Psychopharmacology (2009) 202:457–476
DOI 10.1007/s00213-008-1311-8

REVIEW

Lithium and cognitive enhancement: leave it or take it?

Eleftheria Tsaltas · Dimitris Kontis · Vasileios Boulougouris · George N. Papadimitriou

Received: 28 May 2008 / Accepted: 20 August 2008 / Published online: 10 September 2008

Abstract
Rationale Lithium is established as an effective treatment of acute mania, bipolar and unipolar depression and as prophylaxis against bipolar disorder. Accumulating evidence is also delineating a neuroprotective and neurotrophic role for lithium. However, its primary effects on cognitive functioning remain ambiguous.
Objectives The aim of this paper is to review and combine the relevant translational studies, focusing on the putative cognitive enhancement properties of lithium, specifically on learning, memory, and attention.
Discussion These properties are also discussed in reference to research demonstrating a protective action of lithium against cognitive deficits induced by various challenges to the nervous system, such as stress, trauma, neurodegenerative disorders, and psychiatric disorders.
Conclusions It is suggested on the basis of the evidence that the cognitive effects of lithium are best expressed and should, therefore, be sought under conditions of functional or biological challenge to the nervous system.

Keywords Lithium · Enhancer · Cognition · Learning · Memory · Attention · Neuropsychiatric disorders · Cognitive enhancer

E. Tsaltas (✉) · D. Kontis
Experimental Psychology Laboratory, Department of Psychiatry,
Eginition Hospital, Athens University Medical School,
74, Vas. Sofias Avenue,
115 28 Athens, Greece
e-mail: tsaltasl@med.uoa.gr

D. Kontis
Psychiatric Hospital of Attica,
Athens, Greece
e-mail: jimcon@hol.gr

V. Boulougouris
Department of Experimental Psychology and the Behavioural and Clinical Neuroscience Institute (BCNI),
University of Cambridge,
Downing Site,
CB2 3EB Cambridge, UK
e-mail: vb257@cam.ac.uk

G. N. Papadimitriou
Department of Psychiatry, Eginition Hospital,
Athens University Medical School,
74, Vas. Sofias Avenue,
115 28 Athens, Greece
e-mail: gnpapad@med.uoa.gr

Introduction

Lithium is a mood stabilizer considered to be a first-line treatment of bipolar disorder (Buckley 2008). Apart from its therapeutic role in the acute and maintenance phase of bipolar disorder, it is an effective augmenting agent in treatment-refractory depression (Crossley and Bauer 2007). Aside from these well-established clinical benefits of lithium, growing recent evidence suggests that it is an effective neuroprotective and neurotrophic agent (Bearden et al. 2007a, b). Its documented effects on a number of cellular proteins, which regulate cell atrophy and death, have led to the hypothesis that this possibly "overlooked cation" may be useful in the treatment of neuropsychiatric disorders involving cell atrophy and loss (Chuang and Manji 2007). However, in spite of the emerging neuroprotective and neurotrophic actions of lithium, the evidence for corresponding functional benefits on the cognitive–behavioral level is rather equivocal. The putative role of lithium as a cognitive enhancer is challenged by the complaint of mental

slowing made by patients receiving it (Joffe et al. 1988; Lenzer et al. 1989). This discrepancy has stimulated human and animal studies to investigate specific neurocognitive effects of lithium administration. However, the resulting reports on the impact of lithium on cognitive functions, learning and memory in particular, remain controversial.

Taken as a whole, early clinical studies link lithium treatment to cognitive blurring and memory deficits (Ananth et al. 1987). More recent neuropsychological studies raise the possibility that the negative cognitive effects so far attributed to lithium may in fact be the result of bipolar disorder itself (Pachet and Wisniewski 2003). Finally, recent clinical studies show results promising of a beneficial impact of lithium on cognition in patients with dementia (Terao et al. 2006; Nunes et al. 2007; Engel et al. 2008).

The animal literature on cognitive effects of lithium also presents inconsistencies. Recently, however, studies are emerging which demonstrate potentiation of cognitive processes in normal animals after chronic lithium treatment at doses relevant to human maintenance and therapeutic levels. Chronic lithium has been shown to enhance spatial working memory and to promote long-term retention of a weak aversive contingency (Tsaltas et al. 2007a, b). It has also been shown to promote learning in three different spatial cognitive tasks involving positive reinforcement (Nocjar et al. 2007).

Stimulated by the inconsistencies in the reported effects of lithium on cognitive processes and by these recent encouraging observations, the present paper aims to review and combine the relevant human and animal literature, focusing on the putative cognitive enhancement properties of lithium. Apart from examining neuropsychological/behavioral data collected from human patients, normal controls, and normal animals subjected to lithium treatment, studies are reviewed which treat the putative protective action of lithium against cognitive deficits induced by various neuropsychiatric conditions and their animal models. This task is necessitated by the great benefit involved in the potential use of this clinically tested, inexpensive substance as a cognitive enhancer in psychiatric disorders such as depression, bipolar disorder, schizophrenia, or dementia (Zhong and Lee 2007).

Effects of lithium on basic behaviors

Given that an attempt is made to integrate human and animal literature in the following sections, a word of caution is necessary with respect to lithium regimes used in the two domains, as this may be the source of inconsistencies. The range of lithium doses used in clinical studies, and corresponding serum levels reported as "maintenance" or "therapeutic," are well-established and uniform (0.5 to 1.2 mEq/L: Gelenberg et al. 1989). In contrast, animal studies, the early ones in particular, are often limited by the possibility of nonspecific toxic effects of high lithium doses or by diurnal plasma level oscillations associated with intraperitoneal administration (O'Donnell and Gould 2007; Gould et al. 2008). The discrepancies often noted between the results of early and later animal studies on the behavioral impact of lithium are at least in part attributable to the fact that the former often fail to report serum lithium levels and tend to use acute or subchronic administration regimes, while the latter generally adhere to chronic administration of doses yielding serum lithium levels relevant to human therapeutic levels.

Aside from the administration regime problem, another complication arises from the fact that lithium influences a broad spectrum of central neurochemical mechanisms, thereby being suspect of diverse nonspecific effects on behavior. In order to evaluate its impact on higher cognitive processes, it is essential to delineate its effects on basic behavioral parameters such as locomotion, exploration, responsiveness to reward and punishment and, of course, mood.

Lithium, activity, and exploration

There are no consistent reports on lithium effects on human activity levels. Early animal studies report reduced activity levels after chronic lithium (see Hines and Poling 1984). More recent studies describe either mild hypoactivity in the running wheel and open-field (Jahkel et al. 1994; Pascual and Gonzalez 1995) or normal open-field performance (Vasconcellos et al. 2003; Gould et al. 2008). Given that the later studies report therapeutic plasma lithium levels, one can conclude that therapeutic doses of lithium have little or no effect on spontaneous locomotion and activity.

However, lithium appears dose-dependently to decrease exploratory locomotion and rearing in novel environments such as the open-field (Smith and Smith 1973; Johnson 1976; Pascual and Gonzalez 1995). This may suggest an impact of lithium on attentional processes (see the "Lithium and attention" section). However, lithium-treated animals show normal distractibility by novel stimuli when given a second open-field test, that is they reduce their exploration similarly to controls (Pascual and Gonzalez 1995) or when observed over a period of time (Gould et al. 2008).

Lithium and the impact of rewarding and aversive stimuli

Information on the effects of lithium on human reactions to reward can be deduced from studies on its interaction with drugs of abuse, mainly alcohol. Although it has been evaluated as an aid in the management of alcohol abuse, it does not consistently affect alcohol consumption in alcoholics (Lejoyeux and Ades 1993). Also, it appears to have no effect on the subjective evaluation of the hedonic effects of alcohol in normal subjects (Judd et al. 1977a). In

animals, there are reports of decreased voluntary alcohol consumption with lithium (Ho and Tsai 1976; Alexander and Alexander 1978), but also of facilitation of adjunctive alcohol drinking, suggesting an increase in the reinforcing value of alcohol (Hines and Henslee 1986; Hines 1986a). Data on lithium effects on morphine intake are also controversial: in humans, it appears to potentiate its euphoric effect (Jasinski et al. 1977), but it reportedly decreases intake in morphine-addicted animals (Tomkiewicz and Steinberg 1974). Finally, a direct examination of the impact of various types of reward on learning (food vs. social interaction) reports enhanced learning in lithium-treated animals regardless of reward type (Nocjar et al. 2007). This may suggest that lithium increments the impact of positive reinforcement, a rather unexpected effect given its antimanic properties.

The well-documented effects of lithium as a nausea- and taste aversion-inducing agent raise the possibility of generalized effects on nociception, as pleasant and unpleasant flavors and odors can modulate pain perception (Vasconcellos et al. 2006a). It must be noted, however, that generation of taste aversion requires significantly higher doses than those within the therapeutic range (Nachman and Ashe 1973; Masaki and Nakajima 2006). Older animal studies report decreased reaction to foot shock and attenuation of shock-induced activity suppression (Hines and Poling 1984; Hines 1986b), more recent ones do not (Tsaltas et al. 2007b). Discrepant effects have also been reported on the effects of lithium on opioid-induced analgesia (Johnston and Westbrook 2004 vs. Karakucuk et al. 2006). Finally, an interesting recent finding is that lithium restores analgesia affected by sweet taste preexposure, which is abolished by chronic variate stress: this suggests that lithium may counteract stress-induced anhedonia (Vasconcellos et al. 2006a).

In conclusion, given the equivocal results on the impact of lithium treatment on reward and nociception, it is necessary to examine the cognitive effects of the substance through the parallel use of appetitive and aversive paradigms.

Lithium, anxiety, and fear

An early study (Hines 1986b) reported that lithium attenuated shock-induced suppression of open-field activity controlled by conditioned fear stimuli without affecting suppression produced by shock itself. However, recent studies report no effect of subchronic lithium on conditioned freezing, though lithium does dose-dependently potentiate the antianxiety effects of various antidepressants (Muraki et al. 1999; Kitaichi et al. 2006). Also, chronic lithium spares fear conditioning in on- and off-the-baseline conditioned emotional response procedures (Tsaltas et al. 2007a, b), as it does active avoidance (Hines and Poling 1984). An acquisition deficit in passive avoidance has been reported by an early study (Hines and Poling 1984), but passive avoidance retention actually shows improvement after subchronic (Pascual and Gonzalez 1995) or chronic (Tsaltas et al. 2007a) lithium treatment. Although the majority of data show no effect of lithium on the acquisition of fear, it has been recently demonstrated that chronic lithium treatment to rat pups causes long-lasting increases in anxious behavior (Youngs et al. 2006).

These equivocal results on lithium effects on fear/anxiety support the earlier conclusion that it is essential to examine the cognitive effects of the substance through the parallel use of appetitive and aversive paradigms.

Lithium and stress

The interaction of lithium with the effects of stress are currently commanding significant interest, as accumulating data suggest that chronic lithium at therapeutically relevant doses protects from, and possibly reverses, the detrimental neuroanatomical, neurochemical, and behavioral concomitants of stress. In animal models, chronic lithium decreases indices of anxiety which are raised by stress, such as the hypokinesia induced by shock administration, isolation, or immobilization (Hines 1986b; Frances et al. 1981; Kofman et al. 1995; see also effects on depression). It also appears to counteract stress-induced lack of response to pleasant stimuli (Vasconcellos et al. 2006a). Chronic lithium also appears to protect from, and even reverse, some of the cognitive effects of chronic variate stress, such as the compromise of spatial reference memory in the water maze (Vasconcellos et al. 2003, 2005). In the same paradigm, lithium presented antioxidant properties in the hippocampus (decrease of stress-induced free radicals production), though it was not able to prevent oxidative damage induced by chronic variate stress (Vasconcellos et al. 2006b).

Given that lithium appears to modify the effects of stress on activity, hedonic parameters, and cognitive processes as well, it is clear that any effects of the substance on learning and memory emerging from procedures involving stress need to be documented through the use of corresponding, appetitively motivated procedures such as rewarded alternation (Tsaltas et al. 2007a, b).

Lithium and depression

As mentioned earlier, clinical studies demonstrate that lithium is one of the most effective augmenting agents of antidepressant action in refractory unipolar depression (Bauer et al. 2003; Crossley and Bauer 2007). These findings are corroborated by animal data collected in a variety of animal models of depression (Hascoet et al.

1994; Nixon et al. 1994; Redrobe and Bourin 1997; Redrobe and Bourin 1999). Animal studies tend to associate this potentiating effect with increases in 5-HT neurotransmission induced by lithium treatment: more specifically, to a modulatory action of lithium on 5-HT1B autoreceptors in the cortical area, in case of acute treatment, or in the hippocampus, in case of chronic treatment (Chenu and Bourin 2006).

In spite of its unquestionable effectiveness as an add-on to antidepressants, lithium does not emerge as an effective acute treatment of unipolar depression, though it is superior to placebo in the acute treatment of bipolar depression (for review, see Souza and Goodwin 1991). However, this metaanalytic study suggests that lithium is an effective prophylactic treatment against unipolar illness. Given this profile, one would not expect clear antidepressant-like action of lithium alone in animal models of depression. In fact, the relevant data are more controversial than the animal data which establish the effectiveness of lithium as an adjunct to antidepressants. In rats, chronic lithium at clinically relevant plasma levels significantly reduced hypokinesia induced by immobilization stress (Kofman et al. 1995). It also had an antidepressant-like effect in the forced swim test (Eroglu and Hizal 1987). However, in the same test, acute, low-dose lithium treatment reportedly produced a prodepressant rather than antidepressant effect of increasing immobility (Tomasiewicz et al. 2006), while acute, clinical-range doses had no effect on immobility (Wegener et al. 2003). In mice, an antidepressant-like effect has also been reported after acute (Hascoet et al. 1994) and chronic administration (Bersudsky et al. 2007; Gould et al. 2007; Shaldubina et al. 2006). A recent, systematic study of both acute and long-term lithium administration to mice (in both cases documented to produce serum and brain levels within the human therapeutic range) also demonstrated a robust antidepressant-like effect in the forced swim test in both cases, which was also apparent after intraventricular administration of lithium (Gould et al. 2008). The same study examined the effects of acute and chronic lithium in the tail suspension test and also documented an antidepressant-like effect of both regimes in mice (Gould et al. 2008). The effects of lithium on the learned helplessness model of depression are more inconsistent. In rats, one study actually reported aggravation of the escape deficit induced by inescapable shock after acute or chronic lithium administration (Geoffroy et al. 1991). Another study reported no effects (Stewart et al. 1991), while a third (Teixeira et al. 1995) found that chronic but not acute lithium treatment at a serum level within the prophylactic range prevented learned helplessness.

In conclusion, lithium does not appear to influence general motor activity, although it transiently decreases exploratory activity. Evidence on effects on reward is sparse, but lithium appears to have a moderating influence on the impact of aversive stimuli and stress. Therefore, paradigms involving punishment and stress, such as animal models of conditioned fear and depression, must be treated cautiously in the examination of the cognitive effects of lithium. Results produced through such paradigms should be interpreted in conjunction to data generated by appetitively motivated procedures.

Effects of lithium on cognition

Reports on the effect of lithium on cognition are controversial. Lithium-treated patients as well as lithium-treated normal volunteers often complain of cognitive "slowing" or "blurring" (Judd et al. 1977b, c; Kropf and Müller-Oerlinghausen 1979), but these effects have not so far been documented as specific cognitive dysfunctions (Stip et al. 2000; Pachet and Wisniewski 2003; O'Donnell and Gould 2007). Below, human and animal studies examining learning, memory, attentional functions, and executive functions are reviewed.

Lithium and learning

Human studies

Little formal information exists on the influence of lithium on human learning. The available data are generally "byproducts" of memory tests used in clinical and occasionally in normal populations. Learning efficacy is deduced from the first recall of word lists or from the emergence of practice effects after repeated testing of memory or attention functions. Given the complaints of cognitive slowing expressed by lithium-treated patients and the evidence of decreased vigilance in normal volunteers subjected to 2 weeks of lithium treatment (Kropf and Müller-Oerlinghausen 1979), objective data on compromised learning in either clinical or normal populations treated with lithium is unexpectedly sparse (Table 1).

In a study comparing the performance of long-term lithium-treated outpatients to the general norms, Lund et al. (1982) noted results within the normal range apart from a minor deficit in memory and perceptual processing, which was attributed to lithium effects on arousal. Marusarz et al. (1981) reported that memory performance and the underlying organizational processes of lithium-treated bipolar patients were not adversely affected by lithium treatment, compared to unmedicated controls. In bipolar outpatients on and off lithium treatment, Shaw et al. (1987) report a normal course of practice effects between consecutive test sessions. Finally, Yucel et al. (2007) who evaluated verbal learning and memory, concurrently monitoring hippocampal volume of bipolar patients over a 4-year lithium

Table 1 Human studies on the effects of lithium on cognition

Study design	Learning	Immediate and short-term verbal memory	Delayed recall and long-term verbal memory	Visual memory	Attention	Executive functions
Lithium patients versus controls	Ø Lund et al. 1982	↓ Kusumo and Vaughan 1977	↓ Loo et al. 1981	Ø Loo et al. 1981	Ø Lund et al. 1982	↓ Van Gorp et al. 1998[a]
	Ø Marusarz et al. 1981	↓ Loo et al. 1981	↓ Lund et al. 1982	Ø Van Gorp et al. 1998	Ø Van Gorp et al. 1998	↓ Mur et al. 2007
		↓ Lund et al. 1982	↓ Van Gorp et al. 1998			↓ Goswami et al. 2002
		↓ Senturk et al. 2007	Ø Kusumo and Vaughan 1977			Ø Senturk et al. 2007
		↓ Van Gorp et al. 1998	Ø Marusarz et al. 1981			
		Ø Jauhar et al. 1993	↑ Kusumo and Vaughan 1977			
		Ø Marusarz et al. 1981				
Patients on and off lithium treatment	Ø Shaw et al. 1987	↓ Christodoulou et al. 1981	↓ Christodoulou et al. 1981	Ø Squire et al. 1980	Ø Sharma and Singh 1988	Ø Sharma and Singh 1988
		↓ Kocsis et al. 1993	↓ Kocsis et al. 1993	Ø Sharma and Singh 1988	Ø Squire et al. 1980	Ø Squire et al. 1980
		↓ Reus et al. 1979	↓ Reus et al. 1979	↓ Christodoulou et al. 1981		
		↓ Shaw et al. 1987	↓ Shaw et al. 1987			
		Ø Sharma and Singh 1988	Ø Sharma and Singh 1988			
		Ø Squire et al. 1980	Ø Smigan and Perris 1983			
		Ø Telford and Worrall 1978	Ø Squire et al. 1980			
		Ø Smigan and Perris 1983	Ø Telford and Worrall 1978			
Patients on chronic lithium	↑ Yucel et al. 2007					
Normal volunteers	↓ Kropf and Müller-Oerlinghausen 1979 (2 weeks treatment)	↓ Kropf and Müller-Oerlinghausen 1979	↓ Karniol et al. 1978; ↓	↓ Judd et al. 1977b, c	↓ Judd et al. 1977b	Ø Judd 1979
		Ø Calil et al. 1990	↓ Kropf and Müller-Oerlinghausen 1979		↓ Judd 1979	
	↓ Stip et al. 2000 (3 weeks treatment)	Ø Karniol et al. 1978	Ø Stip et al. 2000		Ø Calil et al. 1990	
		Ø Kolk et al. 1993			Ø Stip et al. 2000	
	Ø Calil et al. 1990 (8 weeks treatment)	Ø Stip et al. 2000				
		Ø Weingartner et al. 1985				
	Ø Karniol et al. 1978 (1–7 days treatment)					

↑ improved cognitive performance in lithium-treated subjects, ↓ compromised cognitive performance in lithium-treated subjects, Ø unaffected cognitive performance in lithium-treated subjects

[a] Impairment encountered only in the presence of alcohol dependence comorbidity

treatment period, report an improvement in verbal learning. These reports do not suggest that lithium has any major detrimental effect on learning in bipolar patients and even give indications to the contrary.

In normal volunteers under subchronic lithium (1–7 days), there was no impairment in immediate retrieval of words (Karniol et al. 1978). However, another study (Kropf and Müller-Oerlinghausen 1979) reported that, after 14 days of treatment, their lithium group showed a slower learning slope than the placebo group, needing significantly more learning trials in order to learn a 16-word list. Stip et al. (2000), examining normal volunteers (3-week lithium–placebo administration), found that a placebo control group showed a posttreatment improvement in recall between two time-points on an explicit recall task, attributed to a practice effect. The lithium group did not demonstrate as great an improvement, indicating that lithium has probably a negative impact on learning. A delay in the emergence of practice effects was noted in the lithium group also in the context of an attentional task. However, in a longer trial (8-week lithium–placebo administration), Calil et al. (1990) reported no learning deficits. Both the lithium and the placebo groups demonstrated an improvement of performance over testing repetitions, suggesting normal practice effects under lithium treatment. These results indicate that, in normal subjects, lithium may compromise learning in the initial administration stages (subchronic administration), perhaps due to general influences on arousal and mood. These adverse effects are not apparent with more prolonged administration.

Animal studies

It has been pointed out earlier that aversively motivated procedures are not, on their own, reliable tests of lithium effects on cognition, given its effects on nociception, stress, and fear. Thus, in evaluating animals studies on learning and memory under lithium treatment, more weight must be given to data generated though spatial reference and working memory tasks such as the Morris water maze and various conventional maze procedures like rewarded alternation (Table 2).

Older studies using aversively motivated procedures generally report deficits. Thus, in rats under subchronic lithium, a persistent deficit in active avoidance learning was noted by Richter-Levin et al. (1992). However, passive avoidance was reported unimpaired after chronic lithium treatment in another study (Hines and Poling 1984). Subchronic lithium reportedly delayed acquisition of conditioned fear, in a way analogous to the delay noted if stimulus salience is decreased by detailed exploration of the apparatus before initiation of conditioning (Cappeliez and Moore 1988). In line with this study, rats under chronic lithium showed impaired acquisition of an exploration-

Table 2 Effects of lithium administration on learning—animal studies

Animals	Lithium regime	Behavioral paradigm	Effects	Reference
Rats	Subchronic	Active avoidance learning	↓	Richter-Levin et al. 1992
Rats	Chronic	Active avoidance learning	Ǿ	Hines and Poling 1984
Rats	Subchronic	Passive avoidance learning	↑	Pascual and Gonzalez 1995
Rats	Chronic	Passive avoidance learning	↓	Hines and Poling 1984
Rats	Chronic	Passive avoidance learning	↑	Tsaltas et al. 2007a
Rats	Subchronic	Conditioned fear acquisition	↓	Cappeliez and Moore 1988
Rats	Chronic	Conditioned fear acquisition	Ǿ	Tsaltas et al. 2007b
Rats	Acute	Maze learning	Ǿ	Roussinov and Yonkov 1975
Rats	Subchronic	Visually cued labyrinth learning	Ǿ	Richter-Levin et al. 1992
Rats	Subchronic	Discrimination learning, easy and difficult	Ǿ	Lalonde and Vikis-Freibergs 1982
Rats	Subchronic	Cued Y-maze discrimination learning (low-salience cue–high-salience distractor)	↓	Cappeliez et al. 1989
Rats	Subchronic	Cued Y-maze discrimination learning (high-salience cue, low-salience distractor)	Ǿ	Cappeliez et al. 1989
Mice	Acute	Spatial rewarded alternation, four-arm maze	Ǿ	Furusawa 1991
Rats	Chronic	Exploration-reinforced position discrimination	↓	Hines 1985
Rats	Chronic	Zero-delay rewarded alternation acquisition, T-maze	Ǿ	Tsaltas et al. 2007a
Rats	Chronic	Delayed rewarded alternation, T-maze	↑	Tsaltas et al. 2007a
Rats	Chronic	Hole-board spatial discrimination learning	↑	Nocjar et al. 2007
Rats	Chronic	Spatial discrimination learning	↑	Nocjar et al. 2007
Rats	Chronic	Delayed rewarded alternation, T-maze	↑	Nocjar et al. 2007
Rats	Chronic	Learning ability (cortex/subcortex weight ratio)	↑ (↑)	Gallo et al. 1990

↑ improved performance in lithium-treated subjects compared to controls, ↓ compromised performance in lithium-treated subjects compared to controls, Ǿ unaffected performance in lithium-treated subjects compared to controls

reinforced position discrimination under conflict (Hines 1985) and delayed acquisition of passive avoidance (Hines and Poling 1984). However, in more recent studies, subchronic and chronic lithium treatment reportedly improved passive avoidance acquisition (Pascual and Gonzalez 1995; Tsaltas et al. 2007a) and did not affect fear conditioning (Tsaltas et al. 2007b).

In mice, lithium had no significant effect on rewarded alternation learning in a four-arm maze (Furusawa 1991). In rats, acute administration of lithium before and after maze learning had no effects on performance (Roussinov and Yonkov 1975) and normal learning of two appetitive discrimination tasks varying in terms of cognitive difficulty was noted (Lalonde and Vikis-Freibergs 1982). Subchronic lithium did not interfere with discrimination learning in the Y-maze when reinforcement was signaled by a high-salience cue with a low-salience distractor. However, discrimination learning in lithium-treated rats was compromised when a low-salience cue and a high-salience distractor were used (Cappeliez et al. 1989). In the Morris water maze, when training began 3 days after lithium treatment onset, lithium animals showed a significant deficit in locating the platform on the fifth treatment day: the deficit dissipated by day 6. When training began after 10 days of lithium treatment, lithium animals were indistinguishable from controls (Richter-Levin et al. 1992). In learning a visually cued labyrinth after subchronic lithium treatment, rats on high lithium doses did not try to navigate the maze, a motivational deficit which disappeared within 48 h of lithium interruption. Rats on a lower dose, after 8 days of lithium treatment, performed the task significantly slower than controls due to retracing, but did not make more choice errors than controls (Richter-Levin et al. 1992).

With respect to chronic lithium treatment, a number of studies employing appetitively motivated tasks have actually demonstrated enhancement of learning by lithium. Gallo et al. (1990) demonstrated that chronic lithium administration in young rats had effects similar to those of increased environmental stimulation: both manipulations significantly enhanced learning ability and also increased the cortex/subcortex weight ratio. Chronic lithium had no effect on the acquisition of a zero-delay rewarded alternation task in the T-maze and improved performance of delayed alternation (Tsaltas et al. 2007a). Finally, rats under chronic lithium trained in three different appetitively motivated spatial cognitive tasks (hole-board spatial discrimination, T-maze delayed alternation and social place-preference) demonstrated enhanced learning in all three paradigms, regardless of the reward received (food or social interaction: Nocjar et al. 2007).

In conclusion, the sparse data addressing learning per se in bipolar patients and normal controls under lithium treatment do not suggest that lithium has any major detrimental effect, beyond its dampening effect on performance. Data from normal humans suggest that lithium may compromise learning in the initial administration stages (subchronic administration), perhaps due to general influences on arousal and mood. These adverse effects are not apparent with more prolonged administration. This observation is corroborated by animal data, showing that, when learning occurs less than 10 days after onset of lithium treatment, animals show sluggishness (which would influence latency measures) without actual increases in errors. Also, deficits which appear if behavioral training begins soon after lithium onset fail to emerge if training begins later (Richter-Levin et al. 1992). In contrast to the subchronic ones, studies employing prolonged lithium administration in normal animals consistently show learning improvements under lithium, in one instance (Gallo et al. 1990) correlated with increased cortex/subcortex weight ratio in lithium-treated rats.

Lithium and memory

Human studies

Taken as a whole, early clinical studies associated lithium treatment with memory deficits (Ananth et al. 1987), a view corroborated by some recent work (Honig et al. 1999; Kocsis et al. 1993; Van Gorp et al. 1998). The relevant studies have examined lithium effects on various types of memory, including immediate and short-term verbal memory, delayed recall and long-term verbal memory, and visual memory. Subject samples include psychiatric patients (mainly bipolar) occasionally compared to healthy volunteers or medication-naïve bipolar patients and in normal subjects. The latter studies have the advantage of isolating the neuropsychological effects of lithium from those of bipolar disease processes and should, therefore, be given special consideration (Table 1).

Lithium, immediate, and short-term verbal memory

The results of clinical studies comparing mood disorder patients on lithium to unmedicated controls are equivocal. Affective disorder patients on long-term prophylactic lithium treatment showed impaired performance in immediate recall tasks and short-term verbal memory tests, compared to drug-free normal controls or the standardized norms (Kusumo and Vaughan 1977; Loo et al. 1981; Lund et al. 1982). However, when euthymic bipolar outpatients on (a) lithium and (b) valproate monotherapy were compared to controls on immediate verbal memory, lithium and valproate were associated with comparable deficits, suggesting that either the two medications influence this function in a similar fashion or that the deficit is intrinsic to bipolar

disorder (Senturk et al. 2007). Another study comparing two groups of bipolar patients with and without a history of alcohol dependence to normal controls could not dissociate the cognitive effects of lithium from those of bipolar disorder (Van Gorp et al. 1998). Finally, two controlled studies failed to find lithium-induced short-term memory impairments in bipolar patients (Marusarz et al. 1981) and bipolar disorder vs. major depression (Jauhar et al. 1993).

Another strategy used for examining the impact of lithium on cognitive functioning is the evaluation of the effects of lithium discontinuation in mood disorder patients. In such discontinuation studies, euthymic bipolar patients continuing lithium treatment showed impaired immediate and long-term memory compared to euthymics after lithium discontinuation (Reus et al. 1979). Similarly, bipolar patients retested 16 days after lithium discontinuation showed significant improvement (Christodoulou et al. 1981). In lithium-treated affective patients tested on immediate recall during treatment, under discontinuation, and after reinstatement of the lithium regime, one study (Kocsis et al. 1993) demonstrated reestablishment of the original immediate verbal memory deficit upon reinstatement of lithium in bipolars and patients with recurrent major depression. However, a similar study (Shaw et al. 1987), which also noted significantly improved immediate recall under lithium discontinuation, failed to find reversal of this improvement after lithium reinstatement. Finally, discontinuation studies using double-blind cross-over designs of lithium and placebo treatment found no difference in immediate memory and short-term memory (Squire et al. 1980; Sharma and Singh 1988). Two more discontinuation studies testing short-term memory soon after discontinuation and as long as 12 months after lithium treatment also failed to note a lithium-induced deficit (Telford and Worrall 1978; Smigan and Perris 1983).

Data on the effects on lithium in short-term memory performance of healthy volunteers are as follows: Kropf and Müller-Oerlinghausen (1979) reported significant impairment. In contrast, Weingartner et al. (1985) reported no impairment when the memory function was examined on the basis of attending to and remembering ongoing events. However, lithium appeared to have a "blurring" effect on cognition, as it reduced the ability to discriminate between material seen and similar but not previously seen distractors. Kolk et al. (1993) who examined the effects of a single dose of lithium in healthy volunteers found no lithium-induced impairment in short-term memory. Similarly, Karniol et al. (1978) found no impairment in the immediate retrieval of normal subjects crossing from lithium to placebo after 7 days. Two other studies using more prolonged lithium–placebo randomized double-blind cross-over designs (Stip et al. 2000; Calil et al. 1990; 3 and 8 weeks, respectively) also failed to find lithium-induced impairments in short-term memory.

Lithium, delayed recall, and long-term verbal memory

Studies comparing mood disorder patients on lithium with controls on delayed recall tasks generally report deficits (Loo et al. 1981; Lund et al. 1982). However, in a recent study which noted short-term and delayed verbal memory deficits in bipolar patients with and without alcohol dependence compared to normal controls, the authors stated that medication alone did not account for their findings (Van Gorp et al. 1998), while another study found no delayed recall impairments (Kusumo and Vaughan 1977). In contrast to the delayed recall studies, studies examining long-term memory in bipolar patients on lithium compared to controls report either no deficit (Marusarz et al. 1981) or even improved long-term memory in patients with depression (Kusumo and Vaughan 1977)

Several lithium discontinuation studies investigating delayed verbal recall report deficits during their lithium administration periods (Christodoulou et al. 1981; Shaw et al. 1987; Kocsis et al. 1993). However, an even greater number of studies fail to replicate this finding (Telford and Worrall 1978; Squire et al. 1980; Smigan and Perris 1983; Sharma and Singh 1988). These studies also report intact long-term recall, being at odds with a single study reporting impaired long-term memory performance (Reus et al. 1979).

In healthy volunteers under lithium treatment, Karniol et al. (1978) found no immediate recall impairment, but a significant deficit in long-term recall of words compared to performance under placebo. Similarly, Kropf and Müller-Oerlingshausen (1979) reported that normal volunteers after 14 days on lithium recalled significantly fewer words learned pretest compared to a placebo group. However, Stip et al. (2000) noted an absence of significant effects of lithium on long-term recall.

Lithium and visual memory

Data on lithium effects on verbal memory are equivocal, but they do suggest an overall compromise due to lithium. In contrast, no significant effects of lithium emerge in the area of visual memory in psychiatric patients. Immediate visual memory is reported unimpaired by lithium administration in most relevant studies (Sharma and Singh 1988; Squire et al. 1980; Loo et al. 1981;Van Gorp et al. 1998) with a single study (Christodoulou et al. 1981) reporting transient impairments. With respect to delayed recall in visual memory tasks, one study (Sharma and Singh 1988) reported no lithium-associated decrease in performance, whereas another reported a reversible deficit (Christodoulou et al. 1981). In normal subjects under lithium for 2 weeks (Judd et al. 1977b, c), there were lithium-related performance deficits in visual–motor function, but these appear to

be caused mainly by a general slowing down in performance reported by these authors.

In summary, of a total of 22 studies reviewed in this paper on the effects of lithium on immediate and short-term verbal memory, nine studies reported deficits which ten other studies failed to reproduce. Two studies were inconclusive, while one study actually reported enhanced short-term memory under lithium. With respect to the effects of lithium on delayed recall and long-term memory, of the 16 studies reviewed, eight reported impairments while seven noted no adverse effects and one was inconclusive. Obviously, methodological issues play a major role in this inconsistency (e.g., lack of reliable diagnoses, somatic comorbidities with negative neuropsychological effects, use of different neuropsychological tests) and elude attempts at metaanalysis of the results. However, this remarkable 50–50 distribution does not suggest specific detrimental effects of lithium on memory. It is possible that a general slowing down in performance contributes to the confusing picture (e.g., Judd et al. 1977b, c).

Perhaps it is safest to draw conclusions (albeit tentative ones) on the basis of the studies treating lithium effects on normal subjects alone. Acute administration of lithium does not appear to affect short-term memory performance. More prolonged administration seems to spare basic short-term memory function, allowing normal remembering of ongoing events. However, increased demands such as those imposed by formal neuropsychological testing occasionally reveal mild deficits in short-term memory under subchronic lithium. These deficits may be transient, since more prolonged treatment appears to lead to normal performance. A similar picture emerges with respect to lithium effects on long-term recall.

At this point, a recent longitudinal magnetic resonance imaging (MRI) study on bipolar patients deserves special mention, although it does not include a control group. Patients were studied before ever receiving pharmacotherapy and then over a 4-year period of lithium treatment. Improved immediate verbal memory was noted, along with MRI evidence of increased hippocampal volume over that period (Yucel et al. 2007). This study is one of the few showing combined neurotrophic and functional (memory-enhancing) effects of lithium.

Animal studies

Older studies assessing memory in aversive tasks in rats reported that chronic and subchronic lithium delayed passive avoidance acquisition (Hines and Poling 1984; Cappeliez and Moore 1988), while effects on active avoidance were controversial (Hines and Poling 1984 vs Richter-Levin et al. 1992). However, recent studies report significant improvements in the long-term retention of passive avoidance under subchronic or chronic lithium administration at clinically relevant doses (Pascual and Gonzalez 1995; retention of a weak aversive contingency unable to produce avoidance in controls: Tsaltas et al. 2007a) (Table 3).

Spatial procedures such as the Morris water maze and various conventional maze procedures are in agreement with the latter studies. Only two such studies note memory deficits after lithium treatment. An early study on rats (Roussinov and Yonkov 1975) reports deficient recall of maze learning after subchronic but not acute lithium. Impaired spatial working and reference memory was also found in black molly fish under chronic lithium, during alternation in a plus maze (Creson et al. 2003). All other available studies note either no effect or actual memory improvement under chronic lithium. In mice, lithium had no effect on working memory in the four-arm maze rewarded alternation (Furusawa 1991). In rats, lithium reversed stress-induced memory deficits in the Morris water maze (Vasconcellos et al. 2003): the same study presented data suggestive of lithium-induced memory enhancement (increased number of crossings over the initial position of the escape platform by the lithium-treated, unstressed group, compared to unstressed controls). Tsaltas et al. (2007a) found chronic lithium not to affect reference memory in T-maze rewarded alternation, but noted significant working memory improvement in lithium-treated animals when delay increases between forced and free-choice trials resulted in near-chance performance in control animals. Similarly, improved memory in delayed T-maze alternation has been noted by Nocjar et al. (2007) under chronic lithium, along with improved performance in the hole-board spatial discrimination and in social place-preference conditioning. Finally, rats under chronic lithium exhibited normal object recognition memory in the object recognition task and a transient deficit in the acquisition of spatial discrimination food search task in a hole-board maze with normal spatial memory in later performance (Al Banchaabouchi et al. 2004).

To conclude, little is known on the acute effects of lithium on memory. Subchronic and chronic administration of lithium doses sustaining clinically relevant serum levels in normal animals do not appear to affect spatial reference or object recognition memory. However, spatial working memory appears to be enhanced by lithium treatment, particularly under parameters which challenge the working memory capacity of normal, untreated animals (Tsaltas et al. 2007a; Nocjar et al. 2007). Similarly, long-term retention of weak aversive contingencies (based on few conditioning trials, as is generally the case with step-through passive avoidance) appears to be improved by chronic lithium (Pascual and Gonzalez 1995; Tsaltas et al. 2007a).

Table 3 Effects of lithium administration on memory—animal studies

Animals	Lithium regime	Behavioral paradigm	Effects	Reference
Rats	Subchronic	Passive avoidance retention	↓	Cappeliez and Moore 1988
Rats	Subchronic	Passive avoidance retention	↑	Pascual and Gonzalez 1995
Rats	Chronic	Passive avoidance retention	↓	Hines and Poling 1984
Rats	Chronic	Passive avoidance retention	↑	Tsaltas et al. 2007a
Rats	Subchronic	Active avoidance retention	↓	Richter-Levin et al. 1992
Rats	Chronic	Active avoidance retention	Ø	Hines and Poling 1984
Rats	Chronic	Fear conditioning retention	Ø	Tsaltas et al. 2007b
Rats	Acute	Maze learning recall	Ø	Roussinov and Yonkov 1975
Rats	Subchronic	Maze learning recall	↓	Roussinov and Yonkov 1975
Rats	Chronic	Spatial reference memory, zero-delay rewarded alternation, T-maze	Ø	Tsaltas et al. 2007a
Fish	Chronic	Spatial working memory, plus maze	↓	Creson et al. 2003
Mice	Acute	Spatial working memory, four-arm maze rewarded alternation	Ø	Furusawa 1991
Rats	Chronic	Spatial working memory, delayed rewarded alternation, T-maze	↑	Tsaltas et al. 2007a
Rats	Chronic	Spatial working memory, delayed rewarded alternation, T-maze	↑	Nocjar et al. 2007
Rats	Chronic	Hole-board spatial discrimination	↑	Nocjar et al. 2007
Rats	Chronic	Place-preference conditioning	↑	Nocjar et al. 2007
Rats	Chronic	Object recognition task	Ø	Al Banchaabouchi et al. 2004
Rats	Chronic	Hole-board spatial discrimination	↓ (transient, Ø)	Al Banchaabouchi et al. 2004
Rats	Acute (3 days)	Morris water maze	↓	Richter-Levin et al. 1992
Rats	Subchronic (10 days)	Morris water maze	Ø	Richter-Levin et al. 1992
Rats	Chronic	Morris water maze	↑	Vasconcellos et al. 2003

↑ improved performance in lithium-treated subjects compared to controls, ↓ compromised performance in lithium-treated subjects compared to controls, Ø unaffected performance in lithium-treated subjects compared to controls

Insofar as these results do not suggest major memory deficits due to lithium treatment in normal animals, they are compatible with the general lack of prolonged detrimental effects of the substance in short- and long-term memory in normal humans. The memory improvement noted in normal animals under certain conditioning parameters is interesting and deserves further exploration, particularly as it suggests that lithium may act as a memory enhancer when task difficulty or compromise of the memory system, as for example by stress (Vasconcellos et al. 2003), lead to marginal performance in untreated controls. This hypothesis would appear to accommodate the memory enhancement seen in bipolar patients after prolonged lithium treatment, along with increased hippocampal volume over that period (Yucel et al. 2007). Evidence of changes (enhancement in synaptic plasticity) in the hippocampus after lithium treatment is supplied by the animal literature as well. Enhanced long-term potentiation (LTP) has been documented after subchronic lithium treatment (increases in excitatory postsynaptic responses, synaptic strength, and cell firing of hippocampal granule cells in the rat dentate gyrus: Shim et al. 2007; Son et al. 2003). Given that LTP is thought to be a neurophysiological basis for the development of learning and memory (Bliss and Collingridge 1993), these data are congruent with the functional memory enhancement seen in some of the animal studies.

Lithium and attention

Human studies

Sharma and Singh (1988) compared patients with affective disorders matched for socioeconomic factors and intelligence quotient scores receiving either lithium or placebo. They found no lithium-associated decreases in attention or concentration. In two studies comparing mood disorder patients with controls which also evaluated attentional performance (Lund et al. 1982; Van Gorp et al. 1998), no negative influence of lithium on attention was noted. Similarly, in a lithium discontinuation study (Squire et al. 1980), no impairments in attention were found under lithium administration (Table 1).

Results on normal volunteers treated with lithium are somewhat more equivocal. Calil et al. (1990), who conducted an 8-week lithium–placebo cross-over study, found no attentional impairments in the lithium group. Stip et al. (2000), using alertness task as well as divided, selective, and sustained attention tasks, also failed to find attentional deficits during a 3-week lithium–placebo administration period. In contrast, Judd et al. (1977b) and Judd (1979) reported that 14 days of lithium administration impaired attentional performance in healthy individuals. However, the authors suggest that the deficits are probably due to a

lithium-induced slowing of performance, consistent with the reports of subjective effects in normal subjects.

Animal studies

Several older animal studies examining the effects of subchronic and chronic lithium on attention in rats suggest that lithium narrows the breadth of attention onto high-salience cues with a corresponding attenuation of reactivity to low-salience stimulation. Thus, rats treated with chronic lithium and trained in an active avoidance task responded predominantly to the cue stimulus, making significantly fewer precue avoidance responses than controls (Hines and Poling 1984). It also attenuated shock-induced suppression of open-field activity when that suppression was under the control of mild or moderate conditioned stimulus parameters, but did not affect suppression produced by shock itself (Hines 1986b). In a discrimination learning task in the Y-maze with compound cues, rats treated with subchronic lithium showed increased readiness to focus onto the reward-relevant cue if this was highly salient (brightness relevant/spatial cues irrelevant). After an extradimensional shift was made (spatial cues relevant/brightness irrelevant), the performance of the lithium-treated rats deteriorated (Cappeliez et al. 1989). However, normal distractibility was seen in rats treated with subchronic lithium in a second open-field test where they reduced their exploration as readily as control animals did. In the same study (Pascual and Gonzalez 1995), lithium-treated rats were slightly less active than controls during the first exposure to the open-field (Table 4).

With regard to latent inhibition, one study has proposed that lithium reduces rats' ability to learn to ignore irrelevant stimuli, since subchronic lithium blocked latent inhibition (Cappeliez and Moore 1988). However, a recent study using chronic lithium at therapeutically relevant serum levels demonstrated intact latent inhibition in the rat (Tsaltas et al. 2007b). Finally, the effects of lithium on sensorimotor gating, as examined by the prepulse inhibition test, are equivocal. Lithium appears to block deficits induced on prepulse inhibition by apomorphine (Umeda et al. 2006) or by D-amphetamine (Ong et al. 2005), but not by ketamine (Ong et al. 2005). In another study, chronic lithium promoted inhibition in one strain of mice but compromised it in another (O'Neill et al. 2003).

In conclusion, human studies examining lithium effects on attention in clinical and normal populations quite consistently report normal attentional functioning. Animal studies, mainly those using subchronic lithium regimes, report narrowing of attention onto high-salience cues at the expense of less prominent ones. However, distractibility appears uncompromised, as does learned irrelevance under chronic lithium.

Lithium and executive functions

Human studies

Impaired executive function is considered to be an important characteristic of bipolar disorder (Frangou et al. 2005). Therefore, the effects of lithium on executive functions of bipolar patients are not easy to assess. Bipolar patients on lithium treatment have been reported to present compromised executive functions relative to controls only in the presence of alcohol dependence comorbidity (Van Gorp et al. 1998). A recent study on eurythmic bipolar patients on lithium monotherapy or lithium in combination with other psychotropics also noted executive and response inhibition deficits in the lithium monotherapy group compared to controls (Mur et al. 2007). Two other studies compared euthymic bipolar patients on monotherapy with lithium and valproate. One reported that the lithium and valproate monotherapy groups and drug-free euthymic bipolar controls performed worse on executive functioning tests than healthy controls (Goswami et al. 2002). This

Table 4 Effects of lithium administration on attention—animal studies

Animals	Lithium regime	Behavioral paradigm	Effects	Reference
Rats	Subchronic	Cued Y-maze discrimination learning (low-salience cue–high-salience distractor)	↓	Cappeliez et al. 1989
Rats	Subchronic	Cued Y-maze discrimination learning (high-salience cue, low-salience distractor)	Ǿ	Cappeliez et al. 1989
Rats	Chronic	Active avoidance	↓ (fewer precue responses)	Hines and Poling 1984
Rats	Chronic	Conditioned suppression of open-field activity	↓	Hines 1986b
Rats	Subchronic	Open-field test, exploration reduction in second exposure	Ǿ	Pascual and Gonzalez 1995
Rats	Subchronic	Latent inhibition	↓	Cappeliez and Moore 1988
Rats	Chronic	Latent inhibition	Ǿ	Tsaltas et al. 2007b
Mice	Chronic	Prepulse inhibition	↓/↑ (species difference)	O'Neill et al. 2003

↑ improved performance in lithium-treated subjects compared to controls, ↓ compromised performance in lithium-treated subjects compared to controls, Ǿ unaffected performance in lithium-treated subjects compared to controls

suggests that the executive deficits are not due to lithium, but nor are they reduced by it. The other study noted that the two bipolar groups did not differ from each other or from controls in terms of executive functioning, as assessed by the Wisconsin card sorting test (Senturk et al. 2007). Other data relevant to the effects of lithium on executive functions concern visual–spatial constructional ability, which was found unimpaired by lithium in two studies involving psychiatric patients on and off lithium (Sharma and Singh 1988; Squire et al. 1980) and one involving healthy volunteers (Judd 1979) (Table 1).

Animal studies

Very little information is available on the effects of lithium on executive functions in animals, apart from the reports of enhanced working memory discussed earlier (Vasconcellos et al. 2003; Tsaltas et al. 2007a; Nocjar et al. 2007). To our knowledge, there are no reports directly examining lithium effects on behavioral flexibility or response inhibition, and little is known on its effects on extinction, particularly of appetitively motivated behavior. One report alludes to increased response inhibition, reporting failure of lithium-treated rats to show extinction of activity suppression after shock removal (Hines 1986b). At this time, it is, therefore, not feasible to evaluate the effects of lithium on executive functions until further work, especially on normal individuals receiving lithium, becomes available.

Effects of lithium on cognitive–behavioral deficits induced by challenges to the central nervous system

It is well-documented that lithium is neuroprotective against several cytotoxic processes (Chuang et al. 2002; Jope 2003), such as oxygen and glucose deprivation (Cimarosti et al. 2001; Nonaka and Chuang 1998), serum starvation (Hongisto et al. 2003), and glutamate-mediated excitotoxicity (Nonaka et al. 1998). Aside from its effects on normal cognitive processes, increasing evidence suggests that the neuroprotective effects of lithium are translatable to functional "cognitive enhancer" capacity on substrates of cognitive deficits induced by various challenges to the central nervous system (CNS). Such challenges include psychobiological factors as stress, trauma to the nervous system by excitotoxic factors, ischemia or irradiation, neurodegenerative disorders, and psychiatric disorders.

In assessing the value of lithium as a putative cognitive enhancer, clearly, it is not sufficient to rely on clinical reports of therapeutic efficacy. Proof of improvement of cognitive dysfunction in the context of a given disease requires, additionally, rigorous placebo-controlled clinical trials demonstrating significant improvement or slowed rate of decline in cognitive function as a result of lithium treatment, as well as converging evidence from animal models associating lithium action with the underlying neurochemical substrate of the disease process suspected as a cause of the cognitive dysfunction (Kennedy et al. 2007). Accordingly, an attempt is made below to combine recent clinical and animal studies, where those are available, on the effects of lithium on cognitive dysfunction associated with various challenges to the nervous system which compromise cognitive function.

Lithium and cognitive–behavioral deficits induced by stress or CNS trauma

In this area, information is provided mainly by animal studies. With respect to stress, chronic lithium pretreatment reportedly reduced stress-induced hypokinesia in the forced swimming test (Kofman et al. 1995) and attenuated spatial reference memory deficits in the Morris water maze (Vasconcellos et al. 2003). In a later study, lithium also prevented stress-induced reduction in hippocampal Na^+/K^+-ATPase activity (Vasconcellos et al. 2005). These stress-related neurochemical and cognitive deficits were also reversed by poststress lithium treatment. Accordingly, it was suggested that Na^+/K^+-ATPase activity modulation may be one of the mechanisms of lithium's therapeutic action (el-Mallakh 1983; Vasconcellos et al. 2005). It must be noted that this study focused on hippocampal Na^+/K^+-ATPase activity, since this region is particularly sensitive to stress effects. Therefore, the possibility that lithium has similar effects on other brain structures cannot be excluded. The variate stress regime used in the two studies mentioned above (Vasconcellos et al. 2003, 2005) was also shown to cause oxidative damage in the hippocampus (Vasconcellos et al. 2006b). Although chronic lithium presented some antioxidant properties (decreased free radicals production in hippocampus), it was not able to block the stress-induced oxidative damage (Vasconcellos et al. 2006b).

Finally, chronic variate stress which induced immobility in the forced swim test was also shown to reduce cell proliferation/differentiation (as evidenced by the use of specific proliferation and differentiation markers) and increase apoptotic rate and glycogen-synthase-kinase-3beta (GSK-3beta) in the hippocampus. Administration of lithium (2.5 mEq/kg body weight) during exposure to chronic stress prevented both its behavioral and neurochemical effects. The authors suggest that lithium may prevent the deleterious effects of stress on behavior and cellular functions by regulating GSK-3beta activity (Silva et al. 2008).

Subchronic lithium pretreatment reportedly attenuated the effects of cholinergic excitatory neurotoxicity, protecting from both the neurochemical and behavioral concomitants of ibotenic acid lesions to the nucleus basalis

magnocellularis. Specifically, it attenuated the exploration deficit and the passive avoidance retention deficit induced by the lesions (Pascual and Gonzalez 1995). Cranial irradiation (which can cause lifelong neurocognitive deficiency in humans) of newborn mice was shown to induce hippocampally dependent learning and memory deficits in the Morris water maze, along with apoptosis and decreased neurogenesis in the subgranular zone of the hippocampus. One week lithium pretreatment improved the observed cognitive deficits and protected irradiated hippocampal neurons from apoptosis. Mediation of this effect was attributed to multiple pathways, including GSK-3beta and Bcl-2/Bax, since lithium exposure in combination with ionizing radiation in vitro was shown to induce GSK-3beta inhibition and an increase in Bcl-2 protein expression, as well as decreased expression of the apoptotic protein Bax (Yazlovitskaya et al. 2006). Finally, the 2-week lithium pretreatment attenuated the neurological and cognitive deficits induced by transient global cerebral ischemia, which included defective beam balance, hyperactivity in the open-field, and compromised learning and memory in the elevated plus maze and the Morris water maze. In parallel, it decreased cell death in hippocampal CA1 region (Yan et al. 2007a, b). This lithium regime was shown to increase ERK1/2 activation after ischemia and lead to significant increase and elevated survival rates of Brdu-positive cells in the hippocampal dentate gyrus. It was suggested that lithium upregulates the generation and survival of newborn cells in the hippocampus by the ERK pathway (Yan et al. 2007b).

Lithium and cognitive deficits resulting from neurodegenerative disorders

Given the evidence of lithium's inhibitory action on the formation of beta amyloid and hyperphosphorylated tau protein (Sun et al. 2002), the possibility that it may offer clinical benefit against Alzheimer's disease is of obvious interest, so it is now under assessment both in clinical studies and in animal models of the disorder.

The results of two clinical studies comparing lithium-treated patients with age-matched controls not on lithium were not very encouraging. Primary care patients on lithium and patients who had not taken lithium were assessed with respect to diagnosis of dementia, and it was noted that lithium-treated patients had a higher risk of a dementia diagnosis. There was also a trend toward increasing dementia risk with increasing numbers of lithium prescriptions (Dunn et al. 2005). Elderly lithium-treated patients without a diagnosis of dementia and matched controls who had never been prescribed lithium did not differ in mini-mental state examination (MMSE) scores. Only when patients who had previously received lithium and/or were currently on lithium were included, their MMSE scores were significantly better than those of controls (Terao et al. 2006).

However, these studies did not control for the fact that affective disorders are associated with increased risk for dementia (elderly bipolar patients vs. age-matched controls: 14% vs. 3.4%; Kessing 1998) while, also, patients with dementia show increased risk of mania and depression and are, therefore, more likely to receive lithium treatment (Nilsson et al. 2002). The results of a recent study which did take this factor into account were more encouraging. When two groups of elderly euthymic bipolar patients (comparable in terms of previous depressive and manic episodes), one on lithium and the other not currently or recently on lithium, were compared, Alzheimer's disease was diagnosed in 33% of the group off lithium and in only 5% of the lithium-treated group. Lithium treatment, therefore, reduced the prevalence of Alzheimer's disease in patients with bipolar disorder to levels of the general elderly population (Nunes et al. 2007). On the basis of this evidence as well as evidence of reduced GSK-3 beta expression in primary cultures of hippocampal neurons from lithium-treated rats and in leukocytes of elderly bipolar patients undergoing chronic lithium therapy, these authors suggest further investigation of the potential protective effect of lithium in Alzheimer's disease, as this could represent a low-cost universally available strategy to reduce its prevalence (Gattaz et al. 2007).

Data on the effects of lithium from animal models of Alzheimer's disease are also encouraging, though not lacking in controversy. Amyloid precursor protein (APP) transgenic mice expressing mutant human APP under the Thy1 promoter (hAPP tg) exhibit memory deficits in the Morris water maze, offering a putative transgenic model of Alzheimer's disease. Under lithium treatment, these mice displayed improved water maze performance, decreased tau phosphorylation, and preserved dendritic structure in the frontal cortex and hippocampus (Rockenstein et al. 2007). The authors suggest that modulation of the GSK-3beta signaling pathway by lithium may have neuroprotective effects in this model of Alzheimer's disease by regulating APP maturation and processing. In another transgenic model (aged 3xTg-AD mice, exhibiting plaques and tangles), however, lithium treatment did reduce tau phosphorylation, but did not improve working memory deficits. As lithium did not significantly alter the A beta load in this study, it is suggested that combining lithium with other anti-A beta interventions may be an efficacious treatment of Alzheimer's disease (Caccamo et al. 2007).

The effects of lithium as a neuroprotector and cognitive enhancer have also been examined in a model of spinocerebellar ataxia type 1, another neurodegenerative disease characterized by progressive motor and cognitive dysfunction. Lithium treatment in a knock-in mouse model of the

disease attenuated the expected reduction of dendritic branching in mutant hippocampal pyramidal neurons and also gave significant improvement in motor coordination, learning, and memory. It was suggested that lithium is an excellent candidate treatment for human spinocerebellar ataxia type 1 patients (Watase et al. 2007).

Lithium and cognitive deficits associated with psychiatric disorders

Little can be added at this point on the therapeutic effectiveness of lithium on the cognitive deficits associated with manic depressive disorder, as most clinical data on lithium's behavioral effects have been obtained from studies on bipolar patients and have been discussed earlier. However, useful additional information comes from recent studies using neuroimaging techniques to assess the neuroanatomical concomitants of bipolar disorder and the effects of lithium thereon.

Bearden et al. (2007a, b), using high-resolution magnetic resonance imaging and cortical pattern matching methods, found that, in bipolar patients, lithium-treated in their majority, gray matter density was significantly greater relative to controls in diffuse cortical regions, particularly in bilateral cingulate and paralimbic cortices, which are associated with attentional, motivational, and emotional modulation. A subsequent study (Bearden et al. 2008a) using surface-based anatomic mapping compared hippocampal anatomy in bipolar patients treated with lithium, unmedicated bipolar patients, and matched healthy controls. Unmedicated bipolar patients showed deficits localized in the cornu ammonis 1 subfields of the right hippocampus, compared to lithium-treated bipolar patients and controls. In contrast, lithium-treated bipolar patients showed total hippocampal volume significantly larger than that of controls and untreated patients. The authors suggest that the memory deficits associated with bipolar illness may be related to this apparent hippocampal pathology, while the increase in hippocampal volume in lithium-treated patients may reflect neurotrophic effects of lithium.

A longitudinal study combined neuroimaging and neuropsychological examination of lithium-treated bipolar patients who had never received pharmacotherapy before lithium initiation, over a period of 2 to 4 years, to determine the long-term effects of lithium therapy on hippocampal volume and on memory performance (California Verbal Learning Test). They reported bilateral increases in hippocampal volume over time, as well as some evidence of verbal memory improvement. These authors also related their findings to the neuroprotective effects of lithium reported by preclinical studies (Yucel et al. 2007).

It should be mentioned at this point that findings associating lithium administration with increases in brain volume (Bearden et al. 2007a, b; Yucel et al. 2007) have recently been challenged as possibly reflecting lithium-induced increase in intracellular water content rather than in gray matter density (Regenold 2008a, b). Although this possibility should be taken into account in evaluating lithium's effects on brain volume and density, there is limited evidence to support it since significant water content increases have only been reported in the frontal cortex in animals chronically treated with lithium (Phatak et al. 2006; Yucel and Mac Queen 2008). Furthermore, as pointed out by Bearden et al. (2008b), changes in intracellular water content may be associated, directly or indirectly, with changes relevant to the therapeutic mechanism of lithium. Future studies using the neuroimaging techniques of T_2 relaxometry and diffusion tensor imaging are needed to clarify the role of water content changes on the neuroanatomic effects of lithium (Bearden et al. 2008b).

Recently, the neuroprotective and therapeutic effectiveness of lithium is being assessed with respect to peri-onset stages of psychotic disorders. Emerging psychosis has been associated with peri-onset structural and metabolic brain changes (Borgwardt et al. 2007). Clearly, interventions which can potentially delay or even prevent transition from a subthreshold to a clinical state of psychotic disorder are of major theoretical and clinical interest. Although caution is necessary when reference is made to as yet unpublished data, a study currently in preparation (Berger et al., personal communication) deserves to be mentioned. These authors employed hippocampal T_2 relaxation time and proton magnetic resonance spectroscopy to assess peri-onset structural and metabolic brain changes in individuals at ultra high risk for psychosis (UHR). They report very encouraging information with respect to lithium effects on these deficits. UHR individuals were assessed before the onset and 3 months after low-dose lithium treatment and compared to a matched UHR group not receiving lithium and to normal controls. Hippocampal T_2 relaxation time differentiated low-dose lithium-treated patients from patients receiving treatment as usual with no lithium. Some metabolic brain changes were also noted, the lithium group showing increases in *N*-acetyl aspartate, myo-inositol, creatine, and choline, which were decreased or unchanged in UHR subjects not receiving lithium. Furthermore, microstructural and metabolic hippocampal percentage change scores correlated with symptomatic improvement. These findings support a neuroprotective and therapeutic role for lithium in psychosis-susceptible individuals.

Summary and conclusions

The general behavioral effects of lithium which may confound examination of its cognitive effects are a

reduction in exploratory activity and a moderation of reactions to aversive, stress- and fear-related stimuli. Therefore, study of the cognitive effects of the substance should encompass parallel use of appetitive and aversive paradigms with more weight given to the former.

The effects of lithium on learning in clinical populations appear to be mildly detrimental, possibly attributable to lithium's generalized dampening effect on performance. They appear most pronounced in the initial stages of lithium administration, as corroborated by animal studies. Therefore, results produced by subchronic regimes should be treated cautiously, as perhaps reflecting general influences on arousal and mood. Indeed, recent animal studies employing chronic lithium administration with clinically relevant serum levels consistently show learning improvements under lithium.

Clinical study results on the effects of lithium on memory in bipolar populations are equivocal, rendering metaanalysis difficult because of methodological inconsistencies. Tentative conclusions from studies in normal subjects are that acute lithium does not affect short-term memory; subchronic administration spares basic short-term memory of ongoing events but higher task demands (as in neuropsychological testing) occasionally reveal mild deficits. As do learning deficits, these too appear transient. A similar picture emerges with respect to lithium effects on human long-term recall. In animal studies, subchronic and chronic lithium with clinically relevant serum levels does not affect spatial reference or object recognition memory and actually enhances working memory under certain conditions. This is consistent with recent clinical MRI findings noting improved immediate verbal memory after a 4-year period of lithium treatment, along with MRI evidence of increased hippocampal volume over the same period.

Human attention is quite consistently reported normal under lithium. Some older animal studies report narrowing of attention onto high-salience cues and compromised latent inhibition, but these results are challenged by more recent data indicating normal function. Finally, information on lithium effects on executive functions is sparse and cannot be evaluated at present. More basic research is definitely needed with respect to lithium effects on attention and executive functions.

Recent reports on lithium effects on the cognitive–behavioral deficits induced by various challenges to the nervous system in animal models are quite promising. Lithium protects against neuroanatomical and neurochemical effects and also moderates cognitive deficits induced by stress or CNS trauma such as irradiation or anoxia. In some cases, such deficits are not simply prevented but appear to be reversed post facto. This combined neuroprotective- and cognitive-enhancing action of lithium is noted primarily with respect to hippocampally related spatial memory tasks. It appears to involve protection against the reduced cell proliferation and increased apoptotic rate noted mainly in the hippocampus under these challenges. Neurochemically, this neuroprotective and neurotrophic action has been associated to a modulating action of lithium on pathways including GSK-3 and Bcl-2/Bax.

A similar picture emerges in relation to lithium effects on the cognitive compromises induced by neurodegenerative disorders. Lithium reduces the prevalence of Alzheimer's disease in bipolar patients, and there is evidence suggesting that this is associated with reduced GSK-3beta expression. Evidence of lithium's moderating action on hippocampally related cognitive deficits also comes from transgenic animal models of Alzheimer's disease. Again, modulation of the GSK-3beta signaling pathway by lithium has been implicated.

In cognitive dysfunction associated with psychiatric conditions, beneficial effects of lithium have emerged on the neuroanatomical level from imaging studies. Lithium treatment of bipolar patients has been associated with hippocampal volume increase and appears to entail concomitant cognitive improvements. These neuroimaging findings are not limited to bipolar patients, but involve people at ultrahigh risk of developing a psychotic disorder where lithium appears to arrest neuroanatomical and neurochemical changes associated with the onset of psychosis.

In conclusion, increasing neuroanatomical and neurochemical evidence from both in vitro and in vivo studies supports that lithium has neuroprotective properties, mainly involving hippocampal cells (Moore et al. 2000; Manji et al. 2001; Sassi et al. 2002; Kim et al. 2004; Chuang 2004; Chuang and Priller 2006). Recent behavioral data suggest that this neuroprotective action is translatable to functional improvement of compromised cognitive functioning. To this picture, one must add recent electrophysiological data. In an investigation of the electrophysiological concomitants of the established neuroplastic action of chronic lithium, electrophysiological studies (Son et al. 2003; Shim et al. 2007) demonstrated increases in excitatory postsynaptic responses, synaptic strength, and cell firing of hippocampal granule cells in the dentate gyrus after 14 days of lithium; LTP increase in area CA1 is also noted after 4 weeks of lithium treatment. Given that LTP in hippocampal neurons is a cellular model of learning and memory (Bliss and Collingridge 1993, Kandel 2004) and that hippocampal volume changes (Toulopoulou et al. 2004; von Gunten and Ron 2004) or structural integrity (Lillywhite et al. 2007) correlate with memory performance, the findings reported above lead to an expectation of a beneficial effect of lithium on learning and memory.

Shim et al. (2007) noted that the direct action of acute lithium is to reduce the excitability of nerve terminals, thus

the release of glutamate, resulting in reduced postsynaptic excitability in the dentate gyrus. Therefore, their results are not attributed to the direct, acute action of lithium on synaptic activity but are related to its neuroplastic actions, which would require at least 2 weeks for the gene expression of proteins involved in neuronal and synaptic plasticity (Lenox and Fraze 2002). This 2-week period corresponds with the emergence of the therapeutic action of lithium (Hirschfeld et al. 2000). The lithium regime under which LTP increases were observed in the hippocampus (Shim et al. 2007) was chronic (14–30 days) with clinically relevant plasma levels (0.51–0.78 mEq/L lithium). It is comparable to regimes which have produced enhancing effects of lithium on learning and memory in the recent animal studies (Vasconcellos et al. 2003; Tsaltas et al. 2007a; Nocjar et al. 2007).

An interesting trend for future exploration emerges from these recent reports of learning and memory improvements noted in normal animals under chronic lithium. Enhancement appears to emerge under conditions of increased challenge to cognitive possessing, either due to task difficulty (Tsaltas et al. 2007a) or due to stress (Vasconcellos et al. 2003). It is reasonable to expect that any learning- or memory-enhancing capacity of lithium is most likely to be expressed under conditions of challenge to the nervous system, be that psychological, psychobiological, or structural compromise as seen in aging, trauma, neurodegenerative, or psychiatric conditions.

Lithium is a low-cost, readily available substance with the administration of which psychiatrists are quite familiar. Although its narrow therapeutic window dictates great caution with respect to toxicity (Donaldson and Cuningham 1983), particularly if it is to be used in the elderly—the group that would most benefit from cognitive enhancement—the findings reported in this paper are encouraging with respect to its potential use as a cognitive protector or enhancer. Certainly, this proposition warrants further study, and the areas which emerge as particularly interesting are the following: Primarily, clinical and basic research have focused mainly on the effects of lithium on the hippocampus and hippocampally controlled cognitive tasks, while its effects on prefrontal tasks involving attention and executive functions require further study. Secondly, the possibility that lithium's enhancing effects on cognition would be more pronounced under increased task difficulty or on a compromised neural substrate should be explored. Apart from manipulating task difficulty, this could be done by examining lithium's effects on normal but aging organisms.

Acknowledgements This work was supported by Grant 70/4/9100 from the Special Account for Research Grants, National and Kapodistrian University of Athens to Dr. E. Tsaltas.

References

Al Banchaabouchi M, Peña de Ortíz S, Menéndez R, Ren K, Maldonado-Vlaar CS (2004) Chronic lithium decreases Nurr1 expression in the rat brain and impairs spatial discrimination. Pharmacol Biochem Behav 79:607–621

Alexander GJ, Alexander RB (1978) Alcohol consumption in rats treated with lithium carbonate or rubidium chloride. Pharmacol Biochem Behav 8:533–536

Ananth J, Ghadirian AM, Engelsmann F (1987) Lithium and memory: a review. Can J Psychiatry 32:313–316

Bauer M, Forsthoff A, Baethge C, Adli M, Berghofer A, Dopfmer S, Bschor T (2003) Lithium augmentation therapy in refractory depression—update 2002. Eur Arch Psychiatry Clin Neurosci 253:132–139

Bearden CE, Thompson PM, Dutton RA, Frey BN, Peluso MA, Nicoletti M, Dierschke N, Hayashi KM, Klunder AD, Glahn DC, Brambilla P, Sassi RB, Mallinger AG, Soares JC (2007a) Three-dimensional mapping of hippocampal anatomy in unmedicated and lithium-treated patients with bipolar disorder. Neuropsychopharmacology 33:1229–1238

Bearden CE, Thompson PM, Dalwani M, Hayashi KM, Lee AD, Nicoletti M, Trakhtenbroit M, Glahn DC, Brambilla P, Sassi RB, Mallinger AG, Frank E, Kupfer DJ, Soares JC (2007b) Greater cortical gray matter density in lithium-treated patients with bipolar disorder. Biol Psychiatry 62(1):7–16

Bearden CE, Soares JC, Klunder AD, Nicoletti M, Dierschke N, Hayashi KM, Narr KL, Brambilla P, Sassi RB, Axelson D, Ryan N, Birmaher B, Thompson PM (2008a) Three-dimensional mapping of hippocampal anatomy in adolescents with bipolar disorder. J Am Acad Child Adolesc Psychiatry 47(5):515–525

Bearden CE, Thompson PM, Dalwani M, Hayashi KM, Lee AD, Glahn DC, Brambilla P, Sassi RB, Mallinger A, Frank E, Kupfer DJ, Nicoletti M, Soares JC (2008b) Reply: lithium and increased cortical gray matter—more tissue or more water? Biol Psychiatry 63(3):19

Bersudsky Y, Shaldubina A, Belmaker RH (2007) Lithium's effect in forced-swim test is blood level dependent but not dependent on weight loss. Behav Pharmacol 18:77–80

Bliss TV, Collingridge GL (1993) A synaptic model of memory: long term potentiation in the hippocampus. Nature 361:31–39

Borgwardt SJ, McGuire PK, Aston J, Berger G, Dazzan P, Gschwandtner U, Pflüger M, D'Souza M, Radue EW, Riecher-Rössler A (2007) Structural brain abnormalities in individuals with an at-risk mental state who later develop psychosis. Br J Psychiatry Suppl 51:s69–75

Buckley PF (2008) Update on the treatment and management of schizophrenia and bipolar disorder. CNS Spectr 13(2 Suppl 1):1–10

Caccamo A, Oddo S, Tran LX, LaFerla FM (2007) Lithium reduces tau phosphorylation but not A beta or working memory deficits in a transgenic model with both plaques and tangles. Am J Pathol 170(5):1669–1675

Calil HM, Zwicker AP, Klepacz S (1990) The effects of lithium carbonate on healthy volunteers: mood stabilization? Biol Psychiatry 27:711–722

Cappeliez P, Moore E (1988) Effects of lithium on latent inhibition in the rat. Prog Neuropychopharmacol Biol Psychiatry 12(4):431–443

Cappeliez P, Moore E, Souliere M (1989) Effects of lithium on appetitive discrimination in the rat. Prog Neuropsychopharmacol Biol Psychiatry 13(5):725–734

Chenu F, Bourin M (2006) Potentiation of antidepressant-like activity with lithium: mechanism involved. Curr Drug Targets 7:159–63

Christodoulou GN, Kokkevi A, Lykouras EP, Stefanis CN, Papadimitriou GN (1981) Effects of lithium on memory. Am J Psychiatry 138:847–848

Chuang DM (2004) Lithium neuroprotection from glutamate excitotoxicity. Lithium and mood stabilizers: mechanism of action. Clin Neurosci Res 4:243–252

Chuang DM, Manji HK (2007) In search of the Holy Grail for the treatment of neurodegenerative disorders: has a simple cation been overlooked? Biol Psychiatry 62(1):4–6

Chuang DM, Priller J (2006) Potential use of lithium in neurodegenerative disorders. In: Bauer M, Grof P, Müller-Oerlingausen B (eds) Lithium in neuropsychiatry: the comprehensive guide. Taylor & Francis Books, London, pp 381–397

Chuang DM, Chen RW, Chalecka-Franaszek E, Ren M, Hashimoto R, Senatorov V, Kanai H, Hough C, Hiroi T, Leeds P (2002) Neuroprotective effects of lithium in cultured cells and animal models of diseases. Bipolar Disord 4:129–136

Cimarosti H, Rodnight R, Tavares A et al (2001) An investigation of the neuroprotective effect of lithium in organotypic slice cultures of rat hippocampus exposed to oxygen and glucose deprivation. Neurosci Lett 315:33–36

Creson TK, Woodruff ML, Ferslew KE, Rasch EM, Monaco PJ (2003) Dose–response effects of chronic lithium regimens on spatial memory in the black molly fish. Pharmacol Biochem Behav 75(1):35–47

Crossley NA, Bauer M (2007) Acceleration and augmentation of antidepressants with lithium for depressive disorders: two meta-analyses of randomized, placebo-controlled trials. J Clin Psychiatry 68:935–940

Donaldson IM, Cuningham J (1983) Persisting neurologic sequelae of lithium carbonate therapy. Arch Neurol 40:747–751

Dunn N, Holmes C, Mullee M (2005) Does lithium therapy protect against the onset of dementia? Alzheimer Dis Assoc Disord 19:20–22

el-Mallakh RS (1983) The Na,K-ATPase hypothesis for manic-depression. II. The mechanism of action of lithium. Med Hypotheses 12:269–282

Engel T, Goñi-Oliver P, Gómez de Barreda E, Lucas JJ, Hernández F, Avila J (2008) Lithium, a potential protective drug in Alzheimer's disease. Neurodegener Dis 5(3–4):247–249

Eroglu L, Hizal A (1987) Antidepressant action of lithium in behavioral despair test. Pol J Pharmacol Pharm 39:667–673

Frances H, Maurin Y, Lecrubier Y, Puech AJ, Simon P (1981) Effect of chronic lithium treatment on isolation-induced behavioral and biochemical effects in mice. Eur J Pharmacol 72:337–341

Frangou S, Donaldson S, Adjulis M et al (2005) The Maudsley bipolar disorder project: executive dysfunction in bipolar disorder I and its clinical correlates. Biol Psychiatry 58:859–864

Furusawa K (1991) Drug effects on cognitive function in mice determined by the non-matching to sample task using a 4-arm maze. Jpn J Pharmacol 56(4):483–493

Gallo C, Poletti G, Cazorla A (1990) Effects of chronic lithium administration on brain weights, acetylcholinesterase activity and learning ability in rats. Life Sci 47(6):507–513

Gattaz WF, Forlenza OV, Nunes PV (2007) Authors' reply. Br J Psychiatry 191:362

Gelenberg AJ, Kane JM, Keller MB, Lavori P, Rosenbaum JF, Cole K, Lavelle J (1989) Comparison of standard and low serum levels of lithium for maintenance treatment of bipolar disorder. N Engl J Med 321:1489–1493

Geoffroy M, Tvede K, Christensen AV, Schou JS (1991) The effect of imipramine and lithium on "learned helplessness" and acetylcholinesterase in rat brain. Pharmacol Biochem Behav 38:93–97

Gould TD, Einat H, O'Donnell KC, Picchini AM, Schloesser RJ, Manji HK (2007) [beta]-Catenin overexpression in the mouse brain phenocopies lithium-sensitive behaviors. Neuropsychopharmacology 32:2173–2183

Gould TD, O'Donnell KC, Dow ER, Du J, Chen G, Manji HK (2008) Involvement of AMPA receptors in the antidepressant-like effects of lithium in the mouse tail suspension test and forced swim test. Neuropharmacology 54:577–87

Goswami U, Gulrajani C, Moore PB et al (2002) Neurocognitive decline in bipolar mood disorder: role of mood stabilizers. J Psychopharmacol 16(Suppl):A45

Hascoet M, Bourin M, Khimake S (1994) Additive effect of lithium and clonidine with 5-HT1A agonists in the forced swimming test. Prog Neuropsychopharmacol Biol Psychiatry 18:381–396

Hines G (1985) Lithium effects on position learning with exploratory and aversive goal-box conditions. Pharmacol Biochem Behav 22 (5):695–698

Hines G (1986a) Lithium effects on adjunctive alcohol consumption. I: comparison with adjunctive water consumption. Pharmacol Biochem Behav 25:1159–1162

Hines G (1986b) Effects of lithium and rubidium on shock-induced changes in open-field activity. Psychopharmacology 88:209–212

Hines G, Henslee DF (1986) Lithium effects on adjunctive alcohol consumption in rats. Psychopharmacology (Berl) 90:236–238

Hines G, Poling TH (1984) Lithium effects on active and passive avoidance behavior in the rat. Psychopharmacology (Berl) 82:78–82

Hirschfeld RMA, Clayton PJ, Cohen I, Fawcett J, Keck P, McCellan J et al (2000) Practice guideline for the treatment of patients with bipolar disorder. In: American Psychiatric Association Steering Committee (ed) The practice guidelines for the treatment of psychiatric disorders: compendium 2000. American Psychiatric Association Press, Washington, DC, pp 509–514

Ho AK, Tsai CS (1976) Effects of lithium on alcohol preference and withdrawal. Ann N Y Acad Sci 273:371–377

Hongisto V, Smeds N, Brecht S, Herdegen T, Courtney MJ, Coffey ET (2003) Lithium blocks the c-Jun stress response and protects neurons via its action on glycogen synthase kinase 3. Mol Cell Biol 23:6027–6036

Honig A, Arts BM, Ponds RW, Riedel WJ (1999) Lithium induced cognitive side effects in bipolar disorder: a qualitative analysis and implications for daily practise. Int Clin Psychopharmacol 14:167–171

Jähkel M, Oehler J, Schumacher HE (1994) Influence of nootropic and antidepressive drugs on open field and running wheel behavior in spontaneously high and low active mice. Pharmacol Biochem Behav 49:263–269

Jasinski DR, Nutt JG, Haertzen CA, Griffith JD, Bunney WE (1977) Lithium: effects on subjective functioning and morphine-induced euphoria. Science 195:582–584

Jauhar P, McClure I, Hillary C, Watson A (1993) Psychomotor performance of patients on maintenance lithium therapy. Hum Psychopharmacol 8:141–143

Joffe R, MacDonald C, Kutcher S (1988) Lack of differential cognitive effects of lithium and carbamazepine in bipolar affective disorder. J Clin Psychopharmacol 8:425–428

Johnson FN (1976) Lithium effects upon components of activity in rats. Experientia 32:212–214

Johnston IN, Westbrook RF (2004) Inhibition of morphine analgesia by lithium: role of peripheral and central opioid receptors. Behav Brain Res 151:151–158

Jope RS (2003) Lithium and GSK-3: one inhibitor, two inhibitory actions, multiple outcomes. Trends Pharmacol Sci 24:441–443

Judd LL (1979) Effect of lithium on mood, cognition, and personality function in normal subjects. Arch Gen Psychiatry 36:860–866

Judd LL, Hubbard RB, Huey LY, Attewell PA, Janowsky DS, Takahashi KI (1977a) Lithium carbonate and ethanol induced "highs" in normal subjects. Arch Gen Psychiatry 34:463–467

Judd LL, Hubbard B, Janowsky DS, Huey LY, Takahashi KI (1977b) The effect of lithium carbonate on the cognitive functions of normal subjects. Arch Gen Psychiatry 34:355–357

Judd LL, Hubbard B, Janowsky DS, Huey LY, Attewell PA (1977c) The effect of lithium carbonate on affect, mood, and personality of normal subjects. Arch Gen Psychiatry 34:346–351

Kandel E (2004) The molecular biology of memory storage: a dialog between genes and synapses. Biosci Rep 24:475–522

Karakucuk E, Yamanoglu T, Demirel O, Bora N, Zengil H (2006) Temporal variation in drug interaction between lithium and morphine-induced analgesia. Chronobiol Int 23:675–682

Karniol IG, Dalton J, Lader MH (1978) Acute and chronic effects of lithium chloride on physiological and psychological measures in normals. Psychopharmacology 57:289–294

Kennedy GJ, Golde TE, Tariot PN, Cummings JL (2007) Amyloid-based interventions in Alzheimer's disease. CNS Spectr 12(12 Suppl 1):1–14

Kessing IV (1998) Cognitive impairment in the euthymic phase of affective disorder. Psychol Med 28:1027–1038

Kim JS, Chang MY, Yu IT, Kim JH, Lee SH, Lee YS et al (2004) Lithium selectively increases neuronal differentiation of hippocampal neural progenitor cells both in vitro and in vivo. J Neurochem 89(2):324–336

Kitaichi Y, Inoue T, Nakagawa S, Izumi T, Koyama T (2006) Effect of co-administration of subchronic lithium pretreatment and acute MAO inhibitors on extracellular monoamine levels and the expression of contextual conditioned fear in rats. Eur J Pharmacol 532:236–245

Kocsis JH, Shaw ED, Stokes PE, Wilner P, Elliot AS, Sikes C et al (1993) Neuropsychologic effects of lithium discontinuation. J Clin Psychopharmacol 13:268–75

Kofman O, Levin U, Alpert C (1995) Lithium attenuates hypokinesia induced by immobilization stress in rats. Prog Neuropsychopharmacol Biol Psychiatry 19:1081–1090

Kolk A, Kathmann N, Greil W (1993) No short-term changes of cognitive performance and mood after single doses of two different lithium retard preparations. Pharmacopsychiatry 26:235–239

Kropf D, Müller-Oerlinghausen B (1979) Changes in learning, memory, and mood during lithium treatment. Approach to a research strategy. Acta Psychiatr Scand 59:97–124

Kusumo KS, Vaughan M (1977) Effects of lithium salts on memory. Br J Psychiatry 131:453–457

Lalonde R, Vikis-Freibergs V (1982) The effects of chlorpromazine and lithium on appetitive discrimination learning in the rat. Psychopharmacology (Berl) 76(3):218–221

Lejoyeux M, Ades J (1993) Evaluation of lithium treatment in alcoholism. Alcohol Alcohol 28:273–279

Lenox RH, Fraze A (2002) Mechanism of action of antidepressants and mood stabilizers. In: Davis KL, Charney D, Coyle JT, Nemeroff CN (eds) Neuropsychopharmacology: the fifth generation of progress. Lippincott Williams & Wilkins, Philadelphia, pp 1139–1163

Lenzer I, Eastwood D, Street P (1989) Reinterpreting memory complaints through neuropsychological assessment. Clin Gerontol 8:57–60

Lillywhite LM, Saling MM, Briellmann RS, Weintrob DL, Pell GS, Jackson GD (2007) Differential contributions of the hippocampus and rhinal cortices to verbal memory in epilepsy. Epilepsy Behav 10(4):553–559

Loo H, Bonnel J, Etevenon P, Benyacoub J, Slowen P (1981) Intellectual efficiency in manic-depressive patients treated with lithium. A control study. Acta Psychiatr Scand 64(5):423–430

Lund Y, Nissen M, Rafaelsen OJ (1982) Long-term lithium treatment and psychological functions. Acta Psychiatr Scand 65:233–244

Manji HK, Moore GJ, Chen G (2001) Bipolar disorder: leads from the molecular and cellular mechanisms of action of mood stabilizers. Br J Psychiatr Suppl 41:s107–s119

Marusarz TZ, Wolpert EA, Koh SD (1981) Memory processing with lithium carbonate. J Clin Psychiatry 42:190–192

Masaki T, Nakajima S (2006) Taste aversion in rats induced by forced swimming, voluntary running, forced running, and lithium chloride injection treatments. Physiol Behav 88:411–416

Moore GJ, Bebchuk JM, Hasanat K, Chen G, Seraji-Bozorgzad N, Wilds IB et al (2000) Lithium increases N-acetyl-aspartate in the human brain: in vivo evidence in support of bcl-2's neurotrophic effects? Biol Psychiatry 48:1–8

Mur M, Portella MJ, Martínez-Arán A, Pifarré J, Vieta E (2007) Persistent neuropsychological deficit in euthymic bipolar patients: executive function as a core deficit. J Clin Psychiatry 68(7):1078–1086

Muraki I, Inoue T, Hashimoto S, Izumi T, Ito K, Ohmori T, Koyama T (1999) Effect of subchronic lithium carbonate treatment on anxiolytic-like effect of citalopram and MKC-242 in conditioned fear stress in the rat. Eur J Pharmacol 383:223–229

Nachman M, Ashe JH (1973) Learned taste aversions in rats as a function of dosage, concentration, and route of administration of LiCl. Physiol Behav 10:73–78

Nilsson FM, Kessing LV, Sorensen TM, Andersen PK, Bolwig TG (2002) Enduring increased risk of developing depression and mania in patients with dementia. J Neurol Neurosurg Psychiatry 73:40–44

Nixon MK, Hascoet M, Bourin M, Colombel MC (1994) Additive effects of lithium and antidepressants in the forced swimming test: further evidence for involvement of the serotoninergic system. Psychopharmacology (Berlin) 115:59–64

Nocjar C, Hammonds MD, Shim SS (2007) Chronic lithium treatment magnifies learning in rats. Neuroscience 150:774–788

Nonaka S, Chuang DM (1998) Neuroprotective effects of chronic lithium on focal cerebral ischemia in rats. NeuroReport 9:2081–2084

Nonaka S, Hough CJ, Chuang DM (1998) Chronic lithium treatment robustly protects neurons in the central nervous system against excitotoxicity by inhibiting N-methyl-D-aspartate receptor-mediated calcium influx. Proc Natl Acad Sci USA 95:2642–2647

Nunes PV, Forlenza OV, Gattaz WF (2007) Lithium and risk for Alzheimer's disease in elderly patients with bipolar disorder. Br J Psychiatry 190:359–360

O'Donnell KC, Gould TD (2007) The behavioral actions of lithium in rodent models: leads to develop novel therapeutics. Neurosci Biobehav Rev 31:932–962

O'Neill HC, Schmitt MP, Stevens KE (2003) Lithium alters measures of auditory gating in two strains of mice. Biol Psychiatry 54: 847–853

Ong JC, Brody SA, Large CH, Geyer MA (2005) An investigation of the efficacy of mood stabilizers in rodent models of prepulse inhibition. J Pharmacol Exp Ther 315:1163–1171

Pachet AK, Wisniewski AM (2003) The effects of lithium on cognition: an updated review. Psychopharmacology 170:225–234

Pascual T, Gonzalez JL (1995) A protective effect of lithium on rat behaviour altered by ibotenic acid lesions of the basal forebrain cholinergic system. Brain Res 695:289–292

Phatak P, Shaldivin A, King LS, Shapiro P, Regenold WT (2006) Lithium and inositol: effects on brain water homeostasis in the rat. Psychopharmacology (Berl) 186:41–47

Redrobe JP, Bourin M (1997) Effects of pretreatment with clonidine, lithium and quinine on the activities of antidepressant drugs in the mouse tail suspension test. Fundam Clin Pharmacol 11:381–386

Redrobe JP, Bourin M (1999) The effect of lithium administration in animal models of depression: a short review. Fundam Clin Pharmacol 13(3):293–299

Regenold WT (2008a) Lithium and increased cortical gray matter—more tissue or more water? Biol Psychiatry 63:e17

Regenold WT (2008b) Lithium and increased hippocampal volume: more tissue or more water? Letter to the editor. Neuropsychopharmacology 33:1773–1774

Reus VI, Targum SD, Weingarter H, Post RM (1979) Effect of lithium carbonate on memory processes of bipolar affectively ill patients. Psychopharmacology (Berl) 63:39–42

Richter-Levin G, Markram H, Segal M (1992) Spontaneous recovery of deficits in spatial memory and cholinergic potentiation of NMDA in CA1 neurons during chronic lithium treatment. Hippocampus 2(3):279–286

Rockenstein E, Torrance M, Adame A, Mante M, Bar-on P, Rose JB, Crews L, Masliah E (2007) Neuroprotective effects of regulators of the glycogen synthase kinase-3beta signaling pathway in a transgenic model of Alzheimer's disease are associated with reduced amyloid precursor protein phosphorylation. J Neurosci 27(8):1981–1991

Roussinov KS, Yonkov D (1975) Comparative studies on the effect of lithium and haloperidol on learning and memory. Acta Physiol Pharmacol Bulg 3–4:51–57

Sassi RB, Nicoletti M, Brambilla P, Malinger AG, Frank E, Kupfer DJ et al (2002) Increased gray matter volume in lithium-treated bipolar disorder patients. Neurosci Lett 329:243–245

Senturk V, Goker C, Bilgic A, Olmez S, Tugcu H, Oncu B, Atbasoglu C (2007) Impaired verbal memory and otherwise spared cognition in remitted bipolar patients on monotherapy with lithium or valproate. Bipolar Disord 9(Suppl 1):136–144

Shaldubina A, Johanson RA, O'Brien WT, Buccafusca R, Agam G, Belmaker RH, Klein PS, Bersudsky Y, Berry GT (2006) SMIT1 haploinsufficiency causes brain inositol deficiency without affecting lithium-sensitive behavior. Mol Genet Metab 88:384–388

Sharma I, Singh P (1988) Cognitive functions in patients of primary affective disorder on prophylactic lithium treatment. Indian J Med Res 88:246–252

Shaw ED, Stokes PE, Mann JJ, Manevitz AZ (1987) Effects of lithium carbonate on the memory and motor speed of bipolar outpatients. J Abnorm Psychology 96:64–69

Shim SS, Hammonds MD, Ganocy SJ, Calabrese JR (2007) Effects of subchronic lithium treatment on synaptic plasticity in the dentate gyrus of rat hippocampal slices. Progr Neuropsychopharmacol Biol Psychiatry 31:343–347

Silva R, Mesquita AR, Bessa J, Sousa JC, Sotiropoulos I, Leão P, Almeida OF, Sousa N (2008) Lithium blocks stress-induced changes in depressive-like behavior and hippocampal cell fate: the role of glycogen-synthase-kinase-3beta. Neuroscience 152 (3):656–669

Smigan L, Perris C (1983) Memory functions and prophylactic treatment with lithium. Psychol Med 13:529–536

Smith DF, Smith HB (1973) The effect of prolonged lithium administration on activity, reactivity, and endurance in the rat. Psychopharmacologia 30:83–88

Son H, Yu IT, Hwang S-J, Kim JS, Lee S-H, Lee Y-S, Kaang B-K (2003) Lithium enhances long-term potentiation independently of hippocampal neurogenesis in the rat dentate gyrus. J Neurochem 85:872–881

Souza FG, Goodwin GM (1991) Lithium treatment and prophylaxis in unipolar depression: a meta-analysis. Br J Psychiatry 158: 666–675

Squire LR, Judd LL, Janowsky DS, Huey LY (1980) Effects of lithium carbonate on memory and other cognitive functions. Am J Psychiatry 137:1042–1046

Stewart KT, McEachron DL, Rosenwasser AM, Adler NT (1991) Lithium lengthens circadian period but fails to counteract behavioral helplessness in rats. Biol Psychiatry 30:515–518

Stip E, Dufresne J, Lussier I, Yatham L (2000) A double-blind, placebo-controlled study of the effects of lithium on cognition in healthy subjects: mild and selective effects on learning. J Affect Disord 60:147–157

Sun X, Sato S, Murayama O, Murayama M, Park JM, Yamaguchi H, Takashima A (2002) Lithium inhibits amyloid secretion in COS7 cells transfected with amyloid precursor protein C100. Neurosci Lett 321(1–2):61–64

Teixeira NA, Pereira DG, Hermini AH (1995) Chronic but not acute Li+ treatment prevents behavioral depression in rats. Braz J Med Biol Res 28:1003–1007

Telford R, Worrall EP (1978) Cognitive functions in manic-depressives: effects of lithium and physostigmine. Br J Psychiatry 133:424–428

Terao T, Nakano H, Inoue Y, Okamoto T, Nakamura J, Iwata N (2006) Lithium and dementia: a preliminary study. Prog Neuropsychopharmacol Biol Psychiatry 30(6):1125–1128

Tomasiewicz HC, Mague SD, Cohen BM, Carlezon WA (2006) Behavioral effects of short-term administration of lithium and valproic acid in rats. Brain Res 1093:83–94

Tomkiewicz M, Steinberg H (1974) Lithium treatment reduces morphine self-administration in addict rats. Nature 252:227–229

Toulopoulou T, Grech A, Morris RG, Schulze K, McDonald C, Chapple B, Rabe-Hesketh S, Murray RM (2004) The relationship between volumetric brain changes and cognitive function: a family study on schizophrenia. Biol Psychiatry 56:447–453

Tsaltas E, Kontis D, Boulougouris V, Papakosta VM, Giannou H, Poulopoulou C, Soldatos C (2007a) Enhancing effects of chronic lithium on memory in the rat. Behav Brain Res 177:51–60

Tsaltas E, Kyriazi T, Poulopoulou C, Kontis D, Maillis A (2007b) Enhancing effects of lithium on memory are not by-products of learning or attentional deficits. Behav Brain Res 180:241–245

Umeda K, Suemaru K, Todo N, Egashira N, Mishima K, Iwasaki K, Fujiwara M, Araki H (2006) Effects of mood stabilizers on the disruption of prepulse inhibition induced by apomorphine or dizocilpine in mice. Eur J Pharmacol 553:157–162

Van Gorp WG, Altshuler L, Theberge DC, Wilkins J, Dixon W (1998) Cognitive impairment in euthymic bipolar patients with and without prior alcohol dependence. A preliminary study. Arch Gen Psychiatry 55:41–46

Vasconcellos AP, Tabajara AS, Ferrari C, Rocha E, Dalmaz C (2003) Effect of chronic stress on spatial memory in rats is attenuated by lithium treatment. Physiol Behav 79:143–149

Vasconcellos AP, Zugno AI, Dos Santos AH, Nietto FB, Crema LM, Gonçalves M, Franzon R, de Souza Wyse AT, da Rocha ER, Dalmaz C (2005) Na+,K(+)-ATPase activity is reduced in hippocampus of rats submitted to an experimental model of depression: effect of chronic lithium treatment and possible involvement in learning deficits. Neurobiol Learn Mem 84:102–110

Vasconcellos AP, Nieto FB, Fontella FU, da Rocha ER, Dalmaz C (2006a) The nociceptive response of stressed and lithium-treated rats is differently modulated by different flavors. Physiol Behav 88:382–388

Vasconcellos AP, Nieto FB, Crema LM, Diehl LA, de Almeida LM, Prediger ME, da Rocha ER, Dalmaz C (2006b) Chronic lithium treatment has antioxidant properties but does not prevent oxidative damage induced by chronic variate stress. Neurochem Res 31(9):1141–1151

Von Gunten A, Ron MA (2004) Hippocampal volume and subjective memory impairment in depressed patients. Eur Psychiatry 19:438–440

Watase K, Gatchel JR, Sun Y, Emamian E, Atkinson R, Richman R, Mizusawa H, Orr HT, Shaw C, Zoghbi HY (2007) Lithium therapy improves neurological function and hippocampal den-

dritic arborization in a spinocerebellar ataxia type 1 mouse model. PLoS Med 4(5):e182

Wegener G, Bandpey Z, Heiberg IL, Mørk A, Rosenberg R (2003) Increased extracellular serotonin level in rat hippocampus induced by chronic citalopram is augmented by subchronic lithium: neurochemical and behavioural studies in the rat. Psychopharmacology (Berl) 166:188–194

Weingartner H, Rudorfer MV, Linnoila M (1985) Cognitive effects of lithium treatment in normal volunteers. Psychopharmacology (Berl) 86:472–474

Yan XB, Wang SS, Hou HL, Ji R, Zhou JN (2007a) Lithium improves the behavioral disorder in rats subjected to transient global cerebral ischemia. Behav Brain Res 177(2):282–289

Yan XB, Hou HL, Wu LM, Liu J, Zhou JN (2007b) Lithium regulates hippocampal neurogenesis by ERK pathway and facilitates recovery of spatial learning and memory in rats after transient global cerebral ischemia. Neuropharmacology 53(4):487–495

Yazlovitskaya EM, Edwards E, Thotala D, Fu A, Osusky KL, Whetsell WO, Boone B, Shinohara ET, Hallahan DE (2006) Lithium treatment prevents neurocognitive deficit resulting from cranial irradiation. Cancer Res 66(23):11179–11186

Youngs RM, Chu MS, Meloni EG, Naydenov A, Carlezon Jr WA, Konradi C (2006) Lithium administration to preadolescent rats causes long-lasting increases in anxiety-like behavior and has molecular consequences. J Neurosci 26:6031–6039

Yucel K, MacQueen GM (2008) Reply: lithium and increased hippocampal volume—more tissue or more water? Neuropsychopharmacology 33:1775

Yucel K, McKinnon MC, Taylor VH, Macdonald K, Alda M, Young LT, Macqueen GM (2007) Bilateral hippocampal volume increases after long-term lithium treatment in patients with bipolar disorder: a longitudinal MRI study. Psychopharmacology (Berl) 195:357–367

Zhong J, Lee WH (2007) Lithium: a novel treatment for Alzheimer's disease? Expert Opin Drug Saf 6:375–383