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Research Paper

Evidence of hyper-plasticity in adults with Autism Spectrum Disorder



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ABSTRACT

Background: Long-term potentiation (LTP) is a form of synaptic plasticity involved in learning and memory. Abnormal levels of LTP have been suggested to contribute to symptoms in a number of disorders, and here we examined the extent to which LTP may be affected in autism spectrum disorders (ASD). While animal models of ASD have suggested LTP may be atypical, the results have been inconsistent in terms of the direction of abnormality.

Method: In the present study a paradigm for non-invasively eliciting LTP in humans was utilized to test a group of adults with ASD and matched controls. This paradigm uses high-frequency visual stimulation as the LTP-inducing stimulus, and the effect of LTP is reflected by an increase in amplitude of the visually-elicited N1b component of the visual evoked potential (VEP).

Result: Main effects for Hemisphere and Tetanus were found. While Group interactions were not found, a Group by Tetanus interaction was approaching significance and was determined to be weak evidence against the null ($p_{H0|D} = 0.44$) therefore, LTP effects were explored within groups for the N1 component. It was found that the ASD group had a greater N1 amplitude compared to controls.

Conclusion: Our results showed that the ASD group had greater N1 amplitude post-tetanus over the right hemisphere compared to controls and demonstrate elevated LTP. These results support the notion of enhanced perceptual functioning, as elevated LTP may be related to superior visual processing due to overspecialised neural networks in ASD.

1. Introduction

Autism spectrum disorder (ASD) is characterised by impairments in social interaction, verbal and non-verbal communication, and co-occurring restricted behaviours and interests ([American Psychiatric Association, 1994, 2013](#)). The most recent revision of the diagnostic criteria DSM-5 includes sensory symptoms (hyper-or-hypo sensitivity) and deficits across auditory, visual and tactile domains. ASD is a growing concern as the disorder now affects 1 in every 68 individuals ([Autism New Zealand Inc, 2011; CDC, 2014](#)). Understanding the underlying cause of ASD is a key objective for neuroscientists.

Recently, a variety of clinical disorders have been suggested to be due, at least in part, to abnormalities in long-term potentiation (LTP; see [Bliss & Cooke, 2011; Clapp, Hamm, Kirk, & Teyler, 2012; Kirk et al., 2010](#) for reviews). LTP is a form of synaptic plasticity by which neural systems change with experience, and is thought to be how learning and memory occur in the brain ([Bliss & Collingridge, 1993a, 1993b; Yuste & Bonhoeffer, 2001](#)). In contrast, long-term depression (LTD) is where the efficacy of the synaptic processes reduced and is thought to be a complementary process to LTP in order to assist learning and memory

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(Massey & Bashir, 2007). Recent evidence suggests that LTP is thought to be compromised in a number of clinical disorders. For example, LTP is reduced in depression (Normann, Schmitz, Fürmaier, Döing, & Bach, 2007) and schizophrenia (Çavuş, Reinhart, Roach, Gueorguieva, Teyler, Clapp, & Ford, 2012; Mears & Spencer, 2012). In contrast, and as outlined below, there is some evidence that LTP may be increased in people with ASD (Oberman et al., 2010, 2012) and which may contribute to hyperconnectivity. Hyperconnectivity itself may manifest as core symptoms such as repetitive behaviours and sensory issues. The aim of the current study was to further address the extent to which there are LTP anomalies in humans with ASD. Specifically, whether or not LTP is different in ASD compared to typical controls.

1.1. Animal models of LTP

While animal models of ASD have been employed to gain insight into LTP in ASD, two animal models of ASD have predicted opposite outcomes in terms of cortical LTP. On one hand, a mouse model for Fragile X Syndrome (FXS), in which the *Fmr1* gene is knocked out (Bakker et al., 1994) has been used to examine ASD. FXS is the largest known genetic cause of ASD, explaining approximately 2–5% of cases (Yun & Trommer, 2011) and shares many characteristics with ASD such as social anxiety and repetitive behaviours (Rogers, Wehner, & Hagerman, 2001). Findings from the *Fmr1*-KO mice suggest hypo-plasticity in the form of decreased cortical LTP (Desai, Casimiro, Gruber, & Vanderklish, 2006; Li, Pelletier, Perez Velazquez, & Carlen, 2002; Zhao et al., 2005). Yet another FXS study suggests that cortical LTP may reach normal levels at higher rates of stimulation (Meredith, Holmgren, Weidum, Burnashev, & Mansvelder, 2007).

On the other hand, the Valproic Acid (VPA) rat model of ASD has been shown to display hyper-plasticity in the form of increased cortical LTP (Rinaldi, Perrodin, & Markram, 2008). In humans, valproic acid was given to treat seizures but was found to cause birth defects and an increased risk of ASD in babies born to women who took VPA while pregnant (Rinaldi, Kulangara, Antonello, & Markram, 2007). This led to the development of the VPA rat model of ASD (Rodier, Ingram, Tisdale, & Croog, 1997). Rats prenatally exposed to VPA display behavioural similarities to human ASD, such as repetitive behaviours and social abnormalities (Schneider & Przewlocki, 2005). Rinaldi et al. (2008) found that VPA rats demonstrated significantly enhanced LTP in the prefrontal cortex relative to the control group.

However, recent evidence from alternative mouse models of ASD such as *Shank3* (G/G) mice (Speed et al., 2015) and mice with *MECP2* mutations – a model of Rett's syndrome (Moretti et al., 2006) have demonstrated hypo-plasticity at the cellular level, while mice with *neuroligin-3* mutation (Etherton et al., 2011) have demonstrated hyper-plasticity similar to that of VPA mice. The dichotomy between the two outcomes in neuroplasticity suggests that the ASD brain model can be characterised with enhancements and impairments which could explain the heterogeneous nature of symptoms seen in ASD (Desarkar, Rajji, Ameis, & Daskalakis, 2015).

The extent to which findings from animal studies can be generalised to humans is limited (Kirk et al., 2010), as highlighted by the contradiction with respect to LTP between mouse models. Of course, it may be that these animal models are probing different pathologies, each resulting in a different outcome for synaptic plasticity (Oberman et al., 2010). In addition, each model could relate to a different subpopulation along the autism spectrum. This leaves uncertainty as to whether or not plasticity, specifically LTP, is affected in human individuals with ASD.

1.2. Human measure of LTP

Methods to study LTP noninvasively in humans have been developed, one technique involves Transcranial magnetic stimulation (TMS) a non-invasive method to stimulate small areas in the brain, in order to measure LTP in humans (Esser, Huber, Massimini, Peterson, Ferrarelli, & Tononi, 2006; Wagner, 2007). TMS is considered safe and a viable alternative to invasive electrical stimulation (Esser et al., 2006). Over the past decade TMS has been investigated as a potential tool to treat secondary and comorbid symptoms in ASD (see Oberman, Rotenber, & Pascual-Leone, 2015; Oberman et al., 2016- for reviews). While results from TMS studies are promising in some instances, the differences in protocol (single, paired, repeated pulses and paired associated – whereby pairs of electrical median nerve are concurrently stimulated with single TMS pulses), variability of symptoms, and variation in the regions of stimulation make it difficult to establish TMS as a diagnostic or therapeutic tool in individuals with ASD (Oberman et al., 2015, 2016).

Much of the LTP work done *in vivo* has been established by repetitive TMS (rTMS) studies. rTMS is where repetitive bursts of transcranial magnetic stimulation are applied to a region of the cerebral cortex (such as the motor cortex) in order to measure the cortical activity. Primary human studies trying to elicit LTP through rTMS have produced inconsistent results, either failed to produce any cortical change or change that were not significantly long lasting to be LTP (Hallett, 2000; Madea, Keenan, Tormos, Topka, & Pascual-Leone, 2000). Work by Huanag, Edwards, Rounis, Bhatia, and Roth (2005) used 3 bursts of 50 Hz rTMS (theta burst stimulation – TBS) applied every 200 milliseconds either continuously (cTBS) or intermittently (iTBS) for 3 min, over the motor cortex (M1). This TBS of rTMS resulted in an increase of the motor evoked potential amplitudes over time demonstrating LTP in typical controls (Huanag et al., 2005). An alternative way to measure LTP non-invasively is through electroencephalography (EEG). In this paradigm, scalp electrodes are used to measure electrical activity from the brain in response to a sensory stimulus. These brain responses are then used to calculate the event-related potential (ERPs). The stimulus is first presented slowly to gain a baseline ERP. The stimulus is then presented rapidly (referred to as tetanus), which is thought to perform the same task as electrical stimulation used in invasive studies (i.e. to induce LTP; such as PAS, Klöppel et al., 2015), followed by a return to the baseline rate of stimulus presentation. Changes in the ERPs before and after the rapid sensory stimulation are analysed to give an index of LTP in order to see

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