Lay Abstract:

Why do some children in susceptible families become autistic, when others don't? What makes a family susceptible in the first place? How does the developing brain get from a subtle susceptibility, which might go either way, onto an unequivocal, snowballing course towards autism? This project aims to help answer these questions by comparing children with autism to not only to unrelated non-autistic children, but also to the non-autistic brothers and sisters of children with autism.

Brain cells, like telephone networks, communicate on more than one scale: though most communications are local within an assembly of neurones, some cover long distances between widely separated brain regions. In order for the correct long-distance connections to be made, the local connections have to be working properly. Although a small abnormality in local connections might not cause much disruption in the laying down of long-distance lines, larger local abnormalities may cause a chain reaction of larger disruptions in long-distance connectivity. This is what might be happening during autistic brain development: abnormalities of local wiring can run in families, and can tip normal processes of brain development over a threshold onto a course that leads to autism. By looking at how the brain functions in brothers and sisters of people with autism – that is, in people who may share some of the local wiring abnormalities that run in families but who have not themselves developed autism, it may be possible to identify qualities that bias towards autism in families, and also qualities that protect against autism in non-autistic brothers and sisters, and to understand how these biasing factors are translated into autism itself. Once this process of development from mere liability to outright pathology is understood, it will become possible to design interventions that block it, preventing a susceptible child from becoming autistic.

Too often, experiments designed to test the cognitive skills of people with autism fail to create an environment in which those skills can be expressed. Such failures usually are treated as failures of the person with autism, when in fact they are failures of the experimenters. In order to provide a rule-based and predictable environment free of untoward anxiety, this study's experiments are embedded in a video game that is engaging and fun for children with autism to play – at their own pace and on their own terms. At first, this video game will be used to study behaviour and brain function, not just in tasks at which children with autism perform poorly but also in tasks at which they are superior, such as finding small details in a cluttered scene. Later, the game itself could become a vehicle for therapeutic intervention and skill learning.

Scientific Abstract:
Autism's social and communicative deficits are its most obvious, most diagnostic and most debilitating symptoms, and tend to overshadow abnormalities – both deficits and superiorities – in other cognitive domains. Social cognitive theories of autism have addressed these symptoms head-on, often positing failures in brain modules for social cognition. Such "social-first" theories, though, have difficulty explaining non-social symptoms such as enhanced sensory perception, narrow and inflexible attention, and executive abnormalities. Likewise, theories addressing each of these lower-level, non-social cognitive domains do not directly explain the social symptoms. Although each of these complementary views seems to capture a piece of the picture, identifying targets for neurobiologically based interventions and treatments demands a deeper, more unified understanding. One route towards such a unification comes in the notion of abnormal neural connectivity: abnormally strong local connectivity within brain regions may interact with normal programs of activity-dependent development to produce abnormally weak long-range connectivity between brain regions. Such a mechanism would be consistent with behavioural observations of difficulty coordinating separate cognitive resources or subsystems, and with physiological observations of difficulty coordinating the activities of separate functional brain regions. If this abnormally weak long-range connectivity is the basis of autism's social and communicative deficits, and if it does emerge from the interaction of local neural properties with normal programs of brain development, then it ought to be possible to block this pathological evolution from local abnormalities to widespread dysfunction. This study addresses the hypotheses that (1) in autism, a perturbation at the level of neural systems produces correlated abnormalities across perceptual, attentional, executive, and social cognitive domains; (2) across this range of cognitive domains and tasks, autism is characterised by abnormally strong induced gamma EEG power within individual EEG sources but abnormally weak coherence between sources; and (3) as a group, the non-autistic siblings of people with autism share low levels of the correlated behavioural abnormalities, and share the abnormally strong induced gamma power but not the abnormally weak coherence – that is, they have brains whose patterns of local activation within regions may at least partially mimic that of autism, but in which these patterns have not become developmentally magnified into widespread failures of long-range functional connectivity between brain regions. To evaluate these hypotheses within an ecologically valid context, experiments addressing perceptual psychophysics, attention, executive function, and social cognition are embedded in a video game. High-density EEG recording is combined with state-of-the-art multivariate analytical methods addressing functional connectivity, and these behavioural and physiological measures in autism probands are compared and contrasted not only to those in unrelated normal control subjects but also to those in sibs, in order to separate familial factors permissive of autism from factors that are more determinative of autism, and to understand how to intervene to prevent these permissive factors from developing into autism. This pilot study lays a foundation for applying the game as a vehicle for behavioural therapy, and for exploring protective factors in unaffected sibs.

Relationship to Autism Speaks Priorities:

This proposal is from a **beginning investigator**; I have recently completed my first year in a faculty post and am still seeking extramural funding. This proposal will **develop preliminary data**; governmental grant proposals will be strengthened with the addition of pilot data from the study proposed herein. Most significantly, this proposal **employs innovative and novel methods** in its video game format and sophisticated EEG analytical strategy.

The proposal's main focus is understanding the **biology** and specifically the neurophysiology of autism, and in so doing, pointing the way to **ætiology**, and laying some of the groundwork for eventual **treatments** that will block autism's development from liability to disorder.

SPECIFIC AIMS:

1. Develop freely available, open-source, extensible software that encapsulates a standard battery of perceptual, attentional, and social cognitive measures in a video-game format suitable for behavioural and physiological measures. The goals of precise experimental control and ecological validity often are at odds, since well controlled stimuli often are too repetitive to sustain subjects' motivation. A growing body of literature demonstrates that video games may provide a way between the horns of this dilemma. The video game format provides the sort of strongly rule-based environment at which children with autism excel, within an engaging, goal-orientated context. Psychophysical measures such as dot motion coherence and embedded figures are easily implemented as, for example, the movement of a star field on a view screen and the detection of an adversary in a cluttered environment. In addition, the strategic and adversarial nature of a video game carries natural opportunities to explore higher-level cognitive measures such as comprehension of game-related narratives and perception of a computer-generated adversary's mental states. The game will be implemented as a project with the Game Design Initiative at Cornell, which trains students for the video games industry.

2. Using behavioural and EEG data, correlate social and non-social phenotypes in 10-to-15-year-old children with autism, and contrast these measures with normal controls. The video game format provides a natural way to encapsulate experiments at multiple levels and domains of processing, from psychophysics to attention and executive function to social cognition. Prior work within each of these domains has demonstrated overall group differences between autistic and non-autistic populations, but also large degrees of variance within the autistic population. Despite this richness of variance within domains, the covariance structure across domains remains largely unexplored since domain-specific experiments have for the most part been conducted in separate studies on separate subject pools. An integrative focus is important since the abnormalities that are most obvious, most diagnostic, and most debilitating in autism may not necessarily be the most ætiologically primary: the theory of interactive specialisation tells us that higher-order capacities which may seem modular may arise in programmed developmental interactions of lower-level capacities with environmental inputs; thus high-level cognitive abnormalities may reflect a systems-level relation with, or may even arise from, perturbations at lower levels of processing.

3. Using behavioural and EEG data, contrast phenotypes in 10-to-15-year-old clinically unaffected sibs of people with autism with those in autism and in normal controls. Observations of what goes wrong in autism are important in tracing its developmental roots, but so are observations of what goes right in people who possess some genetic liability to autism but who do not themselves develop autism. Our newest data indicate that non-autistic sibs share with their autistic family members a delayed and prolonged time course of fronto-cerebellar activation in response to demands on visual selective attention, but that the sibs escape the autistic pattern of impaired functional connectivity between brain regions. The proposed EEG explorations will allow a much finer-grained analysis of the time courses of these activations within brain regions and functional connections between brain regions.

4. Share all stimuli and and analytical methods with other investigators to facilitate future expansion of behavioural and EEG data acquisition to a multi-site population. Facilitate future data mining and discovery by sharing all data (EEG, structural MRI, behavioural, diagnostic, and psychometric) collected during these experiments, in anonymised form, via an online data resource accessible via the World Wide Web by the entire autism research community. Understanding how neural systems connect and communicate demands that scientists themselves communicate, both with each other and with the public whom they serve. Every resource developed in the course of this project – methods, tools, and data – will be made freely available to the scientific community. In addition, people with autism spectrum conditions and their families and educators will be involved as part of outreach efforts, a major focus of Cornell's College of Human Ecology.

Background and Significance:

Answering Autism's Integrative Challenge

Much like the people whom we seek to understand, we autism researchers are prone to a sort of “weak central coherence”: with a multiplicity of hypotheses targeted at particular systems or levels of analysis, our most vexing problem often is not identifying the observational details, but assembling these details into a single, coherent theory. The tragedy of autism research is that its work has been fractionated within many separate models of dysfunction – models which only now are beginning to be combined. Focusing on autism's social deficits, some have characterised autism as a dysfunction in a cognitive module for “theory of mind,” the ability to think in terms of social partners' beliefs and desires (Baron-Cohen et al. 1985, 2002). Others explain both social and non-social phenomena as consequences of a more general dysfunction of executive control (Hill 2004), shifting and distribution of attention (Allen & Courchesne 2001), “central coherence” of gestalt or global-level percepts (Frith & Happé 1994; Happé & Frith 2006), or an enhancement of local processing often at the expense of engaging intact global-level processing (Mottron et al. 2006). Though each of these theories seems to contain at least a piece of the picture, the process of putting these pieces together has begun only recently (Belmonte et al. 2004b; Mottron et al. 2006).

In science as in any human endeavour, what we find is constrained by what we look for. All too often, experiments are framed so as to confirm or to refute hypotheses within one and only one theoretical framework. “Theory of mind” studies show deficits in tasks of attributing false belief (Baron-Cohen et al. 1985), executive function studies show deficits in tasks of planning (Hughes et al. 1994) and inhibition of prepotent responses (Ozonoff et al. 1994), attention studies show slowed shifting (Courchesne et al. 1994) and abnormal distribution (Townsend & Courchesne 1994; Burack 1994) of attention, studies of central coherence show facilitation on tasks of perceptual disembedding (Shah & Frith 1994; Plaisted et al. 1998), and perceptual studies show enhanced discrimination of first-order stimuli (Plaisted et al. 2003; Bertone et al. 2003, 2005). Each of these foundational results has been individually confirmed by further explorations, but each has remained largely unintegrated with other findings.

Significantly, within each of these domains of exploration there is very appreciable variance in behavioural and physiological measures: many children with autism pass tasks of first-order or even second-order belief attribution (Frith & Happé 1994), deficits in executive function vary across task paradigms, executive subdomains, and individuals (Hill 2004; Russo et al. 2007), attention varies between abnormally narrow 'spotlight' and abnormally broad distributions (Townsend & Courchesne 1994), central coherence as measured by the Embedded Figures Test varies substantially within the autism population and in fact correlates with similarly variable performance on “theory of mind” tests (Jarrold et al. 2000), and perceptual variation in motion coherence thresholds is very large with a third of the autism population within the normal range (Milne et al. 2002; Belmonte 2005). Despite this richness of variance within perceptual and cognitive domains, with a few notable exceptions (e.g. Jarrold et al. 2000) the covariance structure between domains remains unexplored. Linking these investigations is important because it can illuminate pervasive abnormalities of neural information processing that span cognitive domains – and this understanding of how the autistic brain goes awry at a neural level is crucial to identifying targets for therapeutic intervention.

Recent theoretical constructions of autism have converged on the notion of a systems-level dysfunction in neural computation (Belmonte et al. 2004ab), one whose interactions with normal programmes of brain and cognitive development may result in perturbations at many levels of processing. Autistic deficits in complex social and communicative skills are comparatively well studied, since these deficits are the most obvious, the most diagnostic, and the most debilitating. However, the relevance of abnormalities at lower levels of function (Rogers & Ozonoff 2005) ought not to be ignored, as perturbations at these simpler, more tractable levels of processing may offer insights at the systems level. In particular, correlation between

behavioural and physiological studies of sensory and attentional phenomena on the one hand, and complex social cognitive processes on the other, may illuminate abnormal modes of development in which a systems-level abnormality perturbs both low and high levels of processing, and/or abnormal developmental cascades in which dysfunction at low levels of processing perturbs activity-dependent development at higher levels. Support for the notion of such multi-level cascades of perturbed development comes from the success of interventions addressing rapid auditory sequence processing in language and communication disorders (Tallal et al. 1996, 2004; Fitch & Tallal 2003), from studies of schizophrenia demonstrating deficits in early sensory processing (Butler & Javitt 2005; Uhlhaas & Silverstein 2005; Butler et al. 2007) and relating auditory frequency discrimination to deficits in affect recognition (Leitman et al. 2007) and visual size discrimination to deficits in theory-of-mind (Uhlhaas et al. 2006), from physiological studies of autism suggesting compensatory processing for dysfunctions in early sensory and attentional computations (Belmonte & Yurgelun-Todd 2003) and behavioural studies linking joint attention to theory-of-mind and pretence (Charman 1997), and even from studies of normal development and ageing showing that deficits in automatic, early processing evoke downstream, compensatory abnormalities in later, more effortful stages of neuro-cognitive processing (Townsend et al. 2006).

Understanding Autism at the Network Level

In particular, the systems-level dysfunction in autism has been characterised as an abnormality of neural connectivity, possibly comprising abnormally strong connectivity within local networks and a resultant failure to develop normal patterns of long-range connectivity amongst brain regions and amongst cognitive subsystems (Brock et al. 2002; Belmonte et al. 2004a; Courchesne & Pierce 2005). This idea is consistent with an emerging collage of autism suscpetibility genes that perturb neural connectivity by altering neurone numbers, synaptic structure, or neurotransmission (Belmonte & Bourgeron 2006), and has been supported by functional imaging results in autism demonstrating abnormally strong activation within brain regions that subserve low levels of processing, abnormally weak activation within higher-order, integrative regions, and abnormally weak functional connectivity between brain regions (Just et al. 2004), as well as by anatomical studies of high local and low bridging white matter volume (Herbert et al. 2004) and low diffusion anisotropy in white-matter regions subserving integrative processing (Barnea-Goraly et al. 2004).

The recency of interest in neural connectivity in autism arises in the context of neuroscience's historical focus on single-variable problems. Scientists are trained to zero in on well framed and tractable hypotheses in which one independent variable is manipulated whilst all other factors are somehow held constant. Historically, this single-variable focus has produced great advances in the understanding of the effects of brain lesions (in which a single anatomical structure is silenced) and single-gene disorders (in which one gene is silenced or gains function). Autism, though, is anything but a single-variable problem. The one truth that has become clear from decades of study is that the behaviourally defined condition known as autism converges from many possible ætiological factors and combinations thereof, and diverges into a welter of endophenotypic variability (Belmonte et al. 2004b). The lesion model is as poor a one as the single-gene model for understanding developmental disorders, since the experience-expectant maturation of any one brain structure depends on its receiving properly patterned inputs from the structures with which it communicates, and thus a perturbation of any one region becomes a perturbation of the entire network of interacting brain regions (Johnson et al. 2002; Karmiloff-Smith 2007), just as variants in a collection of genes combine to produce emergent variation in networks of interacting genes (Belmonte & Bourgeron 2006).

Applying 21st-Century EEG Hardware and Analytical Methods

Despite its crucial role in generating this hypothesis of abnormal connectivity, fMRI is of only

partial use in testing it because its low temporal resolution misses out high-frequency phenomena that evolve over brief temporal intervals. Electroencephalography (EEG), on the other hand, can quantify brain connectivity within processes operating on millisecond time scales, and has been suggested as a method of investigating a physiological basis for weak central coherence in autistic perception (Brock et al. 2002). The time is particularly ripe for renewed EEG studies of autism not only because of EEG's strong relevance to this question of neural connectivity, but also because of this past decade's developments in EEG acquisition hardware and multivariate and time-frequency EEG analytical methods, and because of the groundwork laid by previous EEG studies of autism – studies whose tantalising results demand and deserve replication and re-interpretation in the context of updated methods and theories. Unencumbered by the severe and restrictive conditions of fMRI (need to remain perfectly still, confinement to the magnet bore) or MEG (need to remain very still), EEG maximises subjects' freedom while providing exquisite temporal resolution, and increasingly precise spatial resolution.

A new generation of EEG amplifiers capable of matching much higher scalp impedances (Ferree et al. 2001), combined with electrode sensor webs that parallellise the process of electrode placement and electrolyte application, has significantly reduced electrode application time and demands for subject compliance, enabling high-density EEG recording in a wider range of patients. Even more significantly, during the past decade as biologists have begun to communicate better with physicists and mathematicians, outdated univariate methods of analysis in the time domain have been supplanted by multivariate methods such as Independent Components Analysis (Bell & Sejnowski 1995) and by time-frequency analyses that account not only for signals phase-locked to stimulus or response events but also for signals consisting of perturbations of ongoing oscillations (Makeig et al. 2002, 2004). These advanced analytical methods have now been made available in a well documented and functional software package, EEGLAB (Delorme & Makeig 2004), which largely automates their application. Despite the availability of these techniques, though, most EEG studies still apply twentieth-century strategies of time-domain averaging at just a few electrode sites, ignoring frequency-domain measures such as non-phase-locked spectral perturbations and actually discarding most of the data available from high-density electrode montages. The current project is an opportunity to apply 21st-century methods.

Quantitative time-frequency analysis also opens EEG studies to measurement of temporally extended events, to which brain electrical responses may not be precisely time-locked. Even when the precise timing of an event within a blocked condition is unknown, EEG power and EEG coherence within specific frequency bands, and activity within and coherence between specific neural generators (i.e. specific independent components), can be assayed in a blocked rather than an event-related comparison. This method offers the opportunity to apply EEG's high frequency sensitivity to brain responses arising during comprehension of extended narrative sequences and other complex stimuli particularly relevant to social cognition.

EEG was, of course, one of the first neurophysiological recording methods applied to autism, and the source of several provocative results including the reduction or absence of several frontal event-related potential (ERP) components related to selective attention (Ciesielski et al. 1990; Courchesne et al. 1994), variability of attention-related ERP responses to sensory events (Lincoln et al. 1993; Kemner et al. 1994), and a lack of attentional modulation of sensory ERPs (Buchwald et al. 1992; Townsend & Courchesne 1994; Lincoln et al. 1995) – all of which collectively suggest an absence of modulation of distributed neural systems in response to task context. As autism research expanded over the past decade, though, EEG investigations did not expand as rapidly as MRI-based techniques. Especially in light of current ideas on abnormal neural coupling and dynamics in the autistic brain, many findings from past research on autism call out for replication and extension in ways not amenable to the low-temporal-frequency sampling of functional MRI. Event-related potentials and behavioural studies of

motion perception, for instance, have never been combined within the same set of subjects. The very first studies of γ EEG response during perceptual binding in autism (Grice et al. 2001; Brown et al. 2005) find increases in induced γ power consistent with a hypothesis of abnormally weak neural inhibition within regions and abnormally low coherence between regions, and replication and extension of these findings is important. A deficit in γ synchrony, a putative mechanism for perceptual binding (Tallon-Baudry & Bertrand 1999), has been proposed as a mechanism for weak central coherence in autism (Brock et al. 2002), and initial studies of γ coherence in autism during a delayed match-to-sample task (Belmonte et al. 2004a) suggest abnormally strong frontal γ power but abnormally weak fronto-posterior γ synchrony. As we have observed in the context of brain imaging (Belmonte et al. 2007), understanding how autistic development plays out from genetic and environmental antecedents through many levels of brain structure and function demands correlative work. Our proposed combination of tasks ranging in complexity from sensory and attentional to social cognitive would build such correlative knowledge within the sphere of electrophysiology and, we hope, lay a foundation for future, even more broadly integrative studies that would include other measures of phenotype and genotype.

Achieving Ecological Validity with Strategic Simulations

Perhaps the single most important obstacle to integrative studies is the practical limit on the amount of time that a single experimental subject (especially one from a clinical population) can reasonably be expected to perform before becoming fatigued. Unfortunately, the more controlled and repeatable a stimulus is from the scientist's point of view, the more repetitive and tedious the experiment can seem from the subject's point of view. Behavioural research on autism in recent years has highlighted the importance of motivation, behavioural set, and task instruction in establishing cognitive strategy and determining performance (e.g. Plaisted et al. 1999; Dalton et al. 2005). In light of these considerations, we propose to embed our experimental stimuli in the context of a video game that captures and maintains subjects' interest, transparently collecting behavioural data and synchronising with physiological recording as the subject plays the game. The practical advantages of such an engaging and ecologically valid format over the usual repetitive blocks of trials are legion. Indeed, varying levels and demands of attentional shifting and multimodal integration are natural in the context of video game play, and psychophysical measures such as dot motion coherence and embedded figures are easily implemented as, for example, the movement of a star field on a view screen and the detection of an adversary in a cluttered environment. In addition, the strategic and adversarial nature of a video game carries natural opportunities to explore higher-level cognitive measures such as comprehension of game-related narratives and social attribution to a computer-generated adversary. The video game format is increasingly being used to acquire simultaneous behavioural and EEG observations in ecologically valid contexts, for example in visuomotor tracking (Smith et al. 1999), air traffic control (Brookings et al. 1996), and military command and control simulations (St John et al. 2002, 2004; Berka et al. 2004). Recent results in human-computer interaction (von Ahn 2006) also point to the power of the game context to establish and to maintain motivation in tasks that otherwise might not seem engaging. Also along these lines, the video game format affords subjects more of a chance to become comfortable with the task before entering the laboratory, minimising the potential confound of state anxiety associated with performance of an unfamiliar task in a testing situation. Most significantly, computer games and computer-based training in general are able to deliver the world to persons with autism in a rule-based, systematic and comprehensible way that affords them opportunities to demonstrate their skills, and computer-based training is a promising vehicle for behavioural therapy for autism (Tallal et al. 1996; Golan & Baron-Cohen 2006).

1.5 Contrasting Sibs to Highlight Critical Developmental Differences

There is a very significant genetic component to autism (reviewed in Belmonte 2004b); its sibling recurrence risk is over twenty times its incidence in the general population. Autism may well occur when an accumulation of liability factors interacts to perturb a developmental course permissive of autism into one determinative of autism. Information on the abnormal events surrounding this critical developmental event becomes much more valuable in addressing treatments when it can be contrasted with information on what happens when the event is avoided. Such a contrast can be obtained by studying siblings and other family members of people with autism, people who presumably share some of the genetic susceptibility factors but in whom those factors have not become magnified into the full syndrome of autism. A wealth of behavioural data (reviewed in Belmonte 2004b) suggests that such factors are operative in first-degree relatives and do produce subclinical abnormalities, including impairments of social cognition and superiorities on tasks of perceptual disembedding. In recent years these subclinical familial traits have been recognised as the Broader Autism Phenotype (Piven et al. 1997; Dawson et al. 2002). The first functional imaging studies of autism siblings (Dalton et al. 2007) have begun to add a physiological dimension to this similarity. Our own fMRI work (Belmonte et al., in revision for the *Journal of Child Psychology and Psychiatry*), in a visual attention task involving suppression of incongruent distractors, suggests that delayed and prolonged fronto-cerebellar activation found in autism probands and in clinically unaffected siblings reflects familial, permissive factors, whereas a decrease in functional connectivity between brain regions is found only in probands and reflects more determinative factors. Very recent genetic association and gene expression findings suggest that many sibs may in fact share the underlying pathology that has produced autism in their brothers or sisters, but may themselves have been rescued by protective genetic variants (Sacco et al. 2007). If we can understand how it is that some family members become autistic whilst others escape autism, we will open the door to targeted interventions that may block this evolution from liability to disorder. In our view, the best possible outcome of such efforts would be a world in which the unique perceptual strengths that arise in people with autism and their family members are preserved, but combined with intact communicative abilities that will give these individuals a chance to interact with the surrounding social world and to share their unique gifts.

Preliminary Data:

As a motivation for the proposed analyses, we present data from a recent study of visual attention in autism spectrum conditions which motivate the connectivity hypothesis, and EEG analyses of autistic and control subjects playing a prototype of the proposed video game.

The visual attention study compared 8 10-to-15-year-old boys with autism spectrum conditions (ASC) (diagnosed and included using the same procedure specified below for the proposed study), 7 clinically normal brothers of people with autism spectrum conditions, and 8 unrelated normal boys. The paradigm was a visual divided-attention task in which the congruence of spatially intervening distractors was varied. Subjects had to report, via a forced-choice button-press response, the presence or absence of a conjunction of colour in one location and orientation in another. Both behavioural performance (d') and brain activation (BOLD time courses) were measured as a function of the level of distractor congruence. d' scores differed significantly by diagnosis ($F(2, 84) = 5.99$, $p=0.0037$), being lower than normal in the sib group ($t(62) = 2.36$, $p = 0.0217$), and lowest in the ASC group ($t(66) = 3.42$, $p = 0.0011$). The physiological data (Figure 1, red=normal, blue=autism, magenta=sibs) reveal a pattern of prefrontal and anterior lateral cerebellar activation in both the autism and sib groups that is prolonged far beyond the end of the trial, and which does not peak and to resolve at the rapid rate characteristic of the normal group (comparisons significant in cerebellum and left middle frontal gyrus for autism versus controls). In fact, this delayed activation is even greater in the sib group than in the autism group (comparisons significant in cerebellum, middle frontal gyri, and right intraparietal sulcus (area V7) for sibs versus controls), suggesting that it may reflect a process that compensates for an inefficiency in the rapid deployment of attention, and that this compensatory process is more completely implemented in the clinically unaffected family members. In contrast to this abnormality in the timing of fronto-cerebellar activation manifest both in the autism group and in clinically unaffected sibs, significant decreases in functional connectivity between brain regions were manifest only in the autism group, and differentiated this patient group both from the sibs and from the normal controls (Figure 2: coloured cells denote significant correlations in the correlation matrix; collapsing across all pairs drawn from 76 brain regions in this matrix, $F(2, 1821) = 266.89$ for the omnibus test and $t(1291) = 20.71$ between autism and normal, $t(1139) = 19.84$ between autism and sibs, but $t(1215) = 0.72$ between sibs and normal – the important message in the figure is the overall level of functional correlation, more than the specific pattern of regions involved). **Collectively, these results suggest that abnormal timing of attention-related activation within frontal and cerebellar regions is a familial trait <u>permissive</u> of autism, whereas abnormally low functional connectivity between brain regions may reflect processes more <u>determinative</u> of autism.**

Figure 3 shows differences between an autistic game-player and a normal control player during a dot-motion coherence task, presented in the game as a task of navigating a spaceship through a star field. Drift (coherent motion) calls for the player to make a course correction. The maps at the top of the figure illustrate the scalp topography of an independent component generated in right occipital cortex, localised similarly in both players. The time-frequency plots, however, show differences between the two players in this component's pattern of event-related spectral perturbation (ERSP) around the time of onset and offset of motion coherence: the non-autistic player shows α/β suppression during coherent motion relative to random motion, reflecting heightened visual attention. This suppression is early and protracted in the non-autistic player, but late and minimal in the autistic player. This contrast illustrates a lack of modulation of attention as a function of task context, suggesting that the autistic player remains in a state of heightened attention throughout the task. Additionally, a long-latency, transient γ power increase following coherent motion onset is visible in the autistic data but not in the non-autistic data, consistent with the hypothesis of abnormally strong local γ power.

Figure 1:

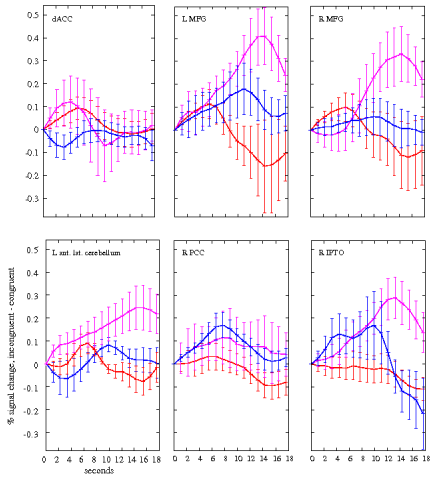


Figure 2:

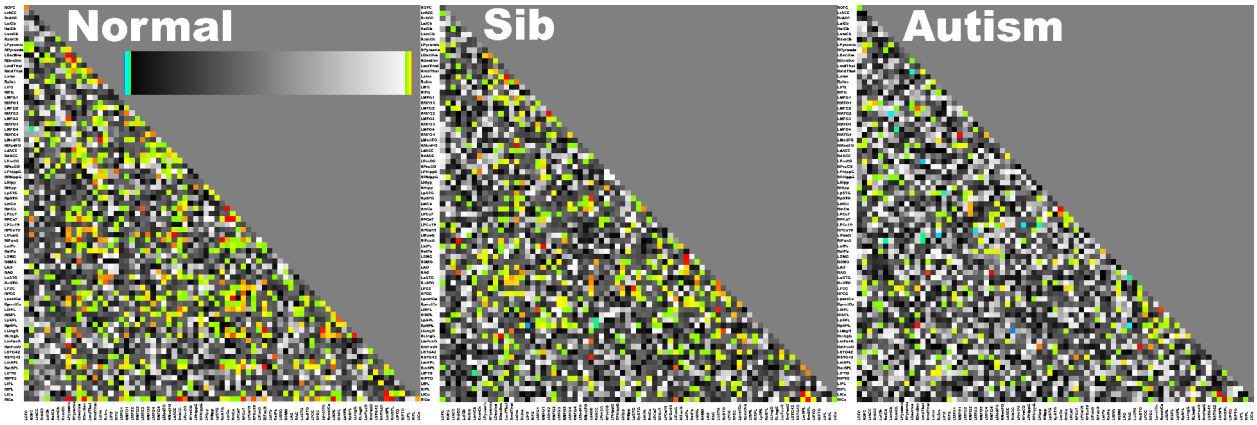
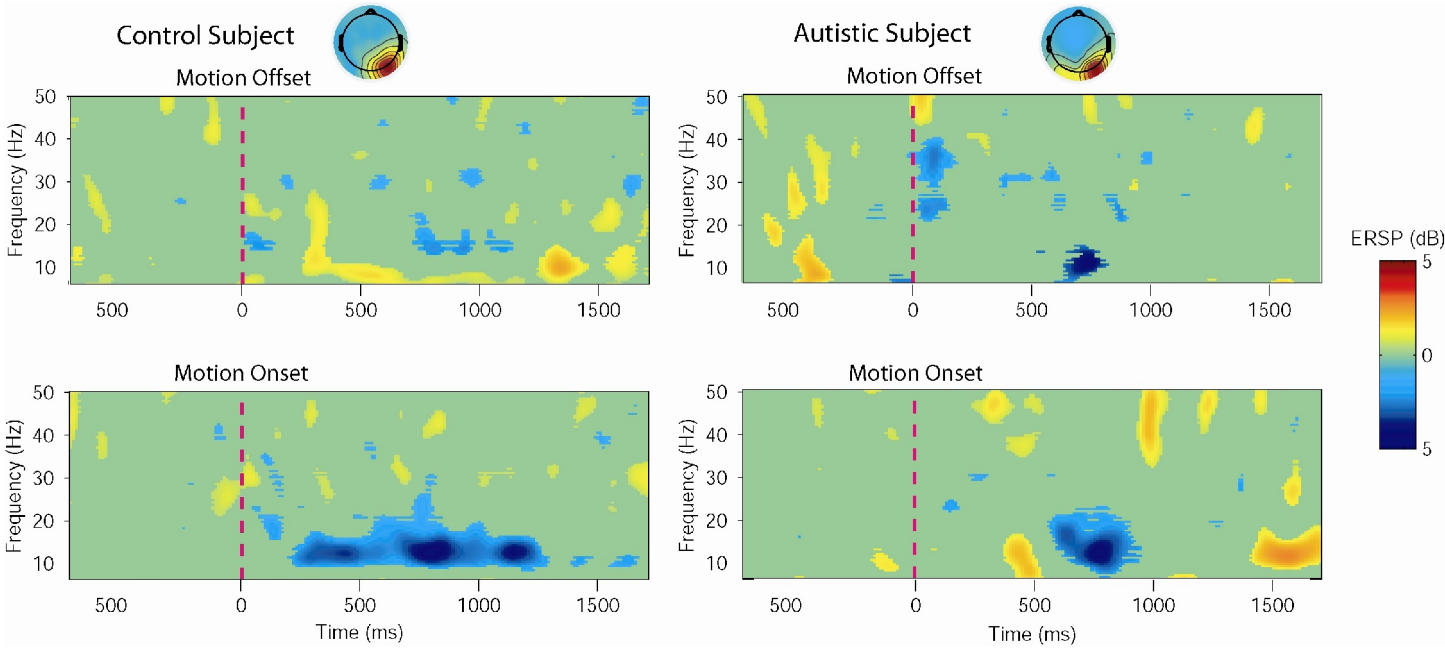


Figure 3:



Experimental Plan and Methods

Methods for Aim 1 (software development): The video game is currently under development as a joint project with the Game Design Initiative at the Cornell University Faculty of Computing and Information Science. The game is written for the widely used Microsoft Windows operating system, using the XNA Game Studio Express SDK and the Visual Studio Express integrated development environment available at no cost from Microsoft. High-resolution timing and display synchronisation within the game ensure millisecond accuracy of the event timing. All game events (stimulus onsets, key presses, &c.) are logged to a plain text file which can be transmitted to a central server for offline analysis. Events also are sent as byte codes to a parallel port for synchronisation with EEG acquisition. The game is organised as an extensible collection of mini-games built around a main game, and documentation is provided for programmers who wish to add new mini-games that will make use of a core collection of subroutines for display manipulation, event logging, and psychophysical parameter estimation. The main game involves the player in the design and construction of a space colony, and shares thematic elements with other player-centred simulation games such as SimCity. In order to construct and to maintain the city, players must enter the mini-games in order to collect resources and to defend against hazards. In addition to supplying a thematic framework around which the mini-games are unified, the strategic element of this core game provides an opportunity to evaluate cognitive planning in a fairly open context. The main experimental measures, though, are built into the mini-games.

The “Meteors” mini-game resembles the arcade games Tempest and Asteroids, and combines tests of motion coherence threshold, motor inhibition, and executive flexibility. The player commands a spaceship, distinguishing friendly from unfriendly ships in a go/no-go task. The mapping between ship types and friend-or-foe status changes periodically as pirates commandeer new types of ships; these changes implement shift and hold trials. Between these engagements the player warps between galaxies and must detect coherent motion in a star field in order to navigate the ship.

The “Turret Command” game resembles the arcade game Missile Command, and tests distribution and shifting of attention, and the effect of multimodal (auditory and visual) versus unimodal cueing. The player defends a base at the bottom centre of the display, by sweeping a weapons turret along a semicircular defence perimeter. Friendly ships and hostile missiles warp into the space outside this defence perimeter, at a random distance from it, then move towards the perimeter. Half of the sessions contain friendly ships (distractors) as well as hostile missiles, whereas in the other half the only contacts are hostile missiles.

The “Tactical Command” game is a variation of the Embedded Figures Test. A target spaceship (an automatically generated geometric form) is embedded within the clutter of a tactical display. The player must detect the spaceship, as rapidly as possible.

The “Signals Intelligence” game is an adaptation of the classic “Sally Anne” test of theory-of-mind, but adapted to a science fiction context. Instead of Sally and Anne with a marble, the characters are space pirates with resources needed by the player's colony. The resource is deposited on planet X by pirate A, then stolen (or not stolen, in a control scenario) and placed on planet Y by pirate B. The player must lay in courses (by moving the mouse) to intercept each pirate, and the latencies of these actions serve as a continuous measure of first-order and second-order theory-of-mind processing.

In order to avoid confounds with verbal ability (e.g. Peterson & Siegal 1999) as much as possible, all game instructions (for example, the assignment of friend and foe ship classes) are given as pictures and animations, and players are prompted to practise key-press responses in the appropriate game contexts. The instruction period provides a further opportunity to measure brain response to these pictorially presented narratives.

Methods for Aims 2 & 3 (behavioural and EEG comparisons of ASC, sibs, and normal controls):

Subjects 10 to 15 years old will be recruited through our existing subject pool and through the Franziska Racker Centers in Ithaca, a treatment centre with which the Department of Human Development has an ongoing relationship. Subject groups will consist of children with ASC, sibs of children with ASC, and unrelated normal children with no psychiatric or neurological history. Groups will be matched for age, sex, Performance IQ, and handedness. Sufficient numbers of subjects will be recruited in order for the study to be completed by ten subjects in each group (30 subjects total). Given time devoted to software development, psychometric testing, and behavioural and physiological recording, these numbers are the limit of what is feasible within the two-year grant period. (We have demonstrated statistically significant behavioural and physiological differences with these numbers of subjects in our previous fMRI work, and we anticipate that results with this group of subjects will provide a strong basis for a federal grant proposal.)

Psychometric measures will be selected from the consensus recommendations of the Cure Autism Now Neuroimaging Summit (Belmonte et al. 2007). Diagnosis of ASC will be verified by administration of the Autism Diagnostic Inventory – Revised (Lord et al. 1994) and the Autism Diagnostic Observation Schedule – Generic (Lord et al. 2000) by qualified raters at each site. Traits of the Broader Autism Phenotype in the sib group will be assessed with the Broader Phenotype Autism Symptom Scale (Dawson et al. 2007) administered by a qualified rater (M.K.B.). In all subjects, IQ will be assessed with the Wechsler Abbreviated Scale of Intelligence (WASI), handedness with the Edinburgh Handedness Inventory, face recognition with the Benton Face Recognition Test, social perception with the Reading the Mind in the Eyes Test (Baron-Cohen et al. 2001), social communication with the Social Responsiveness Scale (Constantino et al. 2003) (completed by a teacher rather than a parent so as to avoid negative bias in sibs' ratings that might arise from parents' comparisons to their ASC children), and autistic or pseudo-autistic traits with the Autism Spectrum Quotient – adolescent version (Baron-Cohen et al. 2006). Subjects in the ASC group will be rated on the Repetitive Behavior Scale – Revised (Bodfish et al. 2000), with scores transformed and scaled according to the established factor loadings and variances for Ritualistic/Sameness Behavior, Self-injurious Behavior, Stereotypic Behavior, Compulsive Behavior, and Restricted Interests (Lam & Aman 2007), and on the Sensory Sensitivity and Distortions Questionnaire (Minshew & Meyer, submitted).

Electroencephalographic (EEG) recordings will be obtained with electrodes distributed evenly across the scalp according to the modified International 10-20 System, using a 128-channel Biosemi ActiveTwo EEG system. The BioSemi system uses active electrode technology, which allows amplification of the EEG signal directly at the head, eliminating amplification of artefacts caused by head and body movements. Placing active electronics within millimetres of the actual electrode contact allows much greater impedances at the scalp-electrode interface, virtually eliminating the need to clean and to abrade the scalp before applying electrodes. Capping time is thereby reduced to less than 20 minutes for 128 channels, helping to ensure that the subject is not fatigued before the experiment begins.

Eye movement artefacts (blinks and saccades) will be recorded by vertical and horizontal EOG electrodes. Offline, electrodes will be referenced to the algebraic average of right and left mastoid. EEG will be amplified using a bandpass of .01 to 200 hz, then digitised online at a rate of 512 samples per second. Movement artefact will be excluded manually, and eye movement and muscle artefact by ICA. Peak amplitudes and latencies will be extracted automatically from averaged signals within the following specified latency windows for components of special interest: P1 (most + in 80-130 ms), N1 (most – in 110-180 ms), P2 (most + in 130-240 ms), N2 (most – in 200-300 ms), P3a (most + 240-300 ms, frontal localisation), P3b (most + in 300-500 ms, parietal localisation). In addition, ICA will be applied to analyse continuous EEG

decompositions. Scalp maps of components derived from these decompositions generally point to compact cortical generators. Power, coherence, scalp distribution and dipole source localisation will be computed using EEGLAB. Using nonparametric (bootstrap) statistical comparisons, group contrasts will be computed for ERP, ERSP, coherence, and Grainger causality measures, and all measures be be entered into an exploratory analysis of covariation.

This study's predictions are motivated by this group's and others' contributions to the altered-connectivity theory of autism, by previous findings within individual experimental paradigms, and by the notion that interactive specialisation during development will produce cross-domain correlations not only in the case of the patient group but also in the case of the sibling and unrelated normal groups. (Specific predictions presented here are necessarily summarised and abbreviated because of the large number of tasks and analyses occasioned within the video game.) Within-domain findings and cross-domain correlations for the ASC group are expected to be largest in magnitude. Findings are expected to include an increase in go/no-go errors of commission and a decrease in accuracy during shift trials, reflecting deficits in inhibition of prepotent responses and in executive flexibility (Ozonoff et al. 1994), an elevation in motion coherence thresholds (Spencer et al. 2000; Milne et al. 2002; Bertone et al. 2003; Pellicano et al. 2005) and a reduction in the normal induced γ EEG synchrony related to coherent motion (Müller et al. 1997) reflecting disordered long-range functional connectivity, superior embedded-figures performance (Shah & Frith 1983), decreased facilitative effect of multimodal versus unimodal cueing and decreased interaction of evoked brain electrical responses to these cues (Molholm et al. 2002; Senkowski et al.. 2007), a reduction in the amplitude of the motor readiness potential (Rinehart et al. 2006), a group-by-distractors attention effect with the ASC group faster than normal in the non-distractor condition (O'Riordan et al. 2001) but slower in the distractor condition (Burack 1994), a group-by-validity-by-SOA effect with slowed shifting in ASC heightening the validity effect at 800 ms relative to 100 ms (Townsend et al. 1996), and slowing in first- and especially second-order theory-of-mind tasks (Baron-Cohen 1995).

In all these visuomotor tasks the altered-connectivity theory (Brock et al. 2002; Belmonte et al. 2004a; Courchesne & Pierce 2005) predicts a reduction in the normally occurring (Frund et al. 2007) γ coherence between frontocentral and occipitoparietal component generators, and an increase in local γ power within generators. In the case of sibs, on the basis of this group's recent results (Belmonte et al., in revision) the predictions are behavioural performance between ASC and normal levels, frontal evoked potentials and local γ power increases resembling those of autism, but sparing of γ coherence. These are group predictions, of course; it is fully anticipated that there will be a great deal of within-groups variance on behavioural and physiological measures – and this variance is in fact what's being counted on, since it will allow exploration of the covariance structure across tasks and domains. Covariation in these measures is predicted in all groups, reflecting developmental interdependence of low- and high-level cognitive processes. This covariation is predicted to be strongest in ASC group, reflecting a systems-level alteration in neural information processing that leads via altered interactive specialisation to differences in all task domains. The alternative hypothesis (Ronald et al. 2006) is that causation in all these domains is indepenent.

3.3 Methods for Specific Aim 4 (sharing data and methods): Source code and executable code for the game software, programmer-level and user-level documentation, and source code for all data analysis programs will be placed in a publicly accessible repository on the World Wide Web, and put in the public domain under the GNU General Public Licence. Anonymised diagnostic and psychometric data along with behavioural log files from the game will be placed in a Web repository. EEG data will be made available to other researchers on request, and will be saved for eventual inclusion in the planned BIRN EEG data archive.

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Budget Justification

NOTE: Where your web form says "2007-2008 budget" and "2008-2009 budget," I've instead entered the figures for 2008-2009 and 2009-2010, respectively. The proposed project would not commence till 2008.

PERSONNEL

Six undergraduate students

One the department's great resources is the intellectual sophistication of its undergraduates who are pursuing research. Preliminary work in this project has made use of undergraduate researchers from the Department of Human Development and from the programme in Computing and Information Science for development of experimental tasks the implementation of these tasks in software. Funds are requested for six undergraduates at half time during the academic year ($4320 per student) and full time during the summer ($2808 per student).

EQUIPMENT

Computers

The video game will be administered on two laptop computers with fast graphics processors ($1700 each, $3400 total).

TRAVEL

Research conference

Funds are requested for travel to the International Meeting for Autism Research annually.

SUPPLIES

Research materials

In Year 1, we request funds for software licenses for MATLAB ($500) and the MATLAB Statistics Toolbox ($200). In addition, psychometric test kits will be a significant one-off expense in Year 1 (ADOS-G $1480, ADI-R $216, Social Responsiveness Scale $168, Wechsler Abbreviated Scale of Intelligence $497). As electrode sets and caps must be regularly replaced in order to maintain high quality of EEG data, we request funds at the close of the grant period for an amortised portion of this replacement cost ($3500).

OTHER DIRECT COSTS

Subject fees

We request $100 per subject, for each of 15 subjects per year (approximately five each in the autism, sib, and control groups), to compensate families for their time in behavioral and EEG recording.

Subject travel

We request transport to Cornell for an average of three visits for each subject, at $20 per return trip. Ithaca is a rural area, subjects are spread all over Tompkins and surrounding counties, and many of the distances involved will be large. This travel total of $60 is multiplied by 15 subjects per year for each of the two years to yield $900, with an annual adjustment for inflation.

Publication costs

We budget for one article at the currently typical open-access publishing rate of $3000 per article.

INDIRECT COST

Autism Speaks' rate of 10% ($10,906 for the full two-year period) is used.

Budget

	YEAR 1	YEAR 2
Undergraduate students, half-time, academic year	25,920	27,216
Undergraduate students, full-time, summer	16,848	17,690
Travel: International Meeting for Autism Research	1800	1800
Subject fees	1500	1500
Subject travel	900	927
Research materials and supplies	3061	3500
Publication costs		3000
Computers	3400	
Indirect cost 10%	5343	5563
	$58,772	$61,196

Facilities and Resources :
Laboratory space for the proposed research will be housed in a suite of rooms on the ground floor of the Martha Van Rensselaer Building at Cornell University. Facilities within the Department of Human Development include a 128-channel BioSemi ActiveTwo EEG system, a state-of-the art EEG system that offers several advantages over others in use and on the market. BioSemi uses active electrode technology: with pre-amplifiers built right onto the electrodes, optical coupling, and battery-powered amplifiers isolated from the power mains, noise pickup from the surrounding electromagnetic environment and from subject movement is minimised – an especially important consideration in autistic children who fidget and rock. Furthermore, the high input impedance of the pre-amplifiers allows the system to match a much higher scalp impedance, obviating the need for scalp abrasion – a property of great value when dealing with persons with autism who are hypersensitive to touch. The system uses two computers, one for stimulus presentation and the other for EEG data recording, synchronised with each other via a parallel-port interface.

The Department of Human Development maintains a close link with the Racker Centers, a major provider of autism services that partners with schools in Tompkins and Cortland counties. Our behavioural studies of autism have been able to recruit about twenty children with autism per year from the Racker Centers.

The Principal Investigator is originally a computer scientist by training and works closely with the Game Design Initiative at Cornell (GDIAC). GDIAC is an interdisciplinary group within the Faculty of Computing and Information Science incorporating computer programmers, artists and designers working cooperatively to transform game concepts into professional-quality video game software. GDIAC supports undergraduate courses in game design and development, graduate student projects in game technology, and collaborative undergraduate research in a wide range of departments and disciplines from economics to fine arts. GDIAC has implemented a multidisciplinary curriculum on the theory and application of video game design including artificial intelligence, network programming, physics, art, music, neuroscience, media studies, and technology and society. Graduates of GDIAC join high-profile video game companies such as Electronic Arts and Microsoft.

Private, secure space is available in the laboratory area for desktop computing, data storage and analysis, and writing. The space includes a waiting area, a small conference room, and a large centre configured to seat up to six research assistants. The offices and research laboratories are equipped with office supplies, printers, photocopiers, and a fax machine, all of which are available for use during the project period. Cornell University provides technical support in writing programs, technical support in preparing graphs and other visual materials, and secretarial assistance. A variety of statistical, graphics, and word-processing programs is available in the Department of Human Development. Dedicated lines in the offices and laboratories provide access to mainframe computer networks that can be used for mass storage, large-scale statistical analyses, and mathematical modelling. The principal investigator has access to all these systems and support services to assist the proposed research. The College of Human Ecology at Cornell University provides a staff help desk that can be accessed seven days per week. The College of Human Ecology also provides free training for principal investigators, research assistants, and other research staff in the use of programming languages and statistical analysis packages.

The computing environment includes Pentium-Pro and –IV equipped platforms, linked in a secure intranet. Each computer is served by a laser or ink-jet printer. Access to off-line data is available through CD-ROM drives. The e-mail system provides for interoffice and interdepartmental electronic transfer of messages and files, as well as message service to the Internet and continuous WWW backbone access, including on-line access to all of the Cornell University Library's networked resources. These resources will be available to the principal investigator and the project team throughout the project period. Research documents and data will be stored on secure subnets (in the case of electronic documents) and in locked filing cabinets (in the case of hardcopies).

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

NAME	POSITION TITLE
Matthew K BELMONTE	Assistant Professor
eRA COMMONS USER NAME MBELMONTE	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	YEAR(s)	FIELD OF STUDY
Cornell University, Ithaca, NY	BA	1990	English and computer science
University of California San Diego, La Jolla, CA	MS	1994	neurosciences
Sarah Lawrence College, Bronxville, NY	MFA	1998	fiction
Boston University, Boston, MA	PhD	2001	behavioural neuroscience
University of Cambridge, Cambridge, UK	postdoctoral	2002-2006	brain imaging

A. Positions and Honors.

Positions and Employment

1997-1998 Scientific Programmer, Howard Hughes Medical Institute, New York University, New York, NY
2001-2002 Senior Research Scientist, Tuneprint Corporation, Cambridge, MA
2002-2006 Senior Research Associate, Autism Research Centre, University of Cambridge, Cambridge, UK
2006- Assistant Professor, Department of Human Development, Cornell University, Ithaca, NY

Other Experience and Professional Memberships

1994-present Cognitive Neuroscience Society
1996-present Society for Neuroscience
2004-present International Society for Autism Research
(interim chair, Publications Committee, 2006)
2000-2006 Scientific Review Council, Cure Autism Now foundation
2006-present Advisory Committee, University of Connecticut biennial conference on Literature and Cognitive Science
2007-present Editorial Board, *Autism Research*

Honours

2006 MRC scholarship to Cold Spring Harbour course on the Biology of Social Cognition
2004 Other Prize, Marlowe Society, Cambridge
2002 selected for IEEE-EMBS International Summer School on Biomedical Imaging
2001 International Society for Magnetic Resonance in Medicine student stipend
2001 Russek Award for outstanding doctoral research, Boston University School of Medicine

B. Peer-reviewed publications (in chronological order).

Original reports:

1. **Belmonte MK**, Egaas B, Townsend J, Courchesne E. NMR intensity of corpus callosum differs with age but not with diagnosis of autism. *NeuroReport* 1995; 6(9):1253-1256.
2. **Belmonte MK**. Shifts of visual spatial attention modulate a steady-state visual evoked potential. *Cognitive Brain Research* 1998; 6(4):295-307.
3. **Belmonte MK**. Abnormal attention in autism shown by steady-state visual evoked potentials. *Autism* 2000; 4(3):269-285.
4. **Belmonte MK**, Yurgelun-Todd DA. Permutation testing made practical for functional magnetic resonance image analysis. *IEEE Transactions on Medical Imaging* 2001; 20(3):243-248.
5. **Belmonte MK**, Yurgelun-Todd DA. Anatomic dissociation of selective and suppressive processes in visual attention. *NeuroImage* 2003; 19(1):180-189.

6. **Belmonte MK**, Yurgelun-Todd DA. Functional anatomy of impaired selective attention and compensatory processing in autism. *Cognitive Brain Research* 2003; 17(3):651-664.
7. Schmidt GR, **Belmonte MK**. Scalable, content-based audio identification by multiple independent psychoacoustic matching. *Journal of the Audio Engineering Society* 2004; 52(4):366-377.
8. Gomot M, Bernard FA, Davis MH, **Belmonte MK**, Ashwin C, Bullmore ET, Baron-Cohen S. Change detection in children with autism: an auditory event-related fMRI study. *NeuroImage* 2006; 29(2):475-484.
9. **Belmonte MK**, Carper RA. Monozygotic twins with Asperger syndrome: differences in behaviour reflect variations in brain structure and function. *Brain and Cognition* 2006; 61(1):110-121.

Reviews:

1. **Belmonte MK**, Cook EH Jr, Anderson GM, Rubenstein JLR, Greenough WT, Beckel-Mitchener A, Courchesne E, Boulanger LM, Powell SB, Levitt PR, Perry EK, Jiang Y, DeLorey TM, Tierney E. Autism as a disorder of neural information processing: directions for research and targets for therapy. *Molecular Psychiatry* 2004; 9(7):646-663.
2. **Belmonte MK**, Allen G, Beckel-Mitchener A, Boulanger LM, Carper RA, Webb SJ. Autism and abnormal development of brain connectivity. *Journal of Neuroscience* 2004; 24(42):9228-9231.
3. Baron-Cohen S, **Belmonte MK**. Autism: a window onto the development of the social and the analytic brain. *Annual Review of Neuroscience* 2005; 28:109-126.
4. Baron-Cohen S, Knickmeyer RC, **Belmonte MK**. Sex differences in the brain: implications for explaining autism. *Science* 2005; 310(5749):819-823.
5. **Belmonte MK**. Abnormal visual motion processing as a neural endophenotype of autism. *Cahiers de psychologie cognitive / Current Psychology of Cognition* 2005; 23(1-2):65-74.
6. **Belmonte MK**, Bourgeron T. Fragile X syndrome and autism at the intersection of genetic and neural networks. *Nature Neuroscience* 2006; 9(10):1221-1225.
7. **Belmonte MK**, Mazziotta JC, Minshew NJ, Evans AC, Courchesne E, Dager SR, Bookheimer SY, Aylward EH, Amaral DG, Cantor RM, Chugani DC, Dale AM, Davatzikos C, Gerig G, Herbert MR, Lainhart JE, Murphy DG, Piven J, Reiss AL, Schultz RT, Zeffiro TA, Levi-Pearl S, Lajonchere C, Colamarino SA. Offering to share: how to put heads together in autism neuroimaging. *Journal of Autism and Developmental Disorders* 2007 (in press).

Current and pending support:

Active: None

Pending:

1. "CAREER: Integrative Behavioural and Neurophysiological Studies of Normal and Autistic Cognition Using Video Game Environments," 16/08/2008 – 15/08/2013, $480,639 total direct costs requested.
US National Science Foundation – Directorate for Social, Behavioral and Economic Sciences
The goal of this project, broadly stated, is to elucidate how attention, perceptual organisation, executive function and social cognition relate to each other developmentally, and to identify the neurophysiological underpinnings of this relationship in contexts of normal and abnormal development. The focus is on normal development, and the case of developmental disorders is used as an informative contrast. Thus the methods resemble those specified in the current proposal, though the objective differs. Full funding for this NSF proposal would overlap fully with the Autism Speaks budget amounts under the categories of equipment, supplies, subject fees and subject travel, and with one half of the personnel costs (i.e., three students).

2. "Video Game Environments for Perception, Attention, and Social Cognition in Autistic Children and their Siblings: A Multi-Site Behavioural and EEG Study," 16/08/2008-15/08/2011, $372,809 total direct costs requested.
US Army office of Congressionally Directed Medical Research
This proposed project is part of a collaborative research network with Martha Herbert at Massachusetts General Hospital and Jeanne Townsend at the University of California San Diego. It emphasises the development of advanced EEG analytical methods and mechanisms for data sharing, and combines EEG measures with structural MRI. The EEG portion of this proposed work uses methods similar to those in the current Autism Speaks application. Full funding for this CDMRP proposal would overlap fully with the Autism Speaks budget amounts under the categories of equipment, supplies, travel, subject fees and subject travel, and with one half of the personnel costs (i.e., three students).

Regarding the partial overlap of both these proposed projects in the category of student personnel costs, it must be emphasised that the rate-limiting step on further development of the video game – into a more comprehensive data-gathering tool and eventually, we hope, into a vehicle for behavioural therapy – is the number of students whom we're able to recruit. Competition for these students is keen, as there are always more potemtial programming projects than there are highly qualified students to work on them. Even in the event that one of these pending proposals were to be funded, therefore, funds from Autism Speaks to round out the full complement of six undergraduate student positions would be very useful indeed.