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Neuroimaging perspectives on fetal motor behavior

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Highlights

- Supraspinal centres are likely to be an important driver in early motor behaviour
- CineMRI has established itself as the optimal modality for the analysis of fetal motor behaviour in health and disease.
- Fetal cineMRI has identified increasing intrauterine constraints as a potential influence for sensorimotor feedback, with implications for CNS maturation
- Motor behaviour analysis is an important biomarker for neurodevelopmental disease, and will be augmented by a multimodal imaging approach.

ABSTRACT

We are entering a new era of understanding human development with the ability to perform studies at the earliest time points possible. There is a substantial body of evidence to support the concept that early motor behaviour originates from supraspinal motor centres, reflects neurological integrity, and that altered patterns of behaviour may precede clinical manifestation of disease. Cine Magnetic Resonance Imaging (cineMRI) has established its value as a novel method to visualise motor behaviour in the human fetus, building on the wealth of knowledge gleaned from ultrasound sonography based studies. This paper presents a state of the art review incorporating findings from human and preclinical models, the insights from which, we propose, can proceed a reconceptualisation of fetal motor behaviour using advanced imaging techniques. Foremost is the need to better understand the role of the intrauterine environment, and its inherent unique set of stimuli that activate sensorimotor pathways and

shape early brain development. Finally, an improved model of early motor development, combined with multimodal imaging, will provide a novel source of in utero biomarkers predictive of neurodevelopmental disorders.

Keywords: fetal; MRI; neurodevelopment; motor behaviour; intrauterine constraints

INTRODUCTION

Motor behaviour is a complex output of the neurological system, and one that evolves during early life. The maturation of neural networks governing motor output is incompletely understood, particularly in terms of normal physiological development in utero.

The analysis of motor behaviour forms an integral part of the clinical assessment of neurological integrity throughout life. A substantial body of evidence has accumulated on the the relationship between neurological lesions and the impact on motor behaviour starting from the prenatal stage. Prematurely born infants have been studied at gestation-equivalent time points, as well as the fetus itself in utero using imaging techniques, finding that aberrations in early motor behaviour are associated with a spectrum of delayed onset neurodevelopmental disorders

There are two fundamental issues that must be addressed in order to make observations of fetal motor behaviour meaningful: firstly, a framework must be defined which contains relevant evidence-based criteria for normal motor behaviour; secondly, an optimal method is required for detecting motor behaviour. Both issues must account for gestational age-related changes, whether from the perspective of the intrinsic developmental neurobiology of the fetus, or possible effects of its extrinsic uterine environment.

This paper will begin by reviewing the current understanding of the neuroanatomical basis of fetal motor behaviour as gleaned from observations in human and experimental animal models, with a focus on emerging evidence for early cortical involvement in generating movements. Next will follow a discussion on the approaches to analysing fetal motor behaviour in utero, and the pathogenesis of

abnormal motor behaviour. The final sections will discuss the rationale for why the time has come to study fetal motor behaviour with MRI, highlight the new insights gained from several recent studies, examine current challenges with this technique, and argue the potential of a multimodal imaging approach to improve in utero neurological analysis and identify biomarkers for neurodevelopmental disease.

1 THE NEUROANATOMICAL BASIS OF FETAL MOTOR BEHAVIOUR

Mature motor behaviour is generated by a network of CNS regions converging on spinal motor circuits, with varied contributions from each element during early development. There are likely to be important developmental roles for independent inputs from the primary motor cortex, brainstem motor centres, cerebellum and spinal cord.

Early theories for motor development proposed the existence of predetermined patterns in the central nervous system (CNS); later it was postulated that the mechanism involved interactions between genetic programmes and environmental signals, within which existed a set of behaviours that were highly conserved, and others that allowed for phenotypic variation.[1] An alternative concept implicated the inherent properties of movement in terms of synergistic muscle forces, which limited the range of activation patterns available to the CNS. Motor development has also been conceptualised as a dynamical system in which behaviours emerge spontaneously through self-organisation, thus not requiring *a priori* representations in the CNS. A somewhat unifying theory emphasised gene-environment interactions mediated through predetermined motor networks which undergo epigenetic regulation based on afferent information generated by motor behaviour. A selection process then

proceeds to retain favourable patterns of motor output.[2]

These hypotheses have in part emerged from observations of the development of motor skills in early life, and so have provided a valuable framework within which to organise and direct experimentation that aims to elucidate the underlying mechanisms. The following section will discuss the experimental evidence from human and animal models for functional motor circuitry in the early CNS.

1.1 SUPRASPINAL INVOLVEMENT IN EARLY MOTOR BEHAVIOUR

The corticospinal tract (CST), originating principally in the primary motor cortex, contains axons that modulate the activation of alpha motor neurons, and is vital to the maturation of motor behaviour.[3] Unmyelinated CST axons reach lumbar regions of the spinal cord by Gestational Age (GA, or post-menstrual) 24 weeks, though maturational processes are not complete until 2 years of age in humans. Evidence for early CST functionality has been found using transcranial magnetic stimulation of the motor cortex in ex utero preterm infants, where motor responses in the upper limbs are evoked from GA 26-equivalent age.[4]

Recent functional MRI (fMRI) studies in preterm infants have provided insights into cortical involvement underlying spontaneous motor activity. Bilateral changes in blood-oxygen dependent level (BOLD) signal are observed in the peri-Rolandic area, which restrict to the contralateral cortex by term equivalent age. Nearer term the BOLD signal changes increasingly focus on an area that corresponds to the anatomical location of the primary motor cortex.[5] However, findings from animal models suggest that CST-directed motor output is contingent on the maturation of connectional specificity with cord neurons, a sufficient capacity for CST synapses to modulate cord circuits, and the formation of the

motor homunculus.[6] More specifically, studies in primates demonstrate that supraspinal motor pathways modulate posture and tone[7,8], and provide a neurological basis for the functional impairments associated with localised CNS lesions.[3] Other neuromotor activity is generated elsewhere but with CST modulation: bulbospinal pathways mediate extension in proximal muscles such as the trunk and neck, and flexion in distal muscles of the hands, both of which are antagonized by the CST. Early motor cortical damage may result in predictable pathological postures: opisthotonus, and highly flexed distal extremities.[9,10] However, a marked degree of early CNS plasticity has been demonstrated with unilateral ablation studies to the motor cortex, which results in the long-term maintenance of both ipsi- and contralateral CST terminals in the spinal cord by the (contralateral) intact motor cortex.[4,11]

1.2 SUBCORTICAL INTEGRATION OF MOTOR BEHAVIOUR

A central component in the motor network is the motor thalamus: primate studies demonstrate that a subset of thalamic nuclei play a key role in the integration and relay of signals within the motor circuitry from central and peripheral regions.[12] The nuclei within the motor thalamus show a degree of overlap with dendritic arbors extending beyond their functional domain, this may allow integration of signals from several networks and contribute to motor learning.[13] The cerebellum and basal ganglia comprise the major projections to nuclei in the ventral thalamus, which in turn projects to the primary motor (M1), supplementary motor (SMA) and premotor cortices.[14] The cerebello-thalamic efferent pathway focuses on M1[15], and appears to generate reactions in response to sensory input[12], as it also projects extensively to the somatosensory cortex and receives input from spinal sensory afferents.[16] The basal ganglio-thalamic pathway converges on the SMA, and is thought to be a contributor to volitional movement selection.[17]

To date there is a lack of study on these aspects of the motor network from a developmental perspective. However, a range of adverse conditions in early life appear to target these regions. Low-risk preterm born infants show thalamic, globus pallidus and putaminal volume reductions[18,19], and altered thalamo-cortical connectivity in a multitude of regions.[20] Infants experiencing intrauterine growth restriction (IUGR) demonstrate a brain-sparing effect with preservation of global brain tissue volumes[21], yet demonstrate altered cortio-striato-thalamic connectivity.[22] Furthermore, studies in utero are required to understand the onset of these changes and how they may relate to altered motor behaviour. However, in early development motor behaviour is considered non-volitional and is likely to have contributors in rostral regions of the neuraxis, for which there is evidence that spontaneous activity in neural circuitry that may be contributing to motor behaviour.

1.3 THE ROLE OF SPONTANEOUS NEURAL ACTIVITY IN GENERATING MOTOR BEHAVIOUR

From an embryological perspective, spontaneous activation of motor circuits is important for the refinement of the pattern of axon terminals.[23] Consistent with the development of visual pathways, nerve terminals that experience relatively higher levels of activity are advantaged in the competition for limited neurotrophic resources.[6,24] Spinal motor neurons exhibit intrinsic depolarisations mediated by calcium-activated potassium channels that control rhythmic firing behaviour.[25] This property of spinal circuits develops prior to muscle fibre innervation to facilitate axonal pathfinding, and eventually drives early limb movements in chick embryos.[26] Vertebrates demonstrate cyclical motor activity in early stages of gestation, which manifests as a synchronous contraction of several muscle groups. In rodent models, this behaviour persists after transection of the spinal cord, suggesting a primary role for motor pattern generation independent of supraspinal influence.[27] Furthermore, sheep models that have begun the transition towards early voluntary motor patterns will revert to cyclical behaviour following

high cervical-spine transection.[28]

In humans this inherent neural activity has not been demonstrated in the spinal cord, contrary to other CNS regions such as the retina and cerebellum which contain pacemaker neurons - specialised cells with unstable membrane potentials that can fire without synaptic input.[24] However, in anencephalic human fetuses, a variable repertoire of spontaneous motor activity has been observed despite the severe cortical and subcortical malformations[29,30], which may support the hypothesis of spinal-located drivers for early motor behaviour. Furthermore, the relatively early development of cortical sensorimotor networks may in part result from afferent neuronal stimulation during spontaneous motor activity. Evidence from electroencephalographic (EEG) data in preterm infants showed delta-brush oscillations being driven by sensory stimulation in a cortical somatotopic pattern.[31]

1.4 DEVELOPMENT OF THE PERIPHERAL CIRCUITRY REQUIRED FOR MOTOR BEHAVIOUR

Beyond the CNS, there is evidence from post-mortem studies demonstrating that by GA 12 motor peripheral nerves in the upper limb have reached and innervated their muscle targets in human fetuses.[32,33] The neuromuscular junction (NMJ) has been observed by GA 9 in the lower limb, and histological evidence for NMJ maturation in the masseter muscles has commenced by GA 12.[34] The neural infrastructure for sensory and proprioceptive feedback appears relatively early in gestation; classical experiments in postmortem fetal tissue demonstrated reflexive responses to tactile cutaneous stimulation very early in development[35,36], while muscle spindles mature between GA 20-30.[3]

These findings complete the neural circuit from the cortex to the effector organs of movement at a

relatively early stage of in utero development, and thus allow for spontaneous motor behaviour to manifest. Early motor behaviour may confer survival advantages and contribute to physiological development; some of the proposed paradigms are discussed in the following section.

1.5 PUTATIVE PHYSIOLOGICAL BENEFITS OF FETAL MOTOR BEHAVIOUR

Preclinical models have found evidence for behavioural adaptation in fetuses using umbilical cord compression as a stimulant, which primarily results in reduced oxygen delivery to the fetus and a state of hypoxia. Cord compression led to a transient phase of hyperactivity in near-term age rodents, followed by a suppression of movement until clamp removal.[37] The fetus demonstrated a hyperkinetic state with curls of its trunk and retroflexions of its head. The authors propose that an accidental cord compression by the fetal body, which is more likely to occur near term, is resolved by the vigorous activity, and is therefore an ontogenetic adaptation that promotes the survival of the fetus in utero. Hyperkinesis during a hypoxic state would be otherwise counterintuitive.

An altogether different physiological relationship is between motor behaviour and mechanical loading for promoting skeletal development. Physical activity from skeletal muscle use is known to have beneficial effects on bone development in preclinical models and human preterm infants. Preclinical models have shown that in early infancy bone is very susceptible to exercise and immobilization, resulting in increased bone formation or rapid resorption.[38,39] These findings are supported by human studies, whereby daily physical activity in the form of manipulation of limbs against passive resistance has been found to increase bone mineralization in preterm infants, a group that is particularly vulnerable to bone deficiency syndromes.[40,41]

The third trimester is associated with a significant increase in calcium and phosphorous across the placenta, which coupled with high levels of oestrogen and calcitonin favour bone formation; it is likely that 'fetal kicking' provides the mechanical load which facilitates the process.[42] It is this missed increase in growth factors and the minimisation of motor activity that is thought to underlie the bone disease of prematurity.[43]

Aside from these physiological benefits for early motor activity, the most studied paradigm is its role as a marker of neurological integrity and maturation. Several approaches have been utilised to interrogate this relationship: imaging modalities to directly visualise the fetus in utero; observations in preterm infants, but with several caveats; lastly, indirect measures of fetal movements that rely on maternal counting or more recently wearable devices. The following section will discuss these topics in greater detail.

2 OBSERVATIONS AND CLINICAL ASSESSMENT OF FETAL MOTOR BEHAVIOUR

2.1 THE ROLE OF ULTRASONOGRAPHY IN FETAL MOTOR ANALYSIS

Ultrasound Sonography (USS) is the traditional method for studying fetal motor function, and is able to capture fetal movements at a high temporal resolution and provide an impression of fetal activity as part of a developmental assessment. In the UK it is routine clinical practice to be offered USS by GA 15, in order to estimate the fetal age, parity, and to screen for gross morphological anomalies.[44] A further USS scan is recommended at GA 20 for the purpose of detecting structural abnormalities.[45] From a research perspective, USS has been used to investigate motor behaviour from its emergence early in gestation through to term age.[46–48] However, a major limitation of USS is the restricted field-

of-view and the consequential partial view of the fetus beyond GA 20. In order to circumvent this problem two USS transducers have been used to increase the field-of-view between GA 20-36[49]; though this approach has not been widely adopted and remains inadequate.[50]

The following sections will describe and synthesise the wealth of information that has been gleaned from several decades of USS-based interrogation of motor behaviour in utero; focussing on the emergence of motor activity, its classification into behavioural states, and how motor behaviour is altered in response to CNS lesions and insults.

2.2 THE ONTOGENESIS OF NORMAL FETAL MOTOR BEHAVIOUR

Fetal motor activity in humans emerges at approximately GA 7. Early work on fetal motor behaviour suggested three categories: exteroceptive elicited reflexes, proprioceptive reflexes, spontaneous movements.[35] The early spontaneous motor repertoire including startles, isolated limb and regional movements, generalised sequences that involve the whole body, twitches, breathing and swallowing (Fig 1).[46,51–53]

Once established, the standard repertoire of motor behaviour spans the whole gestational period up to the commencement of voluntary behaviour at 3-5 months post-term.[46,51,54] The spontaneous motor behaviour that occurs at the highest frequency is General Movements (GM). GM involve the whole body in a sequence of globalised movements of variable speed, amplitude, direction and fluency[55,56]; GM may last from a few seconds to several minutes, and wax and wane in intensity and force, and have a gradual onset and end. During GM limbs will demonstrate flexion/extensions with superimposed rotations and directional changes.[57]

Fetal motor behaviour has also been assessed using alternative perspectives, namely behavioural states and maternal counting of fetal movements. Despite significant research, their clinical utility is limited, though they have provided some useful insights into the organisation of fetal behaviour; their contributions are discussed in the following sections.

2.2.1 THE ESTABLISHMENT OF FETAL BEHAVIOURAL STATES

The level of arousal or 'behavioural state' is known to be a important factor when examining the motor activity of an infant[58], and so it is advisable to make observations when subjects are in non-sleep states, and also when not crying or fussing. Preferably, GM analysis should be performed when in active wakefulness or 'state 4'.[59] In the neonate (including preterm-born infants), behavioural states have been defined based on EEG and phases of rapid eye movements, which can distinguish sleep-like states from wakefulness from approximately GA 27.[60]

In- and ex utero studies have implemented continuous observations for up to 24 hours, and found decreasing trends in overall activity near term.[61–63] Fetal studies have described stable linkages between physiological parameters that categorise behaviour into 4 states (1F to 4F), based on fetal activity, heart rate patterns and eye movements.[64] Several studies have found well-defined cyclical variation in fetal behavioural states from approximately GA 34, and possibly from GA 30.[65–67] This finding appears to have played a significant role in the perspective that it is circadian-type entrainment of behaviour which is the primary and most influential driving force underlying reductions in activity levels later in gestation.[68]

In the fetus, a temporal concordance between phases of rapid eye movement and breathing movements has been found to emerge at a similar age and is indicative of its behavioural state within the sleep-wake cycle.[69] Recent improvements in transabdominal fetal cardiac activity monitoring has allowed better definition of ventricular rate and beat variability.[70] Associations have emerged between relatively greater cardiac variability, but not rate, and better mental development and psychomotor indices.[71] Fetal behaviour is also affected by chemical exposure via maternal circulation, with disruption of behavioural states due to alcohol consumption, steroids, opioids, and possibly caffeine.[72–76]

This body of work has limited use clinically, but has been important in terms of developing a broader understanding of behavioural physiology, and for providing important reference data for how levels of activity change during gestation.

2.2.2 MATERNAL PERCEPTION OF FETAL MOVEMENTS

In more routine clinical practice is fetal movement counting (FMC) by the mother, particularly later in gestation.[77] FMC is postulated as a non-specific indicator of fetal well-being, particularly when there are concerns, though definitions and its implementation vary.[78] Generally FMC is a method whereby the mother quantifies the movements she feels in order to alert caregivers to fetal compromise.[79]

However, there is a significant discrepancy between actual fetal movements and those maternally perceived, with estimates ranging from 16 to 100% depending on the type of movement.[77] This is further complicated by the misappropriated perception of physiological processes, such as breathing or uterine contractions.[80–82] Attempts to devise wearable technology to detect patterns of motor behaviour still demonstrate an accuracy of between 40-80%.[83] Though there may be a limited role for FMC as

part of fetal health monitoring, it is very unlikely to be a useful parameter for improving our understanding of CNS maturation.

It is long established that CNS insults and lesions are likely to result in identifiable neuromotor abnormalities even with subtle neuropathological changes. This concept has been extended to the fetus based on the reference data of normal in utero motor behaviour; the following sections will discuss the context for this discovery and how motor analysis has been applied.

2.3 PATHOGENESIS AND ANALYSIS OF ABNORMAL FETAL MOTOR BEHAVIOUR

Impaired motor function is a common sequela of many pathological conditions in early life. The assessment of motor function has historically constituted an important component of the neurological examination in early infancy[84,85], since abnormalities in posture, tone, reflexes, and gross and fine motor behaviour correlate strongly with neuropathology.[57,86–88] An interactive fetal examination is not feasible, but an assessment of spontaneous motor behaviour may serve as a marker and predictor of neurological integrity.[89]

The sensitivity of the assessment of spontaneous movements has been investigated for the neurological evaluation of the neonate (preterms and up to voluntary movements at 3 months of age), and deemed adequate for incorporation into several comprehensive assessment tools.[88,90] Furthermore, the analysis of spontaneous motor activity, namely General Movements, has been shown to be predictive of cerebral palsy in infants born preterm[58], which when combined with white matter anomalies on structural brain imaging reaches a sensitivity and specificity of 100%.[91,92]

2.3.1 DEFINING ABNORMAL MOTOR BEHAVIOUR

Continuing with the concept of spontaneous motor behaviour being predictive of neurodevelopmental disorders, disruption to the normal GM pattern is defined by altered character, or quality, of motor sequences. There are several descriptive systems for abnormal GM, which rely on the Gestalt analysis of the assessor, for both ex utero infants and the fetus using imaging. The initial step is to judge the normality of an individual's GM in terms of complexity, fluency, and variability. Subsequently the GM sequence can be classified according to the original categorisation, which included the following subtypes: (1) 'Poor repertoire', when a sequence of successive movement components is monotonous and movements of the different body parts do not occur in the normally complex manner. (2) 'Cramped-synchronised', GM appear rigid and lack the normal smooth and fluent character; all limb and trunk muscles contract and relax almost simultaneously. (3) 'Chaotic', GM demonstrate large amplitude movements without fluency, and movements can appear abrupt.[59]

There have been attempts to quantify the subjective assessment of GM using an 'optimality' construct, in which each aspect of the GM is scored 2 for normality, and 1 if abnormal, and the global score used for quantitative analysis; however the overall scores did not lend themselves to re-synthesis of the actual motor behaviour, resulting in the abandonment of this approach.[59] Furthermore, the use of quantitative changes in motor behaviour analysis in pathological cases compared to age-matched healthy controls has not been shown to provide clinically useful information, in terms of parameters such as the number of movements in a given period of time.[29,93,94]

A further classification was suggested in which spontaneous movements were categorised as hypo- or hyperkinetic; a relatively broad spectrum of genetic syndromes were classified, resulting in the

suggestion that autosomal recessive disorders with a predilection for neuromuscular-skeletal-skin disorders tended to show hypokinetic motor patterns. Whereas hyperkinesis-associated conditions consisted of sporadic or rare structural or chromosomal disorders that involve the CNS.[95] It is difficult to generalise this concept as the study sample contained severe diseases with a high mortality rate: only 14% survived but with disability.

Finally, a simpler method of classifying abnormal GM into 'mild' and 'definite' was devised using a set of infants with relatively more common neurological lesions both in preterm and full-term infants. These categories continued to be based on GM complexity, variation and fluency, of which lack of fluency determines mildly abnormal GM; all three features must be altered for definitely abnormal GM. CNS lesions included cerebral oedema, parenchymal haemorrhages, hydrocephalus, and periventricular leukomalacia. In this small study the authors demonstrated a strong association between infants with definitely abnormal GM and neurological disability; the majority of infants with mildly abnormal GM had a normal development.[96]

Using the definitions devised in earlier studies explained above, the following section will explore the strength of the association between the analysis of spontaneous motor behaviour and CNS lesions and neurodevelopmental outcome, beginning with findings from ex utero studies.

2.3.2 ASSOCIATIONS BETWEEN EARLY LIFE ADVERSITY, ABNORMAL MOTOR BEHAVIOUR AND NEURODEVELOPMENTAL OUTCOME

As alluded to earlier, for term-born infants GM analysis is predictive of severe neurodevelopmental disorders with predominant motor symptomatology, such as cerebral palsy[97], particularly in high-risk

cohorts that showed 'definitely abnormal' GM such as periventricular leukomalacia, preterm birth and haemorrhagic or ischaemic stroke.[85] Abnormal GM have particular characteristics that are associated with cerebral palsy and behavioural problems by 8 years of age, motor patterns that show stiff movements and reduced complexity.[98] Up to 75% of infants that experience perinatal asphyxia, based on abnormal cardiotocography, low APGAR, or acidosis, show abnormal GM, of which approximately half normalised by 3 months; long term outcomes remained unknown.[99]

There are emerging associations between abnormal GM and the spectrum of mild neurological dysfunction (MND), albeit with lower sensitivity and specificity.[100,101] MND encompasses several domains including posture, tone, voluntary motor control, coordination and fine motor control.[102] In low risk cohorts postnatally, there is a relatively low proportion of subjects that demonstrate abnormal GM, and very rarely show major neurological disease. Up to 10% may show complex MND in early childhood, that is, several domains assessed as abnormal. There is a weak association between definitely abnormal GMs in the perinatal period and complex MND at 18 months of age.[103] 'Mildly Abnormal' GM soon after birth is associated with abnormal outcomes in childhood such as attention-deficit hyperactivity disorder, and attendance at special educational schools.[98,104] Furthermore, abnormal GM at 2 weeks post-term is associated with MND affecting multiple domains at 18 months and 4 years of age.[103,10565,66]

The fetus has been studied in pathological conditions using USS, although less extensively than pre- and full-term infants, and with smaller sample sizes and largely in single observational studies. The analysis of fetal GM using a robust framework has the potential to allow earlier detection and prediction of neurodevelopmental disorders.

Anencephalic fetuses, though not clinically useful in terms of long term outcomes due to the absolute mortality rate, demonstrate abnormal GM, which are forceful, jerky and large amplitude.[29] This finding is useful to illustrate several issues: that in the presence of severe supraspinal abnormalities motor behaviour continues to be generated , displays abnormal character, and provides some support for infracortical drivers.

A case report of Smith-Lemli-Opitz syndrome, an inborn error of cholesterol metabolism with a broad range of clinical features and outcomes, demonstrated abnormal GM: altered complexity, and preponderance of head and trunk movements over limb involvement.[106] Again, this case represents a severe end of early genetic disorders with neurological sequelae, but with altered motor behaviour that may be reflect specific CNS lesions: ventriculomegaly, abnormal gyrification, corpus callosum abnormalities and cerebellar hypoplasia.

Maternal stress in the form of trauma (motor vehicle and cycling accidents, falls) showed no effect on the quality of GM, and normal neurodevelopmental outcomes at 12 months.[107] However, this sample contained a heterogeneous gestational age range and restricted mechanism of injury, and so presents difficulties in generalisability particularly if the physiological stress response of the mother was not sufficiently induced as suggested by the lack of hypercortisolaemia.

The IUGR population has been studied more than other clinically relevant paradigms with GM analysis. IUGR fetuses demonstrate an overall reduction in the level of spontaneous motor behaviour, and GM that appear abnormal with monotonous, slower and less variable sequences.[108] A later small

longitudinal cohort study showed that uncomplicated IUGR showed no alterations in GM quality. However with worsening condition of the fetus as indexed by heart rate patterns, GM quality changed to poor repertoire, followed by negligible motor behaviour. This study was also able to show that the quality of GM was consistent immediately pre- and postnatally.[109] Interestingly, in IUGR without structural brain lesions on imaging, there appears to be a normalisation of GM quality with increasing age postnatally (noting that GM cease at 3-5 months), which may reflect a degree of CNS plasticity[94,110], but does not imply that there may not be longer standing subtle alterations in structure or functional networks that manifest later in life.

Fetuses exposed to premature rupture of amniotic membranes, with resultant reduction in amniotic fluid volume, had movements of smaller amplitude and reduced speed, which returned to normal appearances rapidly after birth.[111] Later work in larger groups of premature membrane rupture and oligohydramnios also found fetal GM with altered amplitude, speed and complexity.[112]

These studies in infants or fetuses using USS have provided compelling evidence for alterations in motor behaviour either as a result of neurological aberrations, or predating the onset of overt clinical manifestations of a range of subtle and severe neurodevelopmental disorders. Furthermore, some of these studies have presented some of the first human data on the effects of physical restriction on motor behaviour as seen in oligohydramnios, though this may be due to a confounder effect. The following section explores the emergence of MRI as a novel modality for interrogating fetal motor behaviour, presents the rationale for reconceptualising motor behaviour, and discusses the potential for multimodal MRI to provide a comprehensive neurological assessment in utero.

3 RECONCEPTUALISING FETAL MOTOR BEHAVIOUR USING MRI

MRI has transformed our ability to conceptualise neurological integrity at all stages of development; by offering a multimodal approach that MRI data presents the closest measures of in vivo CNS structure and function. In light of several recent studies exploring the role of MRI in human motor behaviour, new insights have been formed on the characterisation of motor behaviour during gestation, and its potential role as a biomarker of neurological disease.

The following section will present an overview of practical aspects of in utero MRI, followed by a discussion on the effects of intrauterine constraints on motor behaviour, and finally how motor behaviour has been shown to reflect the condition of the CNS and neurodevelopmental outcomes. Pertinent evidence from complementary studies in animal models will be used to contextualise the findings from these preliminary studies in humans, as well as provide targets for future directions.

3.1 PRINCIPLES OF MRI AND APPLICATIONS IN THE HUMAN FETUS

MRI is a versatile modality for studying a broad spectrum of biological phenomena throughout human life. Spontaneously generated fetal motor behaviour has previously degraded images of anatomical structures due to long acquisition times. However sub-second image acquisition coupled with post-processing computational methods allow volumetric reconstruction of fetal neuroanatomy which has opened an avenue for accurate objective measures of neurological development.[81] Furthermore, this has allowed MRI studies of dynamic processes such as swallowing, movements at joints, and cardiac motion.[113–116]

Where available, MRI is being used to diagnose and monitor a range of congenital and acquired anomalies, particularly following the detection of a suspicious finding on USS. Fetal MRI and USS have been compared to each other in a variety of pathological states, the consensus being that these two techniques are complementary, often providing a more comprehensive neuroimaging assessment[117–119], though MRI shows improved detection of CNS anomalies.[120,121]

3.1.1 MRI SAFETY IN EARLY NEUROLOGICAL DEVELOPMENT

MRI is a safe, non-invasive and non-ionizing clinical imaging modality. Concerns naturally arise when using any imaging modality in the fetus, both in terms of immediate teratogenicity and long term development effects. In this regard, UK guidelines do not recommend MRI prior to 18 weeks gestation, unless there are exceptional clinical concerns. The magnitude of the primary magnetic field does not occur in natural phenomena, however there are no known adverse biological effects due to such interactions.[122] However repeated radiofrequency pulses result in energy deposition in tissues and can lead to heating effects. This is measured by the specific absorption rate and the distribution of thermal energy deposition has been investigated in pregnancy. Animal models have demonstrated that thermal energy generated by metabolic processes in the fetus dissipate through two routes: thermal energy transfer from fetal to maternal blood in the placenta and directly from the fetal tissues into the surrounding amniotic fluid.[123] Specific absorption rate remains within safety limits if the average radiofrequency deposition based on the adult mother is limited to 2 Watts/kilogram.[124,125] Clinical studies into the long term effects of MRI exposure to fetuses have also shown no adverse outcomes in terms of growth deficits[126], or changes in physiological parameters.[127]

3.1.2 DEVELOPMENT OF CINE MRI SEQUENCES FOR VISUALISING FETAL MOTOR BEHAVIOUR

MRI has emerged as a research method for observing motor behaviour in the fetus with advantages over USS (Fig 2).[128–130] Firstly, MRI has a larger field-of-view, and allows visualisation of the whole fetal body. Secondly, the spatial resolution of MRI is higher than USS which allows for improved representation of fetal anatomy.

Several dynamic MRI sequences (cineMRI) have the potential to capture fetal motor behaviour: Echo-planar imaging is capable of acquiring cine data but has to compromise on signal-to-noise ratio when used at high temporal resolution, thus lowering spatial resolution.[131] Single shot Fast Spin Echo can achieve images at high spatial resolution, but also suffers from low signal-to-noise ratio and incurs a high specific absorption rate when operated at high temporal resolution.[132] Studies have suggested that balanced-steady state free precession cine sequences are particularly suited to imaging fetal movements[128,129,133,134], and has several advantages: firstly, specific absorption rates are lower compared to Spin Echo sequences under equivalent imaging conditions.[135] Secondly, it offers high signal-to-noise ratio and image contrast properties that show fluid/tissue boundaries unambiguously.[133,136]

Fetal cineMRI studies have used slice acquisition times that result in frame rates of approximately 3 frames per second.[129,130] However, simulations of edited video sequences of a postnatal limb movements have suggested that there is no loss of detectable movements.[128] Furthermore, using 30-40mm slices coupled with multislice imaging allowed sufficient spatial coverage to capture all of the fetal limbs together with head and trunk whilst also providing a detailed view of fine movements in the

extremities at all gestations, and helped to track limbs as they moved in 3D space. An early study utilised cineMRI to capture motor behaviour in fetuses with severe neurological abnormalities in comparison to a control group, and suggested a reduction in movement in fetuses with myelomeningoceles.[129]

3.1.3 FETAL MOTOR BEHAVIOUR OBSERVED USING CINE MRI

Observations of fetal motor activity using cineMRI data showed no gestational age-dependent change in the fetal motor repertoire in terms of either the cessation or introduction of new movement patterns. Rotations, flexions, and extensions in the main anatomic regions (upper limbs, lower limbs, head, and trunk) were observed, both in isolation and as part of GM. Fine-motor activity in the fingers was observed from GA 18, as well as grasping and stroking movements. Yawns and other mouthing movements, including swallowing occurred less frequently. Eye and breathing movements were also present at all ages. Non-GM movements involving the whole body occurred irregularly at all GAs, these included kicking, brief twitches, and startles. Fetal GM had an observable pattern similar to those in neonates, usually with a brief isolated twitch indicating the start.[128]

This data is consistent with the findings from the archive of USS studies. However, cineMRI has afforded a significantly improved visualisation of the fetus within the constraints of the intrauterine

environment, and how this relationship changes with age. This has highlighted potentially significant issues with motor analysis in utero, and are elaborated on in the following sections.

3.2 NEW INSIGHTS FROM CINE MRI ANALYSIS OF FETAL MOTOR FUNCTION

3.2.1 THE INTRAUTERINE ENVIRONMENT AND ITS EFFECT ON MOTOR BEHAVIOUR

The fetus is surrounded by the physical barrier of the uterus, which undergoes dramatic changes during pregnancy: organ mass increases from 70 grams to over a kilogram, with volumetric changes of 10 milliliters to 5 litres; uterine wall thickness shows minimal increases from approximately 5 to 7 milimetres, but with regional variability.[137–139] These factors together with intrauterine pressure determine the wall tension, which increases with gestation.[137] These structural changes form the basis of the problem of increasing intrauterine constraints as a function of gestational age, a problem that has been largely overlooked in the USS-based literature. The general consensus being that motor activity is consistent pre and postnatally, and that the overall physiological reduction in activity is solely related to the establishment of behavioural states.[51,140,141] There is now evidence in humans, as well as a significant body of findings from animal studies that require a careful examination of mechanical aspects of the intrauterine environment as the fetus ages. With this information it is erroneous to suggest that fetal GM are similar in the near term period either to those performed earlier in gestation, or to ex utero preterm and term born infants.

Several USS-based studies that posit that fetal movements near term age are performed as freely as earlier in gestation and with no difference to ex utero infants.[142,143] However, they have tended to restrict their analysis to gross body movements, presumably because other movements are more difficult to concurrently identify with USS - a field-of-view limitation. With cineMRI, it is observed

that it may be challenging for the fetus to change from a flexed to an extended posture or vice versa from GA 28 onwards[128], coupled with a lack of uterine stretch under the pressure of fetal kicking. A study modelling limb forces during motor behaviour showed uterine deformation during fetal kicking at mid-gestational age resulted in a maximal deflection of only 7mm.[114] Thus supporting the view that near term fetuses are not as free to move as earlier in gestation.[128]

CineMRI demonstrates that the quality of movements is affected by spatial constraints, as near term fetuses are restricted to smaller amplitude limb movements. There is a quantitative influence of spatial constraints in a localised manner, with a reduction in lower limb movements from GA 31.[128] The lower limb demonstrates a high degree of flexion at the hip and knee joints, corroborating a similar finding in an USS study, but with a cohort whose age was restricted to GA 30 onwards.[144] Full-term infants are also more flexed in their lower limbs than preterm infants at term equivalent age, indicated by smaller joint angles in the knee and ankle.[145] Furthermore, it was estimated that distal lower limb muscles are able to generate over twice the force as proximal muscle groups. Whether this is a direct effect of uterine restrictions requires studies with larger sample sizes.

Moreover, studies have examined limb postures as a possible prognostic marker in the context of neurological lesions in early development, suggesting that frequent movement toward the face is a positive marker.[146,147] CineMRI data suggests that the uterine morphology facilitates fetal shoulder adduction and elbow flexion, thus enabling the extremities to be positioned nearer the face, as there appears negligible amniotic fluid adjacent laterally. This may be a mechanical consequence, whether despite this there continues to be neurological advantages remains unknown. Similar findings have been shown when placing preterm infants in a nest-style bed, which facilitates midline-directed hand

movements.[148]

The concept of pre and post-natal motor behaviour being consistent is challenged by biomechanical studies in ex utero infants, which show that by manipulating lower limb posture divergent behavioural and dynamic effects are manifested: upright postures result in increased resistance to motion at the hip, and so require larger muscle torques to drive flexion, which ultimately leads to smaller amplitude movements and more synchronous movements at the knee joint.[149] The physiological environment of the fetus is fundamentally different, providing a reduced, though not abolished, gravitational exposure, and changing level of mechanical interactions with the uterine walls.[150] These factors are likely to induce a different set of limb and trunk postures than those experienced ex utero, which will influence the forces and amplitudes of joint motion, an issue that has only recently been investigated with a pilot study using cineMRI data.[114] Current findings are restricted to modelling joint motion and forces in healthy fetuses and within a very narrow age range, but do provide a proof of principle for the technique.

Animal models of fetal motor behaviour have explored the possibility of a direct influence of a restrictive environment on motor development.[151] Furthermore, spatial constraints also provide evidence of motor learning in murine models, which have shown an increase and persistence of conjugate limb movements after removing a mechanical restraint between limb pairs.[152] There is also evidence for the abolition of certain fetal movements as free space reduces with gestation, as well as an overall reduction in motor activity; both effects are reversed postpartum and with exteriorization of the murine fetus.[153]

Further studies have recorded the overall level of activity as measured by the total movement frequency of all anatomical regions within a 20-minute widow in fetuses of an altricial species during the last period of gestation (Embryonic day 16-21, rat fetus movement begins on E16).[153,154] The fetuses were observed under several conditions: firstly, in utero (observations were made through a maternal midline abdominal incision); secondly, in amnion (fetuses were externalised but remained within the amniotic membranes); thirdly, in bath (fetuses completely removed from all membranes and placed in a saline bath); in all preparations the umbilical cord remained attached. A significantly higher level of activity was found towards the end of this age range in fetuses in the bath, as compared to both other preparations. Their findings suggest a direct influence of the lack of free space on movement frequency. The environmental changes that are experienced by the rat fetus are remarkably similar to those found in the human, such as the faster volumetric growth of the fetus relative to the uterus, a reduction in amniotic fluid volume near term, and also an increase in fluid viscosity with increasing gestation.[155]

The findings from cineMRI coupled with animal studies show a clear effect of in utero spatial constraints both in terms of influencing motor activity as well as effects on CNS development as suggested by evidence for motor learning in animals. Furthermore, the sensory driven effects of neural plasticity are evident from studies of neural function in utero, with evidence that the environment plays a role in moulding neural circuitry both pre and postnatally. Furthermore endogenous spontaneous brain activity is likely to be an important driver for maturation[156], and as discussed earlier there is mounting evidence for a sufficiently mature sensorimotor network with peripheral connectivity.[5,157,158] The environment of the fetus changes substantially during gestation, likely resulting in an evolving sensorimotor activation pattern. Preliminary work modelling forces involved with motor behaviour, if

extended more broadly across gestation may provide further characterisation of environmental influences driving maturation of sensorimotor networks.[114]

The following section will explore novel findings from cineMRI relating abnormal motor behaviour to CNS lesions, which contains in itself a potential biomarker for CNS-related disease, and is likely to contribute to a comprehensive neurological analysis in utero.

3.2.2 CINE MRI MOTOR ANALYSIS AS A BIOMARKER OF NEURODEVELOPMENTAL DISEASE

Our group performed the first study relating fetal motor analysis with brain structure and associated postnatal neurodevelopmental outcomes.[159] This study used cineMRI to identify normal and abnormal sequences consistent with established GM definitions. A positive association was found between postnatal outcome, structural MRI and GM analysis in a heterogeneous cohort, providing further support that fetal motor analysis reflects pathological deviations in CNS development.

The abnormal subgroup was heterogeneous both in type of CNS lesions and severity; we stratified this group based on severity, and found a positive relationship between GM and neurodevelopmental outcome after a relatively short period of follow up. This may be related to a high representation of ventriculomegaly cases, which are known to be associated with milder outcomes, often requiring a longer duration of follow up to identify cognitive-behavioural adversity.[160] The use of structural brain MRI to assess neurological integrity in the fetus has an important caveat, in that CNS lesions are associated with a variable clinical outcome.[160–162] Again, sufficient follow up will allow for

maturational processes to occur and the emergence of the utimate neurodevelopmental status against which the strength of structural, functional and behavioural biomarkers can be judged.

There is still a need to improve the understanding of fetal motor behaviour, and the classification of abnormal patterns. A detailed characterisation of motor patterns, together with a model of the role of intrauterine constraints will help develop a comprehensive understanding of the maturation of sensorimotor networks, which from studies in preterm infants have been shown to undergo important developmental trajectories early in life, and which are likely affected by the physical environmental.[5]

4 FUTURE PROSPECTS FOR THE ROLE OF FETAL MOTOR BEHAVIOUR ANALYSIS

With the current state of imaging technology and the enormous capacity for plasticity in the developing CNS, it is unwise to function within a paradigm that a single unifying biomarker exists to index neurological integrity. All parameters have an inherent degree of uncertainty. Therefore, an optimal approach is to integrate all feasible parameters to interrogate the CNS and generate a comprehensive characterisation, which ultimately may personalise to the individual. This paper has argued for one such biomarker. This final section will draw together the potential of MRI to generate multiple indices of neurological integrity, and discuss the role of motor behaviour in this emerging landscape.

The last fifteen years has witnessed the adoption of fetal brain MRI as a valid clinical imaging modality. The maturation of fetal image acquisition tools and analytical methods will herald a new era for characterizing and understanding the development of the CNS in vivo. Advances in image registration techniques allow the construction of robust 3D volumes of the brain overcoming image

degradation due to motion artefacts.[163–165] More recently functional MRI (fMRI) derived fetal resting state networks have been acquired[166], again with solutions devised to maintain the integrity of datasets without discarding motion corrupted data.[167] Logical next steps would be to characterise the neural networks involved in motor activity in normal and abnormal cohorts, which may also elucidate further differences with preterms.

From a clinical perspective, with the improved visualisation of the fetus, it would be prudent to develop a robustly designed study with longitudinal assessments, to further explore the utility of an in utero assessment of motor activity. Given the routine use of clinical motor assessment from childhood, and the range of tools available for early postnatal life, there is certainly the potential to incorporate the analysis of spontaneous movements as a biomarker for later impairments. This will require research using homogeneous cohorts of known CNS disease with a spectrum of severity to attempt to identify in which groups a combined structural and neuromotor analysis confers a greater predictive ability.

A potential paradigm for application arises from small longitudinal cohorts of individuals at high risk of schizophrenia-spectrum disorder. There is evidence that neuromotor dysfunction predates the onset of disease by many years, is manifest in childhood, and is restricted to the first 2 years postnatal - a period of rapid neuromotor development.[168,169] This concept is consistent with the neurodevelopmental hypothesis of schizophrenia.[170,171] In the study several neuromotor parameters were assessed including postures, coordination, tone, involuntary movements amongst others, which showed significantly poorer neuromotor abnormalities and motor skills compared to control groups which included unaffected siblings and healthy controls. Aberrant motor behaviour may reflect an in utero exposure related to maternal factors, or an intrauterine insult.[169] It would be logical to perform a prospective

study to investigate for the presence of in utero motor dysfunction coupled with structural and functional imaging biomarkers that might be associated with delayed onset neurological, neurodevelopmental and neuropsychiatric disorders.[172–176]

To reiterate, General Movement analysis as the fetus approaches term will require more detailed study and a novel framework, given that over the last 10 weeks of gestation the character of normal fetal movements is fundamentally different from the large amplitude movements present in preterm infants of equivalent age.[50,142] This should proceed in parallel to improving our understanding of intrauterine constraints, regarding which there are two pertinent issues: firstly, how is the uterus imposing mechanical constraints on movement, particularly with increasing gestation, and if so what are the consequences; secondly, are there active feedback pathways (sensorimotor, proprioceptive), that are stimulated by the fetus' interactions with its immediate physical environment, which modulate and shape its motor development.

These issues may be addressed with progress on automated and quantitative analysis of the mechanics of fetal movement across gestation, for which pilot studies have begun to develop novel methods. This will allow objective tracking of anatomical regions and limbs, in the context of age-related intrauterine constraints, and so define the level of freedom or restriction that a fetus is likely to encounter as it progresses through gestation.[177]

CONCLUSIONS

There now exists an optimised and validated fetal MRI protocol which has been utilised to observe the full range of fetal motor behaviour. CineMRI imaging is an effective method for monitoring and

quantifying movements in late gestation with near full-body coverage, and is thus able to add new information on physiological motor development beyond what was capable previously with USS. The nature of the intrauterine environment has been highlighted as an important influence, which imposes both global and localized spatial restrictions on fetal movements. Animal studies have paved the way for in vivo human studies, and can suggest how to address the question of how early neuromotor development may be modulated by sensory and proprioceptive feedback mechanisms. Further work is required to improve the characterisation of fetal motor behaviour in the context of CNS lesions, and then to draw associations with potential findings from advanced imaging techniques that will provide an insight into the functional circuitry driving these changes.

Ethical Approval

For this type of submission formal consent or approval is not required.

Author Contributions

TTAH and MAR wrote and conceived the manuscript.

Competing Interests

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Figure Captions

Figure 1 Onset of Fetal Motor Behaviour

Fetal motor activity appears to emerge at 7 weeks of gestation, with a slow truncal flexions. Over the subsequent weeks internal organic develop slightly earlier to limb movements. Generalised motor activity also begins at approximately 8-9 weeks, lastly eye movements are observed towards the end of the first trimester.[1,46,141]

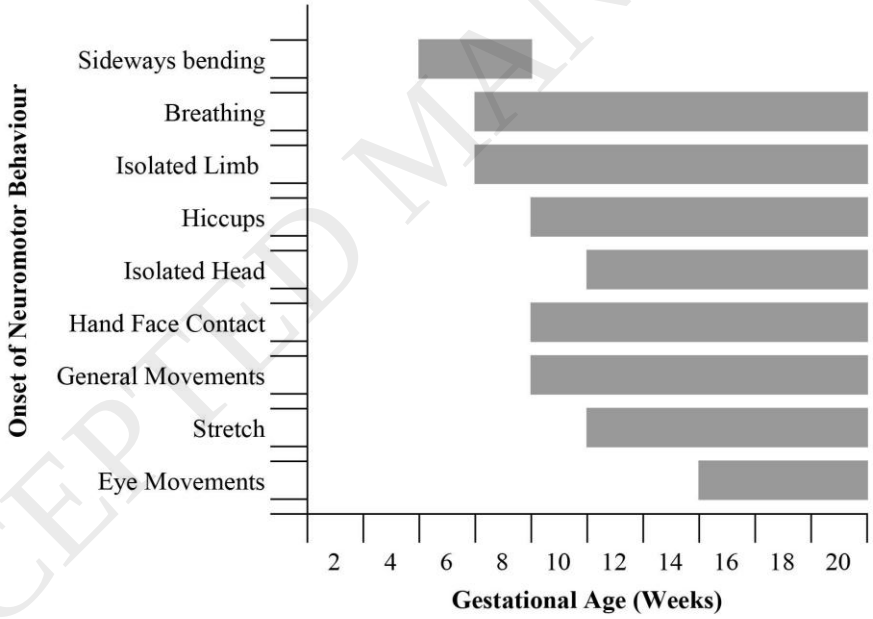

Figure 2 Cine MRI Acquisition of Fetal Motor Behaviour

Cine MRI affords an unrestricted view of the whole fetus, each row represents a different subject. Current cine sequences are acquired at 3 frames per second. Figures A-B are of a GA 23 fetus, at 5 and 6 seconds (s) of a single movement sequence, where the fetus is able to translocate and rotate its body by kicking. Figures C-D are of a GA 28 fetus at 10 and 12s, where the trunk is able to rotate in plane, and with sufficient space to extend its lower limbs. Figures E-F are at GA 36 at 15 and 19s, where the majority of the intrauterine volume comprises the fetus, thus limiting the amplitude of movements (see supplementary data for complete cine sequences).