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REVIEW

The neural circuit basis of Rett syndrome

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Abstract **Rett syndrome is an Autism Spectrum Disorder caused by mutations in the gene encoding methyl-CpG binding protein (MeCP2). Following a period of normal development, patients lose learned communication and motor skills, and develop a number of symptoms including motor disturbances, cognitive impairments and often seizures. In this review, we discuss the role of MeCP2 in regulating synaptic function and how synaptic dysfunctions lead to neuronal network impairments and alterations in sensory information processing. We propose that Rett syndrome is a disorder of neural circuits as a result of non-linear accumulated dysfunction of synapses at the level of individual cell populations across multiple neurotransmitter systems and brain regions.**

Keywords Rett syndrome, MeCP2, neural circuit, ERP, synapse

Introduction

Rett syndrome (RTT) is a progressive neurodevelopmental disorder characterized by normal development for the first 6-18 months of life, followed by a loss of acquired motor and language skills. Patients with RTT frequently develop seizures, growth retardation, and autistic behaviors. Breathing irregularity, gait abnormalities and hand wringing are also commonly found in RTT patients (Chahrour and Zoghbi, 2007; Neul et al., 2010). Mutations in the X-linked gene encoding methyl-CpG binding protein 2 (MeCP2) are responsible for the majority of RTT cases (Amir et al., 1999).

MeCP2 is a highly abundant nuclear protein that preferentially binds to 5′-methylcytosine in CpG dinucleotides through a conserved methyl-CpG binding domain (MBD) (Lewis et al., 1992; Nan et al., 1997). Through its interaction with a repressor complex that includes histone deacetylases (HDACs) and Sin3a, MeCP2 is believed to repress gene transcription (Jones et al., 1998; Nan et al., 1998) and dampen transcriptional noise (Skene et al., 2010). MeCP2 has also been suggested to act as a transcriptional activator (Chahrour et al., 2008), and regulator of mRNA spicing (Young et al., 2005) and miRNA production (Szulwach et al., 2010; Wu et al., 2010). Furthermore, the functions of MeCP2 appear to be modulated through activity-dependent phosphorylation events (Chen et al., 2003; Zhou et al., 2006).

Mice lacking *Mecp2*, or carrying different *Mecp2* alterations, develop neurological phenotypes resembling those observed in RTT; including motor incoordination, hindlimb clasping, aberrant gait, breathing abnormalities, cognitive deficits and premature lethality (Chen et al., 2001; Guy et al., 2001; Shahbazian et al., 2002; Goffin et al., 2012). Deletion of MeCP2 from postnatal and adult mice revealed a similar manifestation of RTT-like phenotypes (McGraw et al., 2011; Cheval et al., 2012). Intriguingly, reintroduction of MeCP2 into behaviorally affected *Mecp2*-null mice is sufficient to ameliorate RTT-like phenotypes (Guy et al., 2007). These results demonstrate that MeCP2 is required for brain function throughout life and RTT is therefore a neuromaintenance rather than a neurodevelopment disorder.

In this review, we will discuss the mechanisms through which MeCP2 maintains proper brain function. We will first examine the role of MeCP2 in regulating synaptic function. Second, we will discuss how loss-of-*Mecp2* leads to neuronal network impairments and alterations in sensory information processing. And finally, we will compare the function of MeCP2 at the circuit level and at the level of individual populations of cells.

Synaptic dysfunction in RTT

The possibility that RTT may be a disorder of synaptic

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dysfunction was raised a decade ago (Zoghbi, 2003). One prominent feature of RTT and mouse models of MeCP2 dysfunction is reduced cortical connectivity between excitatory glutamatergic pyramidal neurons. Analysis of dendritic morphology showed a significant reduction in the number and length of dendrites in RTT cases and *Mecp2*-null mice (Kishi and Macklis, 2004; Armstrong, 2005; Belichenko et al., 2009a; 2009b). Dendritic spines, the postsynaptic neuronal protrusions that receive neuronal input from an excitatory synapse and serve to translate the incoming glutamatergic input into a biochemical signal, are reduced in numbers on the dendrites of glutamatergic neurons in cortex and hippocampus of *Mecp2*-null mice (Belichenko et al., 2009b). Those remaining spines also show decreased spine head size and increased spine neck length indicative of alterations in synaptic contacts (Belichenko et al., 2009b).

In support of these anatomical findings, a number of elegant electrophysiological experiments support the idea of reduced cortical connectivity between glutamatergic pyramidal neurons. Cortical layer II/III and layer V pyramidal neurons from *Mecp2*-null mice exhibited a reduction in spontaneous firing rate that was caused in part by decreased amplitude of excitatory quantal neurotransmission and a decrease in the number of excitatory synapses onto pyramidal neurons (Dani et al., 2005; Chao et al., 2007; Dani and Nelson, 2009; Wood et al., 2009; Wood and Shepherd, 2010). Similar reductions in glutamatergic quantal amplitude were also found to occur at the retinogeniculate synapse in the thalamus (Noutel et al., 2011). Recently, induced pluripotent stem cells (iPSCs) derived from RTT patients' fibroblasts have allowed the study of MeCP2 function in human patients derived neurons (Marchetto et al., 2010). Neurons differentiated from RTT iPSCs show fewer dendrites and exhibit decreased amplitude and frequency of spontaneous excitatory neurotransmission, similar to that observed in RTT mouse models (Marchetto et al., 2010).

Intriguingly, mice overexpressing MeCP2 present a number of phenotypes that resemble the human *MECP2* duplication syndrome including altered motor function, anxiety, learning and memory (Collins et al., 2004; Na et al., 2012). Electrophysiological examination of these mice revealed an increase in glutamatergic quantal neurotransmission and a corresponding increase in the number of dendritic spines (Collins et al., 2004; Na et al., 2012). These studies suggest therefore that MeCP2 exerts a bidirectional control in excitatory neurotransmission.

These deficits in synaptic function also lead to changes in long-term potentiation (LTP) and depression (LTD), cellular mechanisms of prolonged synaptic plasticity considered to play important roles in learning and memory. *Mecp2*-null mice show deficits in LTP and LTD at hippocampal Schaffer collateral-CA1 synapses and layer II/III of S1 somatosensory cortex induced by either high-frequency stimulation or the more physiological theta-burst stimulation (Asaka et al., 2006; Moretti et al., 2006; Guy et al., 2007; Lonetti et al., 2010; Weng et al., 2011). Mice overexpressing MeCP2 exhibit either enhanced (Collins et al., 2004) or attenuated LTP (Na et al., 2012). Paired recordings from synaptically connected pyramidal neurons in layer V cortical neurons revealed that LTP induced using spike-timing protocols was normal in both pre- and post-symptomatic *Mecp2*-null mice (Dani and Nelson, 2009). These data implicate that deficits in LTP may occur secondary to reduced synaptic connectivity between excitatory neurons (Dani and Nelson, 2009).

Alternatively, these deficits may occur due to changes in NMDA receptor function since loss of MeCP2 is associated with altered composition of NMDARs with decreased NR2A subunits and increased NR2B subunits (Asaka et al., 2006). During development there is a gradual replacement of the contribution of the NR2B subunit with NR2A subunits of NMDARs to the excitatory postsynaptic current (Cull-Candy et al., 2001). This shift in the NR2 subunit composition is believed to facilitate experience- or activity-dependent synaptic plasticity of neural circuits (van Zundert et al., 2004). These data suggest that developmental stagnation in the replacement of NMDA receptors may contribute to the decreased excitability of excitatory neurons.

Another form of synaptic plasticity affected in RTT is synaptic scaling, whereby neuronal activity leads to changes in synaptic strength (Qiu et al., 2012). Synaptic scaling is based on the observation that an increase in neuronal activity leads to a decrease in quantal amplitude and a decrease in activity leads to an increase in amplitude (Qiu et al., 2012). The loss of MeCP2 function in rat hippocampal cultures has been suggested to increase expression of the Ca^{2+}-impermeable GluR2 subunit leading to decreased quantal amplitude and synaptic scaling at glutamatergic synapses (Qiu et al., 2012).

These decreases in glutamatergic neurotransmission would be expected to lead to an excitatory/inhibitory (E/I) imbalance, leading to a secondary increase in inhibitory neurotransmission. Indeed, layer V pyramidal neurons exhibit an increase in the spontaneous IPSC amplitude (Dani et al., 2005). This alteration in inhibitory input appears to occur as a consequence of reduced glutamatergic neuron excitability since no alterations in quantal synaptic activity at inhibitory GABAergic synapses were observed in cortical pyramidal neurons (Dani et al., 2005). However, some deficits in inhibitory synaptic function have been observed, although this is restricted to certain neuron types and brain regions. In the thalamus, inhibitory reticular thalamic nucleus (RTN) neurons show an increase in the frequency of quantal inhibitory neurotransmission whereas excitatory neurons of the ventrobasal neurons show a decreased frequency in spontaneous and unitary inhibitory currents (Zhang et al., 2010). In the medulla, reductions in the frequency of quantal inhibitory currents are also observed (Medrihan et al., 2008). Thus, together these data suggest that RTT phenotypes likely manifest through alterations in E/I balance caused by glutamatergic synaptic dysfunction.

Synaptic deficits have also been observed in other neurotransmitter systems. Dopaminergic neurons in the substantia nigra from *Mecp2*-null mice had reduced cell capacitance, decreased dendritic length and reduced dopamine release (Gantz et al., 2011). Furthermore, loss of MeCP2 is associated with a decrease in dopamine, norepinephrine and serotonin levels (Samaco et al., 2009; Taneja et al., 2009).

The role of MeCP2 in inhibitory neurons was recently illustrated by the conditional deletion of MeCP2 from inhibitory neurons. Deletion of MeCP2 from GABAergic and glycinergic neurons in the brain using *Viaat1*-cre, led to the manifestation of a number of RTT-like phenotypes including hypoactivity, hindlimb clasping, motor incoordination, breathing dysfunction and premature lethality, as well as those not normally seen in *Mecp2*-null mice including forelimb clasping and self-injury (Chao et al., 2010). Although inhibitory neurons constitute only about 20% of neurons in the brain, it has been suggested that they contribute to 80% of the workload. Thus, a loss of MeCP2 from GABAergic neurons has a more profound effect on neuronal activity than the number of neurons affected would suggest, and this is therefore reflected in the recapitulation of many of the phenotypes observed in *Mecp2*-null mice. Despite the fact that no differences in glutamatergic synaptic function were observed in these mice, decreased quantal inhibitory current amplitudes, attributed to decreased quantal GABA release, appears sufficient to produce numerous RTT-like phenotypes (Chao et al., 2010).

These compelling data demonstrate clearly that loss of MeCP2 from inhibitory neurons in the brain leads to numerous RTT-like phenotypes, but do so through a mechanism that may be, at least at the level of synaptic activity, unique to that observed in constitutive *Mecp2*-null mice. Although further investigation is required whether different brain regions or cell types show alterations in glutamatergic synapse function, these results offer the possibility that RTT-like phenotypes can be caused by different alterations in synaptic function.

Neuronal network deficits

One possible explanation for how differences in synaptic deficits lead to common phenotypes is that these synaptic alterations lead to common deficits in neuronal network function. That is, decreased excitatory synaptic function or the increased/decreased inhibitory synaptic function disrupts E/I balance leading to impaired neuronal network function. Neurons receive a balance of excitatory and inhibitory membrane currents during ongoing and stimulated activity. The balance of equal amounts of incoming depolarizing and hyperpolarizing currents is essential for maintaining stability in cortical networks. Moreover, this balance facilitates rapid responses to small changes in synaptic input following sensory stimulation thus allowing for efficient sensory information processing. Indeed, an increasing number of studies are being performed to assess neuronal network activity and how disruption in E/I balance leads to neurological deficits.

Hyperexcitability

Maintaining proper E/I balance is essential for the proper control of neuronal network excitability and destabilizing this balance can lead to hyper-excitability of neuronal networks. Indeed, one of the most debilitating symptoms of RTT is the occurrence of seizures, which range from easily controlled to intractable epilepsy, with the most common types being partial complex and tonic-clonic seizures (Jian et al., 2006). However, generalized seizure incidence is extremely low in constitutive *Mecp2*-null mice and mice overexpressing MeCP2 (Collins et al., 2004; Chao et al., 2010). Despite the lack of seizures, cortical network excitability is disrupted in these mice as assessed through electroencephalographic (EEG) recordings. Male *Mecp2*-null mice and female heterozygous mice exhibit decreased frequencies in theta rhythm and the appearance of spontaneous abnormal rhythmic discharges (D'Cruz et al., 2010; Goffin et al., 2012). Similar hyperexcitability is observed in mice lacking MeCP2 from inhibitory neurons (Chao et al., 2010). Furthermore, *in vitro* studies have suggested hyperexcitability in the hippocampus of *Mecp2*-null mice (Calfa et al., 2011). Thus, MeCP2 dysfunction leads to alterations in synaptic activity leading to overall instability in neuronal networks. It is possible that compensatory mechanisms reduce the frequency or severity of such seizures and future work to understand these mechanisms will provide valuable insight into the etiology of this devastating phenotype observed in many RTT patients and other atypical RTT disorders.

Sensory information processing deficits in RTT

A further consequence of alterations in E/I balance is less effective sensory information processing. Without a proper balance between excitatory and inhibitory synaptic inputs, incoming sensory information would have reduced contrast against background activity thus disrupting sensory information processing. One way to assess sensory information processing is through the examination of neuronal oscillations. Neuronal oscillations are thought to be a fundamental mechanism for the coordination and alignment of neuronal responses throughout the cortex.

Sensory information processing can be measured *in vivo* through EEG recordings during the performance of a cognitive, sensory or motor task. The manifestation of these brain activities is recorded as a series of amplitude deflections in the EEG as a function of time and is referred to as an event-

related potential (ERP). ERPs are small compared to the background EEG but can be resolved by averaging single trial epochs. They are characterized as voltage deflections defined by latency and polarity where the amplitude and latency of the polarity peaks are believed to reflect the strength and timing of the cognitive processes related to the event. Notably, RTT patients, as well as patients with schizophrenia and autism, are reported to show alterations in both the amplitudes and latencies of ERP (Bader et al., 1989; Stauder et al., 2006; Uhlhaas and Singer, 2010; Gandal et al., 2011).

ERP recordings in symptomatic male *Mecp2*-null and mice carrying the MeCP2 T158A mutation revealed decreased amplitudes and increased latencies in the N1 and P2 peaks in ERPs recorded during presentation of auditory stimuli (Goffin et al., 2012). These alterations in ERP responses were not observed in pre-symptomatic mice suggesting that neural networks underlying information processing are disrupted by MeCP2 dysfunction in an age-dependent manner, corresponding to the behavioral onset of symptoms (Fig. 1). Further analysis of these ERP responses using time-frequency analysis obviates the limitations of time-amplitude analysis created due to loss of oscillatory information through signal averaging. This analysis revealed that wild-type mice show an increase in event-related alterations in EEG power and phase-locking during development from postnatal day 30 (P30) to P90. This likely reflects the maturation of the underlying neuronal circuit. In contrast, MeCP2 T158A mice do not show a developmental increase in either event-related power

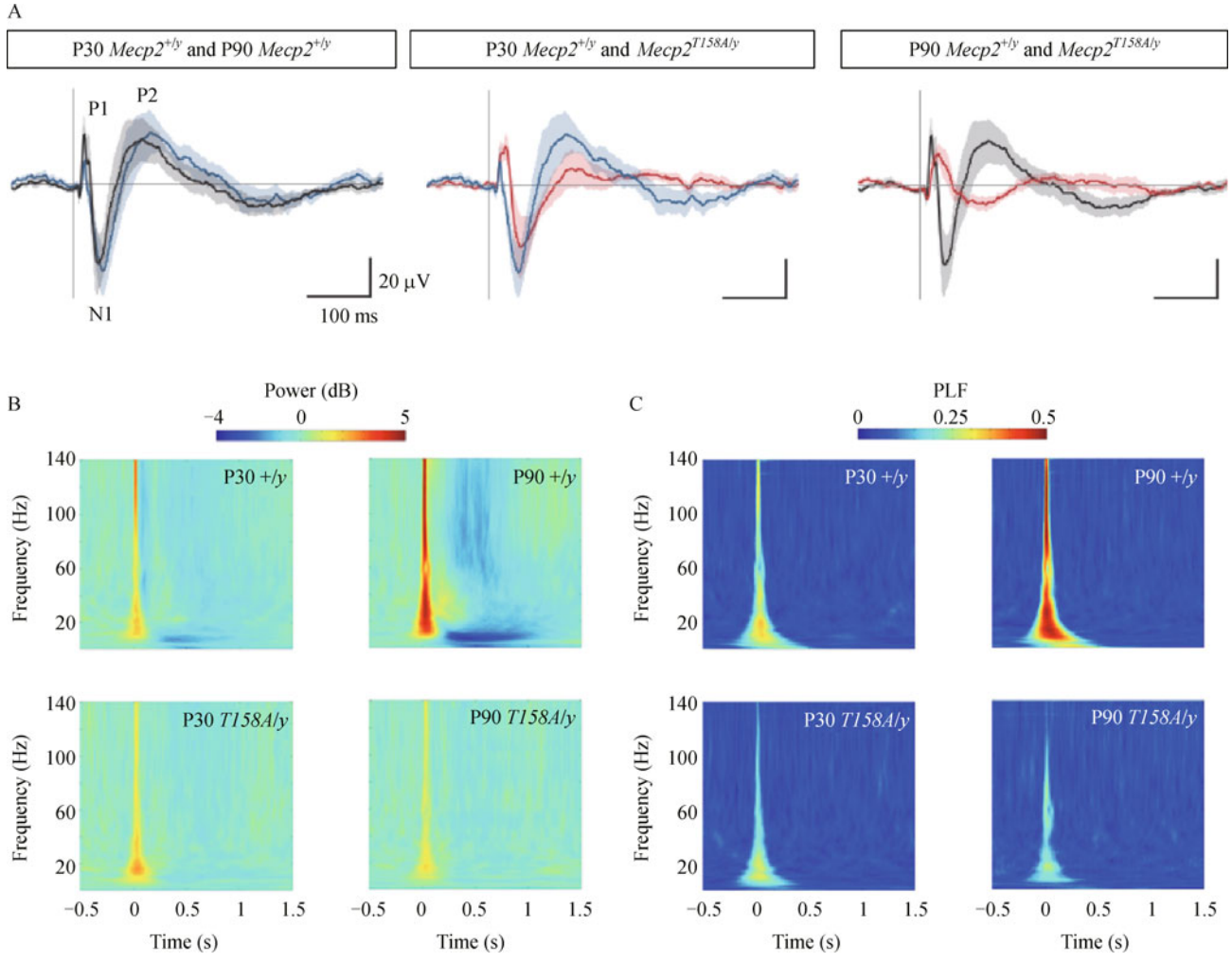

Figure 1 (A) Event-related potentials (ERPs) following 85-dB auditory stimulation in wild-type and MeCP2 T158A mice at postnatal days 30 (P30, pre-symptomatic stage) and P90 (post-symptomatic stage). ERPs are not substantially different between wild-type and MeCP2 T158A mice at P30 but are significantly altered at P90 in MeCP2 T158A mice. (B) Time-frequency plots showing changes in event-related power in response to 85-dB auditory stimulation in wild-type and MeCP2 T158A (T158A/y) mice at P30 and P90. Color represents mean power with warmer colors corresponding to an increased power and cooler colors representing decreased power compared to pre-stimulus baseline. Wild-type mice show clear changes in event-related power from P30 to P90 whereas MeCP2 T158A show no such change. (C) Time-frequency plots showing changes in event-related phase-locking showing development increase in wild-type mice but not MeCP2 T158A mice. Adapted from Goffin et al., 2012.

or phase locking across this time period, suggesting an impairment in age-dependent neural network maturation or a failure in the proper maintenance of functioning networks (Fig. 1).

Alterations in the functional maturation of synaptic circuits have also been shown in other sensory paradigms. Ocular dominance plasticity is a robust experimental paradigm for examining the maturation of visual cortex networks. Deprivation of visual input by suturing one eye induces a functional reorganization of connections in the primary visual cortex, leading to a change in the relative responsiveness of cortical cells to stimulation of each eye. In wild-type mice, these changes are only observed in circuits that are labile and not stable; thus, brief periods of monocular deprivation (MD) trigger ocular dominance plasticity in young but not adult animals. In contrast, ocular dominance plasticity remains in *Mecp2*-null mice at ages when the critical period is normally closed (Tropea et al., 2009). This is consistent with the hypothesis that loss of MeCP2 function leads to deficits in synaptic maturation or stabilization. Similarly, eye-specific segregation patterning undergoes abnormal developmental maturation with the retinogeniculate synapse in *Mecp2*-null mice (Noutel et al., 2011).

MeCP2 is thus required for the maturation and restructuring of neural networks. These alterations are likely to be the result of a loss in sensory experience-dependent remodeling or maintenance of neuronal networks, possibly mediated by activity-dependent phosphorylation of MeCP2 (Zhou et al., 2006; Cohen et al., 2011). It remains to be determined whether these alterations in sensory information processing are conserved among mice lacking MeCP2 from different brain regions and cell-types. However, if this is indeed the case then these results would reveal that it is not the specific alterations in the synaptic function *per se* that is important but rather the effect on overall neuronal network function.

Thus, RTT is not a disorder of specific synaptic modulation and/or maintenance. Rather we suggest that RTT is a disorder of neuronal network modulation and maintenance. That is, RTT is likely the result of the nonlinear accumulated dysfunction of synapses across multiple neurotransmitter systems and brain regions (Fig. 2).

The whole is other than the sum of its parts

Many neurological disorders are considered to have a prominent deficit in one brain area or one neurotransmitter system. Examples of these include Huntington's disease and loss of striatal medium spiny neurons, Parkinson's disease and loss of dopaminergic neurons, amyotrophic lateral sclerosis and degeneration of motor neurons, epilepsy and anxiety through altered GABAergic function, depression and diminished 5-HT function and schizophrenia and impaired NMDA receptor function. Therefore, considerable research effort has been placed in the identification of neuron types and neurotransmitter systems disrupted in RTT.

Previous studies have reported that conditional deletion of MeCP2 from Sim1-expressing neurons in the hypothalamus revealed a role for MeCP2 in aggression, hyperphagia and obesity (Fyffe et al., 2008); loss of MeCP2 from TH-expressing dopaminergic and noradrenergic neurons leads to

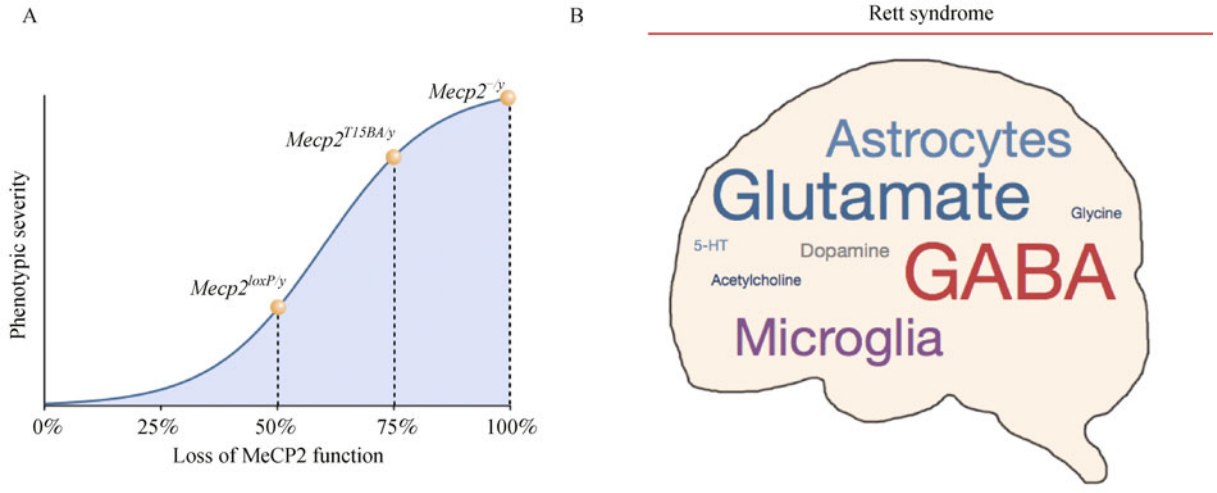

Figure 2 Loss of MeCP2 function leads to a nonlinear accumulative expression of RTT-like phenotypes. (A) The level of MeCP2 function is critical for maintaining proper brain function. Hypomorphic *Mecp2*$^{loxP/y}$ mice show a 50% reduction in MeCP2 protein levels but show mild RTT-like phenotypes. *Mecp2*$^{T158A/y}$ mice show an approximate 75% reduction in MeCP2 function (through decreased binding to methylated DNA and MeCP2 protein stability) but show considerable RTT-like phenotypes approaching those of *Mecp2*-null mice. Deletion of MeCP2 function in postnatal/adult mice demonstrated that even small increases in the loss of MeCP2 function, led to profound changes in RTT-like behaviors. (B) Alterations in the activity of a number of different neuronal types and neurotransmitter systems have been shown to occur in mouse models of RTT. The more the pervasive the loss of MeCP2 the greater the severity of the RTT-like phenotypes.

alterations in motor activity (Samaco et al., 2009); deletion of MeCP2 from serotonergic neurons leads to hyperactivity and aggression (Samaco et al., 2009); and deletion of MeCP2 from forebrain GABAergic neurons led to deficits in motor and social functions (Chao et al., 2010). Surprisingly, deletion of MeCP2 from GFAP-expressing astrocytes led to smaller body size, hindlimb clasping and irregular breathing (Lioy et al., 2011).

Although this conditional deletion of MeCP2 from subsets of neurons and glia uncover the etiology of certain phenotypes, they do not fully recapitulate RTT-like phenotypes observed in constitutive *Mecp2*-null mice. In contrast, deletion of MeCP2 from large brain areas composed of many different types of neurons and neurotransmitter systems led to the identification of increased numbers and severity of RTT-like phenotypes. Conditional deletion of MeCP2 from forebrain neurons led to motor deficits, altered bodyweight, disrupted learning and memory, altered anxiety and decreased brain weight and soma size (Chen et al., 2001; Gemelli et al., 2006). Similarly, deletion of MeCP2 from all GABAergic neurons led to behavioral symptoms including premature lethality, respiratory problems, motor incoordination, self-injury, social abnormalities and cortical hyperexcitability (Chao et al., 2010). Furthermore, deletion of MeCP2 from brainstem and spinal cord revealed critical roles for MeCP2 in the regulation of normal lifespan, control of heart rate and respiratory response to hypoxia (Ward et al., 2011). Moreover, the restoration of MeCP2 function in astrocytes or astroglia significantly improved locomotion and anxiety levels, restored respiratory abnormalities, and prolonged lifespan compared to constitutive Mecp2 null mice (Lioy et al., 2011; Derecki et al., 2012). Thus, while neurotransmitter systems and isolated neuronal populations play important roles in the etiology of particular RTT-like phenotypes, the large-scale disruption of MeCP2 function is required for the appearance of phenotypes that mimic constitutive *Mecp2*-null mice or those mice lacking MeCP2 from the brain (Chen et al., 2001; Guy et al., 2001). Indeed, the greater the number of neurons and glia lacking MeCP2 function the more the severe the consequences: loss of MeCP2 to 8% of wild-type levels leads to premature lethality after approximately 38 weeks of age (Cheval et al., 2012), whereas loss of MeCP2 to 5% of wild-type leads to premature death after 13 weeks (McGraw et al., 2011). That proper brain function and survival is so sensitive to small alterations in MeCP2 is intriguing for understanding the physiological role of MeCP2 and also in the treatment of RTT (Fig. 2).

Together, these results reveal two important properties of RTT. First, deletion of MeCP2 from restricted sets of neuron types is not sufficient to fully recapitulate the phenotypes observed in constitutive *Mecp2*-null mice, as well as the appearance of phenotypes that are not otherwise normally observed in constitutive *Mecp2*-null mice. And secondly, the broader the loss of MeCP2 the greater the RTT-like phenotype. Thus, RTT is the result of the nonlinear accumulated dysfunction of neurological function across neurotransmitter systems and brain regions (Fig. 2). Borrowing from the German psychologist Kurt Koffka, we can state that in regard to MeCP2-related phenotypes: “The whole is other than the sum of its parts.” Since RTT is observed in females heterozygous for MECP2 mutations, whereby individual neurons and glia will stochastically express either wild-type or mutant MeCP2, the degree to which different populations of neurons and glia express wild-type or mutant MeCP2, as well as the degree of X-chromosome inactivation, will play a fundamental role in determining the identity and severity of those symptoms that manifest in individual patients. To paraphrase Koffka, the arrangement of the parts determines which form you see, and the form you see determines how you interpret the parts. This may have several therapeutic advantages since restoring brain-wide MeCP2 function may not be possible in the near future but identifying the neurons/glia and the neurotransmitter systems that mediate different RTT symptoms upon loss of MeCP2 function will allow targeted strategies for their treatment. In addition, restoring the function of MeCP2 in a small number of neurons, not necessarily the entire brain via AAV-mediated gene therapy or reversal of the silenced wild-type MECP2 gene may have significant therapeutic value.

MeCP2 is expressed in every cell in the brain, including excitatory, inhibitory and glial cell populations. Deleting MeCP2 from any one cell type alone is not sufficient to recapitulate the phenotypes of constitutive *Mecp2*-null mice. Conversely, restoration of MeCP2 into one cell type or one part of the brain can lead to the rescue of some but not all phenotypes. Therefore, we believe that RTT is a disorder of large-scale neuronal circuits composed of a broad range of neuronal types and neurotransmitter systems. Thus for future studies, we suggest a dual approach to understand RTT pathophysiology: a systems approach to investigate circuit abnormalities; and a molecular approach to investigate the function of MeCP2 in individual cell types. By combining these two approaches, we can gain a better understanding of the pathophysiology of RTT and also get closer to reaching our goal of providing effective therapeutic treatments for RTT.

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