1 focused on bridging across the experiments specifically employed in the current thesis to point to limitations and future directions. Let us, however, step further away from the detailed empirical results and articulate a number of broader implications of the findings that raise wider research themes regarding fragile X syndrome in particular, but also other disorders of attention and the extent to which these can inform attentional theories.

8.2.1. What can be learned about fragile X syndrome from studying its development?

Theoretical implications

Chapter 1 treated empirical studies and theoretical proposals with respect to executive attention difficulties being a core deficit of fragile X syndrome (e.g., Munir et al., 2000; Wilding et al., 2002; Cornish et al., in press). The current thesis supports such a view, finding impairments in the ability to control eye-movements and simple manual responses from infancy and toddlerhood. These difficulties are apparent from early in development and persist throughout early childhood into the age range tested by Cornish and colleagues, later in childhood. They should therefore be targeted by further investigation and intervention efforts, as discussed later.

However, Chapter 1 also emphasised the distinction between the definition of “core” impairment and that of “selective” deficit within the context of a neurodevelopmental disorder like fragile X syndrome. The former term, “core” deficit, can be interpreted as a most severe deficit that is common across individuals with the condition and affects them more than is expected given their general developmental level. By contrast, the latter expression, that of a “selective” deficit, carries the implication that the domain or process of interest is impaired in the face of other preserved areas of functioning. An understanding of the molecular and cellular pathology of the syndrome is consistent with endogenous attention difficulties being a “core” but not a “selective” deficit for individuals with fragile X syndrome. This is because the condition affects basic mechanisms of neural plasticity and learning that are unlikely to leave specific brain areas and processes “intact”. With this conceptual distinction and biological evidence in mind, I hypothesised that adult areas of proficiency must be the outcome of atypical developmental trajectories, rather than simple measures of selective sparing of cognitive processes and related brain areas. Subtle impairments should be measurable in areas of attention other than endogenous control. Indeed, in general the findings in Chapters 5 to 7 reveal differences compared to controls in the effects of exogenous attentional manipulation and emphasise the importance of following developmental changes and stability. In other words, what has been called “Residual Normality” in the face of a selective deficit is unlikely to hold in developmental

disorders, because of the developmental repercussions of early genetic differences on multiple brain circuits and processes (Karmiloff-Smith, 1998; Thomas & Karmiloff-Smith, 2003).

What are the broader implications of this approach and of the findings for fragile X syndrome? These results suggest that, when trying to understand the role of FMR-1 silencing in brain pathology, caution should be exercised in describing fragile X syndrome in terms of selectively spared or impaired functions for any domain or process of interest. Any such suggestion would have to provide a mechanistic account for such sparing or impairment. For example, researchers would have to demonstrate how the development of that particular brain function and its related cognitive processes do not depend, even minimally, on the morphological and structural changes characteristic of glutamatergic synapses in fragile X syndrome. As examined in section 8.2.2, this logic can apply to multiple disorders of known genetic origin and to the implications that can or cannot be drawn from genotype-phenotype associations.

Emerging research themes for fragile X syndrome

Difficulties in endogenous control

I have repeatedly articulated the need for a converging multidisciplinary approach to understanding the fragile X syndrome, from the cellular, to systems, to cognitive, to behavioural level, across developmental time. Having presented behavioural data suggesting difficulties in attentional control, one is left with an intriguing question: what are the mechanisms leading a change in such a ubiquitous neural property to have relatively larger effect on certain aspects of processing than others? In other words, why is the silencing of FMR-1 more relevant to the development of endogenous control than other cognitive processes? I speculated that the relative weaknesses in attentional control that are characteristic of the syndrome (at all developmental points sampled thus far) may depend on the neural processing demands of attentional control itself. Its high reliance on recurrent excitatory connections and large-scale integration on complex dendritic trees in fronto-

parietal areas would make it particularly vulnerable to the changes that are characteristic of the fragile X syndrome.

However, thus far this proposal remains purely speculative and more direct measures of brain functioning are needed to assess it, from the cellular to the systems level. At the cellular level, mouse models could investigate whether regional changes in dendritic complexity, that are characteristic of the normal phenotype (e.g., Ramon y Cajal, 1937; Nimchinsky, Sabatini, & Svoboda 2002), are affected relatively more for pyramidal neurones in fronto-parietal areas of FMR-1 knockout mice than in other brain areas. Furthermore, while the tasks employed with knockout mice have predominantly focused on spatial cognition, further paradigms need to be developed to test constructs closer to the executive control tasks that have been used with humans (as for example, modified versions of the delayed non-matching to sample task, etc.). Similarly, other human tasks could be modified to resemble more directly those utilised with rodents. This would either provide converging evidence for the validity of mice models, or cross-species differences that may play a critical role in assessing genotype-phenotype correlations.

At the systems level and in humans, the use of non-invasive imaging techniques has already begun to shed light on the structural and functional bases of attentional difficulties in fragile X syndrome (e.g., Cornish et al., submitted; Reiss et al., 1991, 1994, 1995; Menon et al., 200X). These studies have employed volumetric measures, functional magnetic resonance imaging and event-related potentials to show altered structure and function in adults with fragile X syndrome, both at rest and during attentionally demanding tasks. These techniques have been pioneered with typically developing younger children (Casey et al., 2002) and infants (Johnson et al., 2001, for a recent review), but they have not been used with younger children with fragile X syndrome. Furthermore, it remains unclear whether these difficulties are associated solely with localised changes in activity or whether the long-range connectivity across areas in attentional control play an important role in determining atypical activation patterns. I have argued that the former is more likely, given the neuropathology of the syndrome and that both possibilities need to be examined developmentally. Complementing existing results with diffusion tensor imaging (DTI, e.g., Neil, Miller, Mukherjee & Hueppi, 2002 for a review) would address precisely the question

of whether variability in long-range connections across areas also accounts for the atypical localised patterns of activity already measured with fMRI. Recent studies of atypically developing children have shown that DTI measures (such as the degree of anisotropy in white matter tracts) can reveal differences between patients and controls that are not apparent using fMRI alone (Filippi, Lin, Tsiouris, Watts, Packard, Heier, & Ulug, 2003). Such a research program would require designing and validating behaviourally tasks tapping attentional control processes and developing these tasks to be used with converging imaging techniques like fMRI, EEG and DTI. These would need to be used with typically developing adults (e.g., Scerif, Worden, Davidson, Amso & Casey, in prep.) and with children, but eventually could be adapted for use with (at least the highest functioning) individuals with fragile X syndrome.

Atypical effects of exogenous manipulations

The current findings of atypical exogenously-driven effects (and especially their stability across testing sessions) also point to the need to re-assess proficient behavioural performance on various aspects of visuo-perception in the adult profile. Importantly, all these investigations would need to be placed within a developmental context. Indeed, Cornish and colleagues are currently designing a longitudinal investigation of visual thresholds for motion and orientation in young children with fragile X syndrome (Cornish, personal communication). The current results would suggest deviations from the typical developmental trajectory on both types of threshold, but relatively larger group differences for motion thresholds, as these rely more extensively on parietal than temporal circuits (e.g., Gunn et al., 2002). Furthermore, a developmental perspective and longitudinal investigations would provide a vital window into possible relationships or independence across visuo-perceptual functions, as reiterated in the present thesis for influences on attention. Beyond the data collected here, longitudinal studies of strengths and weaknesses would address broader empirical questions about the mechanisms of fragile X syndrome from the cellular to the systems and to the cognitive levels.

Longitudinal changes and predictors of attentional selection

Chapter 7 discussed how longitudinal changes and predictors can address the theoretical issue of the independence of processes and domains. Conflicting theories of brain development, like maturational and interactive specialisation accounts, make different predictions with respect to longitudinal results. The former view would be supported by the lack of a relationship between certain processes and brain functions across development, while interactions would support the latter. Furthermore, longitudinal studies could target predictors of within-group variability, which is, in turn, an indicator of the factors contributing to the phenotype other than the single mutation of interest. In fragile X syndrome, candidates for interactions and within-group variability can be investigated at the cognitive, but also at the neurobiological level.

For example, the current thesis focused entirely on selective attention difficulties in FXS. However, it remains unclear whether these difficulties are independent of other attentional processes, like alerting and arousal. In theories of adult attention, Posner and colleagues speculated an influence of alerting on selection, and such interactions have been maintained in the literature on neuropsychological patients (Robertson, 2001, treated in more detail below). Difficulties with the regulation of arousal have also been documented in fragile X syndrome, both at the level of physiological arousal measures (Roberts et al., 2002) and at the level of the modulation of stress hormones, like cortisol (Hessl et al., 2002). What remains unclear is whether these are developmentally related to difficulties in selection. Furthermore, interactive accounts of development would be tested by implications of early attentional difficulties on later development across domains other than attention. This approach has been successfully used to investigate attentional measures as early predictors of social cognition and carer-infant interactions in Down syndrome (Moore et al., 2002). It could be employed for young children with fragile X syndrome, whose social difficulties are also well documented (e.g., Mazzocco et al., 1994). To what extent would early atypical attention predict later social cognition? The same reasoning could be further extended to early word learning and communication, all of which could be mediated by difficulties in the orienting of social attention (e.g., Laing et al., 2002 for a related case in Williams syndrome).

The issue of variability within fragile X syndrome has been investigated in a number of recent studies (e.g., Hessel et al., 2001, 2002). These studies have tended to focus on the level of FMRP expression as a predictor of performance, focusing on the single gene involved in the condition. However, knockout mice models have already pointed to the role of the remaining genetic background in determining phenotypic expression of FMR-1 silencing (Dobkin et al., 2000). The prospect of studying variability on the rest of the genetic background in humans with the condition seems at the present time intractable. However, candidate genes for important gene-to-gene interactions can be selected on a neurobiological basis. For example, what are the interactions of the fragile X mutation with variability in genes that are involved in the functioning of other crucial neurotransmitter systems? Could this variability on genes other than FMR-1 underlie, at least in part, the variability within a group of individuals with fragile X syndrome? Until now, the sole focus of studies investigating genotype-phenotype correlations has been on expression of FMRP, but it is becoming increasingly clear that this protein plays a role in changing the structure of neurones across cortex at crucial points of interaction with other neurotransmitter systems (Benes, 2001; Nimchinsky, Sabatini, & Svoboda, 2002).

At least two possible gene-to-gene interactions are relevant candidates for fragile X syndrome. First, variable difficulties with arousal (e.g., Roberts et al., 2002), associated with cholinergic tone, suggest that, although FMR-1 silencing may not be directly associated with effects on cholinergic functioning, there may be indirect effects of the fragile X syndrome on this system. Would there be increased risk factors for children who have the fragile X syndrome and a particular variant of genes that would impair the functioning of the regulation of arousal (both in CNS and periphery)? Secondly, Gao and Goldman-Rakic (2003) recently demonstrated very specific modulatory effects on the excitatory microcircuitry of prefrontal cortex by dopaminergic innervation, suggesting that “dopamine's net inhibitory effect on cortical function is remarkably constrained by the nature of the microcircuit elements on which it acts (p. 2836)”. What would therefore be the interactions of FMR1 silencing with variants of genes involved in dopaminergic neuromodulation? There is a burgeoning literature on the candidate genes involved in dopamine functioning, both in disorders of known genetic origins (e.g., Diamond, 1993, 1997, 2000) and typical development (e.g., Casey et al., 2002; Diamond et al., 2003). Would children affected by

FXS develop differently depending on their variant of those candidate genes, like for example the dopamine transporter gene (DAT)? Investigating neurobiological, cognitive, environmental predictors of later outcome, as well as their interactions through development is crucial for both theory and principled intervention.

Implications for developing intervention strategies: Cautionary notes

Are researchers ready to provide recommendations for parents, clinicians and therapists aiming to ameliorate fragile X children's difficulties with attention? Is this mainly an exercise for clinicians, detached from the interests of basic researchers? To address firstly this latter question, a number of studies have shown that theoretically driven intervention programs can enlighten basic research issues. For example, imaging the changes in brain activity that are associated with the effects of training probes the limits of plasticity and skill learning in the adult and developing system. This approach has been taken, for example, in current studies of developmental dyslexia (McCandliss & Noble, 2003; McCandliss, 2003). These researchers proposed that, if difficulties in representing phonology contribute to dyslexia, then training in the discrimination of phonemes should result in measurable changes in brain activity as well as improvements in reading. Similarly, other factors that are theoretically thought to influence reading development, at the cognitive and neural level, can be systematically manipulated to test outcomes and in turn constrain theories on neural plasticity further.

More relevant to attention, a number of intervention strategies have been employed with both adults and children with attentional difficulties (e.g., Dowsett & Livesey, 2000; Kerns, Eso, & Thomson, 1999; Robertson, 2001). Attention training programs have been used for many years with adult neuropsychological patients. However, as reiterated throughout this thesis, the atypically developing system and an adult lesioned brain cannot be automatically assumed to be equivalent. Yet, some of the advances in theoretically motivated intervention programs for adults have guided the design of intervention strategies with atypically developing children and might be applied to fragile X syndrome. For example, Robertson (2001) reviewed the implications of attentional theories on intervention for adult patients with neglect. Theoretical proposals by Posner and colleagues (e.g., Posner & Petersen, 1990; Posner et al., 1998) put forward the view that attention may be modulated by interactions

between spatial and non-spatial mechanisms (like arousal and alertness). On those grounds, Robertson stressed the importance of focusing on both spatial selective attention and on nonselective alerting when designing intervention programs for patients with neglect. Modulation by arousal mechanisms could provide yet another approach for reducing neglect. Indeed, Robertson et al. (1995) employed this strategy with a number of patients, providing them with regular alerting stimuli, and obtained encouraging and long-lasting beneficial effects. Given the difficulties experienced by children with fragile X syndrome with both selective attention and arousal modulation, a similar intervention program could benefit their attention.

Another example of a useful crossover from theory to practice derives from intervention on executive functions. Levine and colleagues (2000) assessed the effectiveness of a training procedure derived from Duncan's theory of goal neglect (Duncan, Emslie, Williams, Johnson, & Freer, 1996). For example, patients were trained to guide their planning and problem solving by verbalising sub-goals to be achieved. Kerns et al. (1999) employed a similar strategy for children with ADHD. These studies point to successful examples of behavioural intervention, but many issues need to be evaluated specifically within a cognitive developmental framework. Which of these strategies would be appropriate for younger children with limited linguistic abilities, as young children with fragile X syndrome? Furthermore, intervention programs would need to assess extensively the generalisation of improvements on specific attentional task, an issue that is not always addressed in behavioural intervention programs such as those described above (cf. Kerns et al., 1999). Moreover, the current findings of longitudinal relationships across measures of performance stress a further thread for evaluation. How could the beneficial effects of compensatory strategies be evaluated within a developmental context? For example, encouraging children to verbalise task sub-goals may be initially effective in directing their attention. However, it might also prompt them to use verbal strategies for tasks that would be better and most efficiently solved using other forms of task analysis. In other words, might some intervention tools have potentially detrimental effects?

Certain issues became apparent from reviewing the current results in terms of their implications for intervention in fragile X syndrome. Attention training programs like those

presented above could be beneficial to individuals with the condition, but any intervention program would need to fulfil a number of criteria. Firstly, the findings stress that the early attentional profile is not necessarily the same as later in childhood or adulthood and that the independence of such processes should not be taken for granted. Therefore, target areas for intervention early in childhood should not be limited solely to the areas of difficulty later in life. This is particularly noteworthy, given that the developmental trajectories leading to later deficits have not been empirically investigated. For example, it is not known whether early atypical effects in responses to exogenous manipulations actually predict later difficulties in endogenous control, or whether these are independent. If the former relationship is confirmed, then intervention should not focus on executive difficulties alone. Secondly, the issue of within-group variability discussed in Chapter 7 becomes crucial for identifying the best predictors of performance and for devising strategies that may best suit subgroups of individuals with fragile X syndrome. Thirdly, cross-domain interactions need to be considered, both across attentional processes themselves as well as across other cognitive and social domains, because intervention on a particular process may have temporarily neutral effects that could turn out to be either beneficial or even detrimental effects with respect to other processes. For example, in the rehabilitation literature on adult patients with neglect, aside from their selective attention difficulties, a focus on alerting systems actually significantly improved performance on measures of both neglect and alerting (Robertson, Tegner, Tham, Lo, & Nimmo-Smith, 1995). A similar logic may well apply to developmental disorders like fragile X syndrome, but any such research must be framed within a developmental perspective and evaluated with respect to theories of attentional development.

8.2.2. What can be learned from fragile X syndrome about other genetic disorders?

Theory: The importance of taking typical and atypical development seriously

The current results emphasise the importance of investigating developmental change and the mechanisms underlying it (Karmiloff-Smith, 1998). They suggest that, for developmental disorders of known genetic origin like fragile X syndrome, the common focus on selective

impairment or selective sparing of high-level functions and processes (e.g., “mentalising” or syntax), is completely at odds with the cellular and systems characteristics of these disorders. The effects may often be ubiquitous in nature. Thus, to understand relative weaknesses and strengths, it is crucial to employ a developmental approach, i.e., to investigate deviance and delay empirically, rather than assuming the static view more appropriate for adult neuropsychological patients. This point is well illustrated for developmental disorders known to affect attention. Currently, the focus of investigation has been primarily endogenous attention and executive control (e.g., Barkley, 1997; Nigg, 2000). However, this thesis argues that the relative contributions of atypical stimulus processing to selection need to be examined. For instance, it may be informative to contrast the temporal dynamics of endogenous and exogenous cues on the orienting of attention, rather than solely focus on aspects of endogenous control.

A number of issues, however, remain to be addressed. The results from fragile X syndrome and the nature of developmental interactions across processes suggest that areas of selective impairment or intact functioning should never be taken as an a priori assumption, but should always be considered as an issue for empirical investigation. Conversely, can one suggest that there may never be genetic disorders for which deficits may affect selective areas of functioning, leaving other processes to function intact? Thomas and Karmiloff-Smith (2003) stressed that, although very unlikely, this is of course an empirical possibility. However, a number of computational constraints would need to be satisfied for “Residual Normality” (i.e., selectively spared functions) to hold in developmental disorders. Without denying this possibility, they present the series of constraints that would need to obtain to this to obtain and conclude that it is highly unlikely. I suggest that a further constraint to evaluating the assumption of “residual normality”, at least in developmental disorders of known genetic origin, is a detailed knowledge of the developmental neuropathology of the syndrome of interest. Neurally plausible computational models represent a powerful tool to assess mechanisms involved in attentional control (e.g., Miller & Cohen, 2001) and could clarify further the differences in effects of acquired brain lesions and developmental disorders that have already been investigated at the cognitive level (e.g., Thomas & Karmiloff-Smith, 2003).

An empirical example may come from the literature on early and continuously treated phenylketonuria (PKU, Diamond, 1996, 2000; Diamond et al., 1997). The condition involves a single-gene disorder causing a dysfunction that has toxic effects on neurones throughout the developing brain. Maintaining a low controlled diet postnatally nonetheless reduces the major impact of phenylketonuria on cognitive functioning. However, dopaminergic neurones projecting to prefrontal cortex are particularly vulnerable to the toxicity associated with phenylketonuria because of their high metabolic rate and tyrosine demands. Diamond and colleagues speculated that this vulnerability would have selective effects on executive functions throughout development. In a comprehensive longitudinal study comparing affected and non-affected siblings, they found that executive functions were selectively impaired in infants and children with PKU. This example illustrates how effects on a dedicated and committed system like striato-frontal dopaminergic projections may indeed be “selective”. However, the study by Diamond and colleagues did not investigate whether there were longitudinal interactions between seemingly unimpaired performance and executive deficits. However, what is important to note here is that, rather than assumed a priori, selective deficits were empirically tested in a longitudinal design.

Research themes: A multidisciplinary enterprise

The approach taken in this thesis carries further implications for future research on other developmental disorders. These range from issues of group comparisons, the implications of developmental delay, interactions across development and the need for a multidisciplinary approach to developmental disorders of genetic origin.

Traditionally, studies of developmental disorders have focused on comparing typical and atypical groups on certain markers of performance. While this is critical to determine the specificity of symptoms to a particular condition, researchers need to consider the implications of both differences compared to controls and similarities in performance at each point in development (Karmiloff-Smith, Scerif & Ansari, 2003) addressed some of them. If atypically developing individuals perform at the level of younger typically developing controls, should this equivalent performance be dismissed as “simple delay” (see discussion in Karmiloff-Smith, 1998)? At each particular developmental time-point, a process may result in equal performance for the typical and atypical group. Now, if we

hypothesise that, at a later time-point, performance on a second process deviates from that of the (younger) control population, and if the two processes are related across time-points, early variability on the former may predict later atypical performance on the latter. This would in turn render early delay a predictor of later deviance, exposing the potential complexities, rather than simplicity, of delay. Simply dismissing delay amounts to implying that two processes are developmentally independent, an issue for empirical investigation rather than a priori assumptions. Indeed, a number of recent studies have investigated the issue of longitudinal interactions between attentional processes and other domains of cognition, especially in atypically developing populations, showing that longitudinal interactions extend beyond relationships amongst cognitive and behavioural measures of control to the social domain. For instance, Moore, Oates, Hobson and Goodwin (2002) have documented in infants with Down syndrome that attentional processes are related to the quality of their interactions with their mothers and to later effects on joint attention. These results emphasise the importance of considering interactions between systems and processes across time, even when these appear initially independent. Moreover, they illustrated how longitudinal studies of developmental disorders of known genetic origin can provide unique information on the cascade of events leading from underlying neurological causes of early attentional difficulties to later interacting effects of cognitive and social processes.

While necessary to our understanding of syndrome-specific characteristics, group comparisons often fail to address the implications of associations of symptoms across syndromes, as well as focusing on dissociations (Bishop, 1997). However, apparent similarities in behaviour may depend on subtly different underlying processes. For example, Scerif et al. (in press) compared search performance in toddlers with fragile X syndrome and toddlers with Williams syndrome, another condition of genetic origin that is known to affect attentional control later in development. We found that, although the search speed and search path employed by these two atypical groups and matched typically developing controls did not differ, the groups displayed striking differences in the errors they committed. This suggested that very different cognitive processes underlie overtly equivalent performance. It is, then, the task of developmentalists to devise measures that are sensitive enough to target these underlying processes. The need to focus on associations across syndromes also applies to the neural level of description of developmental disorders.

Kaufmann and Moser (2000) emphasised the pervasive nature of dendritic dysmorphologies like the one described here for fragile X syndrome in other developmental disorders leading to mental retardation (e.g., Rett syndrome, Down syndrome, William syndrome and many others), as had originally been outlined by Purpura (1974). These commonalities suggest that multiple cellular and system pathways may often lead to common abnormalities. What are the processes leading to this common morphological and functional differences compared to typical development?

Hypotheses about both associations and dissociations need to be empirically tested for multiple disorders and processes, at multiple levels of description. To this end, the present investigation showed why developmentalists should not shy away from the growing knowledge of genetic, molecular and cellular mechanisms of disease, bringing to the research enterprise a crucial focus on change and development. Conversely, it urges neuroscientists interested in the contributions of genomic variation to cognitive functioning to incorporate in their framework a truly developmental perspective.

8.3. Concluding remarks

As studies of genomics and proteomics uncover the molecular and cellular processes underlying more systemic brain processes and eventually cognition and behaviour, the research enterprise facing cognitive neuroscientists becomes increasingly multidisciplinary. In the present thesis, I aimed to show that an in-depth empirical analysis of developmental processes themselves provides crucial contributions to such a fascinating puzzle.

Appendix A. Details of Testing Sessions

This appendix displays the contribution of the children in the final longitudinal sample to the experiments reported in this thesis, excluding the children who did not contribute to any of the experiments or were only seen at Time 1.

<i>Participant Code</i>	<i>CAI (months)</i>	<i>MAI (months)</i>	<i>Contributed to Experim.</i>	<i>CAI (months)</i>	<i>MAI (months)</i>	<i>Contributed to Experim.</i>
<i>HH</i>	7	4		18	16	1, 3
<i>JN</i>	15	7		27	14	1, 3
<i>EN</i>	15	8		27	16	3
<i>EH</i>	31	18	1, 3	41	26	2, 4
<i>DG</i>	37	20		47	23	1
<i>SR</i>	34	19	1, 3	49	23	2, 4
<i>JH</i>	34	30	4, 5	46	37	5
<i>JC</i>	36	19	1	49	24	
<i>SP</i>	40	26	4	52	26	
<i>HT</i>	41	25	1, 2, 3, 4, 5	54	30	5
<i>JBG</i>	36	21		48	27	2
<i>HJ</i>	42	36	2, 4, 5	55	40	5
<i>AHS</i>	43	19		55	24	1, 3
<i>JR</i>	42	23	2, 4, 5	56	31	5
<i>HGJ</i>	42	21	1, 3	54	25	2, 4
<i>RB</i>	44	36	4, 5	58	36	5
<i>GF</i>	44	20		56	23	4
<i>NCB</i>	46	16		60	20	2
<i>HA</i>	48	29	1, 2, 3, 4, 5	59	36	5
<i>JK</i>	48	29	4, 5	60	36	5
<i>BC</i>	50	25	4, 5	60	29	5

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