MicroRNAs (miRNAs) are small 19–23 nucleotide regulatory RNAs that function by modulating mRNA translation and/or turnover in a sequence-specific fashion. In the nervous system, miRNAs regulate the production of numerous proteins involved in synaptic transmission. In turn, neuronal activity can regulate the production and turnover of miRNA through a variety of mechanisms. In this way, miRNAs and neuronal activity are in a reciprocal homeostatic relationship that balances neuronal function. The miRNA function is critical in pathological states related to overexcitation such as epilepsy and stroke, suggesting miRNAs potential as a therapeutic target. We review the current literature relating the interplay of miRNA and neuronal activity and provide future directions for defining miRNAs role in disease.

Keywords: microRNA, synaptic plasticity, stroke, epilepsy, neuroprotective agents
differentiation.

overlapping with genes also identified as involved in neuronal

Gene ontology analysis of target mRNAs revealed an enrich-

ternary complexes were immunoprecipitated and the RNAs from

crosslinked to its mRNA targets in a cell suspension derived from

miR–134 acts by repressing Limk1 expression, a kinase that reg-

miR-138 was identified as a miR-29a/b target in a screen for miRNAs involved in
drugs of abuse-related plasticity (Lippi et al., 2011). Overexpression of
mRNA overexpression should lead to reduced synaptic strength.

miR-134 has been shown to promote spine maturation (right). Colored dots next to miRNA
indicate the target(s) of each miRNA shown to modulate plasticity. See text
for details on individual miRNA targets.

in contrast to the more dynamic filopodia-type spines, which are
associated with weak or absent synaptic transmission (Yoshihara
et al., 2009).

One of the first synaptically enriched miRNAs identified,
miR-134, was shown to be a negative regulator of synaptic spine
volume (Schratt et al., 2006). This pioneering study showed that
miR-134 acts by repressing Limk1 expression, a kinase that reg-
ulates spine morphology by regulating ADF/Coilin interactions

miR-134 overexpression should lead to reduced synaptic

Consistent with this hypothesis, mice overexpressing
miR-134 show defects in the establishment of long-term poten-
tiation (LTP) in the hippocampus (Gao et al., 2010). However, in
this study the authors identified cAMP-response element bind-
ing protein (Creb) as a target of miR-134. It is conceivable that
both studies found true, but different targets of miR-134: the low
level of sequence complementarity required to guide a miRNA to
its target means that every miRNA has potentially hundreds of
targets. This highlights the somewhat arbitrary process of target
identification for miRNAs when performing phenotypic analysis
of miRNA overexpression or knockdown. Importantly, both stud-
ies found that inhibition of miR-134 increased levels of Limk1
and Creb, respectively, and reversed the synaptic and structural
plasticity effects observed when miR-134 is overexpressed.

Structural plasticity-related miRNAs seem to be a prominent
target for miRNAs. This observation is supported by a study
by Chi et al. (2009) where neural miRNA targets were identified
using an unbiased biochemical approach called high-throughput
sequencing of RNAs isolated by crosslinking-immunoprecipitation
(HITS–CLIP). In this approach, the AGO protein was UV-
crosslinked to its mRNA targets in a cell suspension derived from
the cortex of young mice. The crosslinked miRNA–miRNA–AGO
ternary complexes were immunoisolated and the RNAs from
this purification were subject to high-throughput sequencing.

Ran is a founding member of the European Neuroscience Society (ENS). ENS is a new organization that was founded in 2012 with the aim of promoting neuroscience research in Europe. It is a nonprofit organization that is supported by a network of European neuroscience societies and their members. ENS is committed to promoting excellence in neuroscience research and training, and to fostering collaboration between researchers from different countries and disciplines. ENS also provides a platform for networking and knowledge exchange among its members, and it offers a range of services and resources to support their research.
recapitulates the effects on spine density observed in miR-138 overexpression, suggesting that miR-138 acts through A�1 to regulate spine morphology.

The miRNA regulation of structural plasticity extends beyond the hippocampus and cortex. Auditory fear conditioning down-regulates a number of miRNA in the amygdala (Griggs et al., 2013). Bioinformatic analysis suggested that of these downregulated miRNAs, miR-182 could bind to the 3′UTR of a number of key regulators of the actin cytoskeleton in synapses. Infusion of miR-182 mimics into the lateral amygdala led to downregulation of RAC1, cortactin, and to a lesser extent, cofilin. This same infusion protocol impaired long-term amygdala-dependent fear memory suggesting that the miR-182 plays a repressive role in memory formation. However, how precisely miR-182 impacts structural or synaptic plasticity remains to be determined.

In addition to regulating the structural aspects of dendritic spines, a number of miRNAs have been shown to directly regulate components of the post-synaptic density. The synthetically enriched miR-181a can target the GluR2 subunit of the 2-amino-3-(3-hydroxy-5-methyl-isoxazol-4-yl)propanoic acid receptor (AMPAIR) through a conserved binding site in its 3′UTR (Saba et al., 2012). Interestingly, miR-181a is induced by dopamine D1/5 receptor agonist SKF-38393 in vitro and by amphibetamine and cocaine in various anatomical structures in vivo. Surface levels of GluR2 are reduced in neurons overexpressing miR-181a; however, only mEPSC frequency and not amplitude is affected. The authors suggest that AMPAIR-dependent spine development might be affected, explaining reduced mEPSC frequency. However, the possibility remains that miR-181a may have additional relevant targets in hippocampal neurons.

A number of miRNAs encoding post-synaptic density proteins appear to be shared targets of miRNAs and the fragile-X mental retardation protein (FMRP). The FMRP negatively regulates miRNA translation by directly interacting with target miRNAs. In one study, the authors identified miRNA enriched in FMRP-bound RNA immunoprecipitation experiments (Edbauer et al., 2010). Of these miRNAs enriched on FMRP-bound messages, miR-125b and miR-132 had significant effects on structural and synaptic plasticity when overexpressed. While miR-125b overexpression led to thinner spines and decreased amplitude of mEPSC, miR-132 overexpression led to the formation of short, thicker spines and decreased amplitude of mEPSC, miR-132 had significant effects on structural and synaptic plasticity of genes, there is evidence of extensive RISC binding in coding regions (Chi et al., 2009; Helvæk et al., 2013). Alternatively, FMRP binding in 3′UTRs could occlude the binding of other RNA-binding proteins that could otherwise dislodge RISC from its target.

NEURONAL ACTIVITY ALTERS miRNA BIOGENESIS

The miRNA biogenesis is a multiple-step process that begins with the transcription of a primary miRNA transcript (pri-miRNA; Krol et al., 2010b). The pri-miRNA can be derived from a non-coding transcript containing one or many miRNAs, or can be processed from intrinsic sequences. A hairpin structure containing the mature miRNA sequence is recognized by the microprocessor complex, which cleaves the hairpin out of the context of the pri-miRNA transcript, yielding a miRNA precursor (pre-miRNA). The 60–80 nt pre-miRNA is processed by the RNPase III protein Dicer to produce a double-stranded 19–23 bp miRNA. Then one strand is selectively loaded into Ago, yielding a mature miRNA engaged in RISC. Each of these steps are potential control points for the regulation of the cellular miRNA milieu. In this section, we will review how neuronal activity regulates the steps of miRNA biogenesis (Figure 2).

Activity has a strong influence on the transcriptional state of neurons. Creb is one of the primary transcriptional activators that respond to neuronal activity. In a genome-wide screen for Creb binding sites, Vo et al. (2003) identified two consensus binding sites near the miR-212/miR-132 locus. Stimulation of primary neurons with brain-derived neurotrophic factor (BDNF; Vo et al., 2003). KCl depolarization, or bicuculline (Wayman et al., 2008) all induce the production of pri-miR-132 transcript, making it the first recognized mRNA whose expression is regulated by neuronal activation. These observations have been supported by numerous in vivo investigations (Nudelman et al., 2010; Eacker et al., 2011; Melios et al., 2011; Tognini et al., 2011; Wang et al., 2013) among others. Regulation through the cAMP response elements in the putative promoter region of the miR-212/miR-132 cluster were further confirmed by the activity-dependent acquisition of transcription-promoting chromatin marks in the visual cortex after visual stimulation (Tognini et al., 2011). Coupled with the potent effects of miR-132 on structural and synaptic plasticity (see above), it’s activity-dependent transcriptional control suggests that miR-132 is a potent regulator of experience-dependent plasticity in vivo.

A second, larger cluster of miRNAs, the miR-379~410 cluster, has also been shown to be upregulated by neuronal activity (Fiore et al., 2007-00136 — 2013/8/23 — 20:19 — page 3 — #3
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FIGURE 2 | Neuronal activity influences miRNA expression through multiple mechanisms. Activity-dependent transcription induces miRNA production through Me2 and Creb while Lin28a increases expression through an uncertain combination of transcription-dependent and independent mechanisms. Increased levels of Lin28a lead to destabilization of pre-let-7 transcripts through poly-uridynylation. Activity also promotes accelerated miRNA turnover through an additional unknown mechanism(s). Activity-dependent phosphorylation of TRBP stabilizes Dicer, leading to increased mature miRNA production. NMDAR-activation promotes the ubiquitinylation of MOV10, a component of RISC, which may lead to decreased levels of mature-miRNA-loaded RISC. See text for details.

et al., 2009). This miRNA cluster is regulated both by BDNF and KCl depolarization via the tyrosine enhancing factor 2 (Me2) transcription factor. Among the many miRNAs transcribed from this locus is miR-134, a known regulator of structural plasticity through Limk1. In addition to directly regulating Limk1, this study suggests miR-134 may play a broader role in regulating protein synthesis by regulating the RNA binding protein Pumilio 2 (Pum2).

Increased expression of pri-miRNA transcript does not necessarily result in increased mature miRNA levels. One striking example of how neuronal activity can influence mature miRNA levels independently of transcription is through the induction of the Lin28a RNA binding protein by BDNF (Huang et al., 2012). The Lin28 family members can selectively impair the processing of both pri- and pre-let-7 miRNA, though Lin28a primarily targets pre-let-7 through the post-transcriptional addition of poly-uridylate to the 3′ end of the transcript (Thornton and Gregory, 2012). In response to bath application of BDNF in the presence of actinomycin D, hippocampal neurons show increased expression of Lin28a leading to a decrease in mature let-7 levels, resulting to increased translation of let-7 target RNAs. Under the same stimulating conditions, Huang et al. (2012) observed an increase in pre-miRNA processing of non-let-7 miRNAs. This was the result of increased phosphorylation of the Dicer binding partner trans-activation response RNA-binding protein (TRBP). The extracellular signal-regulated kinase (ERK)-dependent phosphorylation of TRBP stabilizes Dicer (Paroo et al., 2009), and in the context of BDNF stimulation leads to increased levels of pre-miRNA processing.

While activity induced by BDNF may lead to increased processing of pre-miRNA, activity through glutamate receptors seems to accelerate mature miRNA turnover (Krol et al., 2010a). Using a variety of transcriptional inhibitors, Krol et al. (2009a) demonstrated that neuronal miRNAs have an unusually high turnover rate compared to other cell types. The turnover rate was further accelerated by addition of glutamate and decelerated by the application of tetrodotoxin (TTX). These findings are strikingly similar to those made in Aplysia where application of serotonin results in the rapid degradation of miR-124 (Rajasethupathy et al., 2009). The mechanism for this rapid, activity-dependent miRNA turnover remains unclear. However, it is worth noting that at timepoints distal to neuronal activation, there are many more miRNAs that are downregulated than upregulated over a number of array-based studies (Eacker et al., 2011; Jimenez-Mateos et al., 2011; Griggs et al., 2013; Risbud and Porter, 2013). This activity-dependent miRNA turnover may allow neurons to rapidly reprogram RISC in a global manner in a way that promotes synaptic plasticity.

There is growing evidence that pre-miRNA processing can occur in dendrites. Biochemical purification of RISC components from synaptosomes showed detectable levels of pre-miRNA (Lugli et al., 2008). Recently, in situ hybridization methods that
allow for specific detection of pre-miRNA have lent credence to the possibility that dendritically localized pre-miRNA may be an important phenomenon (Bicker et al., 2013). Using a clever biochemical approach, the authors of this study identified DHX36, a DExH-box RNA helicase as an interactor with the loop region of the dendritically localized pre-miR-134 transcript. Knockdown of DHX36 reduced dendritic transport of pre-miR-134 and enhanced the translation of reporters of miR-134 activity. The authors propose that DHX36 stabilizes pre-miR-134 for dendritic processing, perhaps in an activity-dependent manner, though this remains to be determined.

The Drosophila protein Armitage (Armi) and its mammalian homolog MOV10 are both implicated in the activity-dependent relief of miRNA repression (Ashraf et al., 2006; Banerjee et al., 2009). Armi and MOV10 are DExH-box RNA helicases that have been shown to be components of RISC (Tomari et al., 2004; Meister et al., 2005). In the case of Drosophila, Armi is degraded via the ubiquitin proteasome following activation of the nicotinic acetylcholine receptor. In mammals, MOV10 is also degraded in a proteosomal-dependent manner in response to NMDA receptor activation (Banerjee et al., 2009; Jarome et al., 2011). In neurons, degradation of MOV10/Armi relieves miRNA-mediated repression by an unknown mechanism, allowing for the translation of mRNAs involved in synaptic plasticity (Ashraf et al., 2006; Banerjee et al., 2009). Biochemical data concerning Armi’s function suggest that it is required for the loading of AGO with mature miRNAs following Dicer processing (Tomari et al., 2004). However, recent genome-wide studies have identified numerous promiscuous interactions between polyadenylated mRNAs and MOV10 (Castello et al., 2012; Sievers et al., 2012), suggesting additional potential interactions of MOV10 and miRNA-mediated silencing. More research is required to elucidate this potentially important interface between the relief of miRNA-mediated repression and activity-dependent protein synthesis.

miRNAs FUNCTION IN DISEASES OF NEURONAL OVEREXCITATION
Excessive neuronal activity is associated with neuronal cell death in a number of contexts. During stroke, neuronal depolarization leads to excess glutamate release that cannot be compensated for by normal reuptake mechanisms. The resulting excess glutamate results in glutamate receptor hyperactivation and excitotoxic cell death via excess calcium influx. As miRNAs are potent regulators of the cellular stress response (Leung and Sharp, 2010; Mendell and Olson, 2012) and neuronal excitability (see above), they are a logical target for the investigation and enhancement of intrinsic neuroprotective pathways (Figure 3). A fair amount of effort has been made toward understanding the global miRNA response to stroke in rodent models. These studies generally rely on comparisons of RNA samples from stroke and sham brains, and subject them to some type of high-throughput array. Not surprisingly, the resulting miRNA expression profiles between different experimental stroke conditions, different laboratories, and different array platforms show almost no overlap. Despite this lack of overlap, there is valuable information that can be gained from a brief review of these studies.

FIGURE 3 | Potential targets for miRNA-mediated therapies in the treatment of stroke and epilepsy. Potential interventions target miRNAs to either reduce excitotoxic calcium influx (top) or reduce the impact of excessive calcium influx (bottom). Potential miRNA targets and be influenced either by introduction therapeutic inhibitors (red x) or mimics (green check). See text for details. Note: Conflicting results of miR-134 inhibition on spine morphology with embryonic neuronal studies described above. See text for details.
One of the best studies that highlights the complexity of the miRNA response to CNS injury was performed on both blood and brain tissue from rats after ischemic stroke, intracerebral hemorrhage, or kainic acid-induced excitotoxicity (Liu et al., 2010). In this study, relatively few miRNAs showed consistent changes in expression either in brain tissue or blood. However, three miRNAs found in the blood (miR-155, miR-298, and miR-362-3p) change expression greater than twofold in response to some of the injuries. This suggests that expression of some miRNAs might be useful biomarkers to identify subtypes of CNS injuries.

In two related studies, the miRNA cortex of mice treated with middle cerebral artery occlusion (MCAO) model of stroke were profiled either by PCR 24 h post-stroke (Yin et al., 2010) or by array over an extended time course (Dharap et al., 2009). There was no significant overlap found between these two studies, perhaps because of methodological differences. Each study did identify some miRNAs that showed reproducible changes in their model. In one case, the authors found that miR-145 showed significant and enduring upregulation following stroke (Dharap et al., 2009). Inhibition of miR-143 with chemically modified antisense oligonucleotides (so-called antagonirs, or anti-miRs) lead to upregulation of superoxide dismutase 2, a predicted target of miR-145. Whether miR-145 inhibition had any therapeutic benefit was not determined. In the second study, the authors identified miR-497 as an upregulated miRNA in cortex following MCAO and in neuroblastoma cells subjected to oxygen–glucose deprivation (OGD), a cell culture model of stroke (Yin et al., 2010). Through a series of experiments, the authors show that Bcl-2 and Bcl-w, two anti-apoptotic molecules are targets of miR-497. Inhibition with antagonirs targeting miR-497 prior to MCAO resulted in reduced infarct volume and reduction in the severity of neurological deficits. Similar results were observed for miR-29b, another miRNA which targets Bcl-w (Shi et al., 2012). The authors observed an increase in miR-29b following MCAO and showed that simple overexpression of miR-29b lead to spontaneous neuronal cell death in a Bcl-w-dependent manner.

Another approach toward finding potentially therapeutic miRNAs for treating stroke is to work backward from a known therapeutic target or pathway and identify miRNA interactors. GPR78 (also known as BIP) is a chaperone that is primarily localized to the ER and plays a key role in the ER-stress response. Ouyang et al. (2012) found that decreased GPR78 levels were linked to increased GRP78, the author demonstrated that inhibition of miR-181 with antagomirs prior to SE induction provided neuroprotection. Inhibition with antagomirs of miR-181 decreased both upregulated in mouse models of TLE (Jimenez-Mateos et al., 2011, 2012). Interestingly, miR-132 induction in this TLE model is suppressed when mice are preconditioned with a low, peripherally administered dose of kainic acid (Jimenez-Mateos et al., 2011). This suggests that impairing miR-132 expression, by whatever means, may be neuroprotective. Indeed this was the case: inhibition of miR-132 by infusion of miR-132 antagonirs before kainic acid injection reduced cell death in the CA3 subfield of the hippocampus. Given the evidence from the synaptic plasticity field regarding miR-132’s ability to stimulate stable mushroom-type dendritic spines suggests that anti-miR-132 treatments may reduce cell death by reducing hippocampal neuron’s excitability, and therefore susceptibility to excitotoxicity. Similarly, miR-134 inhibition with antagonirs prior to SE induction provided neuroprotection. However, unlike miR-132 inhibition, a single injection of miR-134 antagonist provided long-lasting inhibition of recurrent spontaneous seizures (Jimenez-Mateos et al., 2012). Building on the work of Schratt et al. (2006), this study demonstrated that anti-miR-134 treatment reduced spine density in vivo, likely acting via Limk1. The long-lasting nature of the anti-miR-134 protection suggest that miR-134-based therapeutic may hold promise in treating intractable TLE.
CONCLUSIONS AND FUTURE STUDIES

In the relative short time since their discovery, the miRNA field has made a dramatic impact on our understanding of nervous system function. Insights concerning the mechanisms of synaptic plasticity have been of particular interest, potentially coupling activity-dependent protein synthesis with miRNA-mediated regulation at individual synapses and miRNA-targeted mRNAs do not have such single-minded focus (Back et al., 2008; Selbach et al., 2008). Having a more comprehensive view of how individual miRNAs regulate the proteome will be necessary, especially if they are to be used in therapeutics.

Virtually all the studies described in this review rely on antisense oligonucleotides or antagonists to conduct loss-of-function experiments. While these reagents are widely used and proven effective under many circumstances, virtually nothing is known about their distribution and perdurance in the CNS following intracranial injection, making interpretation of how they work problematic. A reasonable complement to antagonist application would be the use of traditional targeted mutations, which are becoming increasingly more available to the general scientific research world (Park et al., 2012).

Finally, the most successful candidate miRNAs for translation to the clinic have arisen from rigorous work in the basic sciences. Both miR-132 and miR-134 have a long track record of careful investigation in the basic synaptic plasticity field and have now been shown to have potential in the treatment of epilepsy. This cross-pollination of basic and translational science seems to be the most fruitful way forward for the future of miRNA-based therapeutics.

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