adult period is totally and partly mimicked by other schizophrenomimetics, dizocilpine and MAP, respectively, and moderately attenuated by the D_2-preferring dopamine receptor antagonist Hal. These developmental, neuroanatomical and pharmacological profiles of *Lmod2* responses suggest that *Lmod2* and its protein products could, at least in part, be associated with the late-developing onset and the specific neuron circuits for the adult type of PCP-induced abnormal behaviour in the rat.

This is the first study to indicate the profound influence of psychotomimetics on brain mRNA expression of the *Lmod2* gene. The Tmod gene family member has so far been considered to represent the muscular tissue-selective expression without its transcripts in the brain. However, we have demonstrated that considerable amounts of *Lmod2* mRNAs are predominantly concentrated in the thalamus among the brain tissues. The expressional changes in the thalamic *Lmod2* by psychotropic drugs may imply the possible involvement of the molecule in the regulation of psychological and motor functions. This assumption appears to be supported by the similar time-course in up-regulation of *Lmod2* expression and stereotyped behaviour after PCP (Fig. 3*a*, *b*). On the other hand, the present study also revealed the obvious discrepancy between the postnatal development of the above molecular and behavioural responses to PCP (Fig. 2*d*, *e*). Thus, the exact regulatory roles of the gene await further elucidation.

The possibility that the post-weaning marked increase in *Lmod2* transcript levels by PCP could be due to a non-specific phenomenon appears to be denied by the observations that PCP failed to influence (1) the thalamic expression of other Tmod family genes in the infant and adult periods and (2) *Lmod2* mRNA levels

---

121 ± 4 ($p > 0.05$ *vs.* saline-treated controls, n.s., no significant difference) (two-way ANOVA, organ effect: $F_{1,16} = 25.109$, $p < 0.001$; PCP treatment effect: $F_{1,16} = 85.035$, $p < 0.0001$; organ × PCP treatment effect: $F_{1,16} = 24.988$, $p < 0.001$). (*b*) Thalamic region-restricted *Lmod2* mRNA expression in the adult rat (PD 50) brain 60 min after acute PCP administration (7.5 mg/kg s.c.) as revealed by *in-situ* hybridization histochemistry with ^{35}S-labelled RNA probe for *Lmod2*. Both of the basal (saline-treated control animals) and PCP-induced *Lmod2* mRNA signals were confined to the thalamic regions in the brain (scale bars, 2 mm). For the radiolabelled *in-situ* hybridization, the slide-mounted fixed brain sections were rinsed in distilled water and then acetylated with 0.25% acetic anhydride in 0.1 M triethanolamine. After rinsing in PBS, the sections were dehydrated in an ascending ethanol series (70%, 95%, and 100%), defatted in chloroform, rinsed in ethanol, and air-dried. Radiolabelled probes (4×10^7 cpm per slide) in hybridization buffer [50% deionized formamide, 0.3 M NaCl, 20 mM Tris–HCl (pH 8.0), 5 mM EDTA, 10 mM PBS, 10% dextran sulfate, 1× Denhardt's solution, 0.2% sarcosyl, 500 μg/ml yeast transfer RNA, and 200 μg/ml salmon sperm DNA] were denatured for 5 min at 80 °C, quenched on ice, and placed on the sections. Hybridization was performed overnight at 55 °C in a humid chamber. Hybridized sections were rinsed briefly in 5× SSC and 1% 2-mercaptoethanol at 55 °C and washed in 50% deionized formamide, 2× SSC, and 10% 2-mercaptoethanol (high-stringency buffer) for 30 min at 65 °C. After rinsing the sections in RNase buffer [0.5 M NaCl, 10 mM Tris–HCl (pH 8.0), and 1 mM EDTA], they were treated with 1.0 μg/ml RNase-A in RNase buffer for 30 min at 37 °C, and washed in RNase buffer. The sections were then incubated in high-stringency buffer as described above, rinsed in 2× and 0.1× SSC for 10 min each at room temperature, dehydrated in an ascending ethanol series, and air-dried. mRNA localization was assessed by X-ray film autoradiography. (*c–e*) DIG-labelled *in-situ* hybridization on the sagittal brain sections of 50-d-old adult rat. As a pre-hybridization procedure, the slide-mounted brain sections were incubated for 2 h at 58 °C in hybridization buffer (50% deionized formamide, 5× SSC, and 40 μg/ml salmon sperm DNA). Hybridization of DIG-labelled RNA probes was performed in a humid chamber overnight at 58 °C, and then washed with 2× SSC for 30 min at room temperature, and rinsed in 2× and 0.5× SSC for 60 min each at 55 °C. After rinsing in buffer 1 [100 mM Tris (pH 7.5), and 150 mM NaCl], the sections were incubated for 2 h in buffer 1 and sheep anti-DIG antibody conjugated with alkaline phosphatase and washed twice for 15 min in buffer 1. The *Lmod2* mRNA signals were detected as purple-coloured staining by the DIG-labelled RNA probe, and the cell nuclei are counterstained by Methyl Green as shown in blue. The positions of the two arrowheads in panel (*c*) correspond to those of the respective coronal sections represented in panels (*f*) (rostral) and (*l*) (caudal). Scale bars: (*c*, *d*) 2 mm; (*e*) 20 μm. Abbreviations: (*d*) AM, Anteromedial nucleus; LP, lateral posterior nucleus; LD, lateral dorsal nucleus. (*f–l*) *In-situ* hybridization with ^{35}S-labelled RNA probe for *Lmod2* on the coronal brain sections of the 50-d-old adult rat at levels of the thalamic regions. The sections are aligned in the orientation from caudal to rostral. (*f–l*) Positions of panels (*f*) and (*l*) are represented in panel (*c*). The details of the experimental procedures of radiolabelled *in-situ* hybridization are described in the legend of panel (*b*). (*m*) This panel, at the same level as panel (*i*), was hybridized with the corresponding sense probe. Scale bars: (*f–m*), 2 mm. (*n*, *o*) Schematic illustration of the structures of the thalamus at the level of panel *h* (*n*) and panel *j* (*o*). AD, Anterodorsal nucleus; AMd, anteromedial nucleus, dorsal part; AV, anteroventral nucleus; CM, central medial nucleus; CL, central lateral nucleus; IAM, interanteromedial nucleus; LD, lateral dorsal nucleus; mtt, mammillothalamic tract; PCN, paracentral nucleus; RE, nucleus reunions; RH, rhomboid nucleus; RT, reticular nucleus; SMT, submedial nucleus; VAL, ventral anterior-lateral complex; VM, ventral medial nucleus; VPL, ventral posterolateral nucleus; VPM, ventro posteromedial nucleus; V3, third ventricle; ZI, zona incerta.

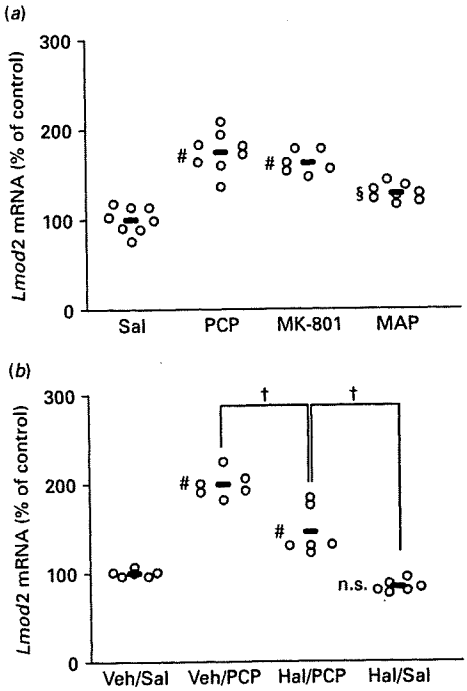

Fig. 5. Effects of acute administration of psychotomimetic and antipsychotic drugs on *Lmod2* mRNA expression in the thalamus. (*a*) Effects of PCP, MK-801 and methamphetamine (MAP) on thalamic *Lmod2* mRNA. Relative expression levels of *Lmod2* mRNA in the thalamus of the adult (PD 50) rat (*Lmod2*:GAPDH mRNA ratio) were assayed by the real-time RT–PCR method 60 min after acute PCP (7.5 mg/kg s.c.), MK-801 (0.5 mg/kg s.c.), and MAP (4.8 mg/kg s.c.) administration. Results are shown as scatterplots with the means of data (*Lmod2*:GAPDH mRNA ratio) obtained from six or eight rats per group and are expressed as a percentage of the values of the saline-treated controls. Saline (Sal) 100±5%, PCP 174±8#, MK-801 162±5#, MAP 128±3 (# $p<0.01$, § $p<0.05$ *vs.* saline-treated controls). (*b*) Effects of pretreatment with haloperidol (Hal) on PCP-induced up-regulation of thalamic *Lmod2* mRNA. The adult (PD 50) rats were pretreated with Hal (1.0 mg/kg, i.p.) or vehicle (Veh) 30 min before PCP or saline (Sal) administration, and the relative expression levels of *Lmod2* mRNA in the thalamus (*Lmod2*:GAPDH mRNA ratio) were assayed by the real-time RT–PCR method 60 min after acute PCP (7.5 mg/kg, s.c.) or saline injection. Results are the means with S.E.M. of data (*Lmod2*:GAPDH mRNA ratio) obtained from six rats per group and are expressed as a percentage of the values of the vehicle-pretreated and saline-injected controls. Vehicle-pretreated saline-injected controls (Veh/Sal) 100±2%, vehicle-pretreated PCP-injected animals (Veh/PCP) 200±6#, Hal-pretreated PCP-injected animals (Hal/PCP) 145±11#, Hal-pretreated saline-injected animals (Hal/Sal) 83±3 (# $p<0.01$ *vs.* Veh/Sal controls; † $p<0.01$ between Veh/PCP and Hal/PCP animals and between Hal/PCP and Hal/Sal animals). n.s., No significant difference. Veh: 0.15% tartaric acid.

in the heart of the adult animal. The ontogenic differences in brain *Lmod2* induction by PCP might solely depend on those in the time-course of the pharmacodynamics of PCP or the general responses of the brain. However, this explanation seems to be contrary to the observation that (1) PCP caused no change in thalamic *Lmod2* transcript levels even up to 6 h post-injection in the infant rat despite the pronounced increase in those of the adult rat during the same time (Fig. 3*a*), and (2) a similar time-course of the acute PCP-induced increase in *c-fos* gene expression was seen in the various brain areas of the rat at PD 8 and 50 (Sato *et al.* 1997).

The PCP-induced thalamus-selective up-regulation is more likely to be associated with a psychotomimetic action generated by reduced NMDA receptor function and excessive dopaminergic transmission because potent schizophrenomimetic drugs, the selective NMDA antagonist MK-801 and the dopamine signal potentiator MAP, caused an elevation in thalamic *Lmod2* expression. However, MAP elicited a smaller magnitude of elevation than PCP and MK-801 (Fig. 5*a*). The selective D_2 dopamine receptor antagonist, Hal, is found to partially attenuate the increasing effects of PCP on *Lmod2* expression. Together with the fact that NMDA receptor blocking results in the augmented cerebral dopaminergic activities (Umino *et al.* 1998), these observations suggest that the mechanisms underlying PCP-induced up-regulation of *Lmod2* expression may consist of NMDA receptor-related D_2 receptor-sensitive and -insensitive components. These pharmacological features allow us to assume that *Lmod2* or its protein products could participate in the molecular cascades that are dysregulated in the dopamine-dependent positive symptoms and NMDA receptor-associated dopamine-uncoupled negative symptoms and cognitive disturbances in PCP psychosis and schizophrenia (Javitt, 2004; Nishikawa *et al.* 1991; Petersen & Stillman, 1978).

From this pharmacological point of view, it is also plausible that the distinct developmental changes in the responses of *Lmod2* to PCP could be attributed to the neuroanatomical and functional development of the NMDA receptor subunits (Watanabe *et al.* 1992) and/or the cerebral dopamine systems (Pérez-Navarro *et al.* 1993) and in turn this transcript might be an excellent marker for the developmental maturation of the response of the thalamus to increased dopaminergic transmission. The acquisition by the *Lmod2* gene of thalamus-selective responsiveness to PCP after the weaning period (Fig. 2*d*) further argues that the maturation of a specific information-processing system in the thalamus containing *Lmod2* transcripts or proteins as its molecular elements might be required for the

PCP-induced up-regulation of *Lmod2*. Such a system could be disturbed in the schizophrenomimetic-induced abnormal behaviour in experimental animals, schizophrenia-like psychosis and schizophrenia.

In fact, the restricted rostral thalamic regions including the anterior and lateral nuclei that show PCP-induced *Lmod2* expression have been found to display aberrant 2-deoxyglucose uptake, activity-dependent gene expression or cerebral blood flow after ketamine, MK-801, PCP and amphetamine application in experimental animals (Duncan *et al.* 1999) and/or humans (Långsjö *et al.* 2003). Furthermore, *in-vivo* neuroimaging studies describe schizophrenia patients exhibiting reduced activation following cognitive tasks (Andrews *et al.* 2006), decreased *N*-acetylaspartate signals in magnetic resonance spectroscopy (Jakary *et al.* 2005), and increased diffusivity of magnetic resonance diffusion tensor imaging (Rose *et al.* 2006) in these thalamic regions. Biochemical and histochemical analyses using post-mortem brains from schizophrenia patients have revealed various changes in the glutamate system such as altered expression of the L-α-amino-3-hydroxy-5-methylisoxazole-4-propionate (AMPA), kainate and NMDA-type ionotropic glutamate receptors (Ibrahim *et al.* 2000) and glutaminase and glutamine synthetase mRNA (Bruneau *et al.* 2005) in the above *Lmod2*-associated nuclei. Dopaminergic imbalance has also been noted in the thalamus of schizophrenia patients while the major observations concerning the imbalance concentrate on the mediodorsal and posterior nuclei (Takahashi *et al.* 2006).

The series of thalamic aberrations in schizophrenia and its pharmacological models, and the glutamate and dopamine signal-related, late-developing and thalamus-specific nature of the PCP-induced modification of *Lmod2* reinforce the hypothesis that *Lmod2*-expressing cells might compose a part of the information-processing system or neuron circuitry that is specifically distorted in schizophrenia. Accordingly, detection of the schizophrenomimetic-induced *Lmod2* mRNA signals might be a useful tool for tracing the cells and circuits that play a central role in the pathogenesis or pathophysiology of schizophrenia. Because the distribution pattern of *Lmod2* mRNA is similar to that of [^{3}H]muscimol binding to the $GABA_A$ receptor in the thalamic area of the adult rat (Palacios *et al.* 1981), it would be useful to clarify the glutamate–dopamine–GABA interaction in *Lmod2*-expressing cells that is thought to be dysregulated in schizophrenic brains (Lisman *et al.* 2008).

The molecular and functional consequences and the pathophysiological significance of the schizophrenomimetic-induced changes in thalamic *Lmod2* expression are still unknown. Although the biological roles of *Lmod2* protein in brain tissue have not yet been analysed, the characteristic motifs and domain structures of the Lmod2 protein buttress its potential contributions to neuronal and mental functions. Similar to other Tmod family members, the Lomod2 protein has been shown to regulate the organization of the actin-cytoskeletal system through the tropomyosin-binding domain and leucine-rich repeats. A body of evidence has accumulated indicating that actin-based morphological changes in the dendritic spines are involved in synaptic plasticity, which is one of the most essential neural processes for higher brain functions, e.g. learning and memory (Carlisle & Kennedy, 2005).

The polyproline motifs, which the Lmod2 protein possesses at its carboxy-terminal, have been considered to interact with the Src-homology 3 (SH3) domains that are implicated in synaptic organization or reorganization (Segura *et al.* 2007). Moreover, the nuclear localization signal-like amino-acid sequence was found in Lmod2 protein (see Results section). This could be extrapolated to the idea that the possible intranuclear link between Lmod2 and actin could join the integration of gene expression in the thalamus, because nuclear actin has recently been demonstrated to be required for the chromosomal movement that may be connected to the positioning of genes within the nuclear volume for the appropriate transcriptional activity (Dundr *et al.* 2007).

As a consequence, we can presuppose that the quantitative or structural alterations of thalamic *Lmod2* mRNA or proteins would lead to disintegrated synaptic transmission and/or plasticity that may underlie the characteristic symptoms of schizophrenia and related psychoses. Although no studies identified the expressional changes in the mRNA or protein of this gene in schizophrenic brain tissues, and regions of the human genome in which *LMOD2* is located (7q31.32) have not been suggested to be associated with an altered risk of schizophrenia, it would be valuable to investigate the possible involvement of *LMOD2* in schizophrenia because the chromosome 7q31 region includes the *PTPRZ1* (Buxbaum *et al.* 2008) and *FOXP2* (Sanjuán *et al.* 2006) genes that have been indicated to be related to the susceptibility of schizophrenia.

In conclusion, the present findings indicate that PCP can affect the expression of *Lmod2* in an age-dependent, schizophrenomimetic cross-reactive and thalamus-selective manner in mammalian brains (the rat). These figures seem to be consistent with the view that a thalamic neuronal system influenced by PCP may be equipped with a signal pathway containing *Lmod2* or its protein and be functionally

late-developing. Therefore, our PCP data would suggest that changes in *Lmod2* expression should be present in the thalamus of subjects with schizophrenia and a study measuring the expression of that gene in post-mortem CNS is required to confirm this hypothesis.

Acknowledgements

The authors thank Dr Kiyama (Osaka City University) for his generous guidance in DIG- and radioisotope-labelled *in-situ* hybridization techniques and Dr Yoshioka (Teikyo University) for his helpful advice in statistical analyses of the data. This work was partly supported by research grants-in-aid from the Ministry of Health and Welfare, Japan, the Ministry of Education, Culture, Sports, Science and Technology, Japan, and the Social Insurance Agency Contract Fund Commissioned to the Japan Health Sciences Foundation. We received assistance in English editing in the preparation of the present paper by the US Office of the International Technology Exchange Society (an English editing agency) and we are entirely responsible for its scientific content.

Statement of Interest

None.

References

Andreasen NC, O'Leary DS, Flaum M, Nopoulos P, Watkins GL, Boles Ponto LL, Hichwa RD (1997). Hypofrontality in schizophrenia: distributed dysfunctional circuits in neuroleptic-naïve patients. *Lancet* **349**, 1730–1734.

Andrews J, Wang L, Csernansky JG, Gado MH, Barch DM (2006). Abnormalities of thalamic activation and cognition in schizophrenia. *American Journal Psychiatry* **163**, 463–469.

Bruneau EG, McCullumsmith RE, Haroutunian V, Davis KL, Meador-Woodruff JH (2005). Increased expression of glutaminase and glutamine synthetase mRNA in the thalamus in schizophrenia. *Schizophrenia Research* **75**, 27–34.

Buchanan RW, Carpenter Jr. WT (2005). Concept of schizophrenia. In: Sadock BJ, Sadock VA (Eds), *Kaplan & Sadock's Comprehensive Textbook of Psychiatry*, 8th edn (pp. 1329–1345). Baltimore: Lippincott Williams & Wilkins.

Buxbaum JD, Georgieva L, Young JJ, Plescia C, Kajiwara Y, Jiang Y, Moskvina V, Norton N, Peirce T, Williams H, *et al.* (2008). Molecular dissection of NRG1-ERBB4 signaling implicates PTPRZ1 as a potential schizophrenia susceptibility gene. *Molecular Psychiatry* **13**, 162–172.

Carlisle HJ, Kennedy MB (2005). Spine architecture and synaptic plasticity. *Trends in Neuroscience* **28**, 182–187.

Clinton SM, Meador-Woodruff JH (2004). Thalamic dysfunction in schizophrenia: neurochemical, neuropathological, and in vivo imaging abnormalities. *Schizophrenia Research* **69**, 237–253.

Conley CA, Fritz-Six KL, Almenar-Queralt A, Fowler VM (2001). Leiomodins: larger members of the tropomodulin (Tmod) gene family. *Genomics* **73**, 127–139.

Dragunow M, Faull RL (1990). MK-801 induces c-fos protein in thalamic and neocortical neurons of rat brain. *Neuroscience Letters* **111**, 39–45.

Duncan GE, Miyamoto S, Leipzig JN, Lieberman JA (1999). Comparison of brain metabolic activity patterns induced by ketamine, MK-801 and amphetamine in rats: support for NMDA receptor involvement in responses to subanesthetic dose of ketamine. *Brain Research* **843**, 171–183.

Dundr M, Ospina JK, Sung MH, John S, Upender M, Ried T, Hager GL, Matera AG (2007). Actin-dependent intranuclear repositioning of an active gene locus in vivo. *Journal Cell Biology* **179**, 1095–1103.

Fischer RS, Fowler VM (2003). Tropomodulins: life at the slow end. *Trends in Cell Biology* **13**, 593–601.

Gouzoulis-Mayfrank E, Heekeren K, Neukirch A, Stoll M, Stock C, Obradovic M, Kovar KA (2005). Psychological effects of (S)-ketamine and N,N-dimethyltryptamine (DMT): a double-blind, cross-over study in healthy volunteers. *Pharmacopsychiatry* **38**, 301–311.

Greifenstein FE, Devault M, Yoshitake J, Gajewski JE (1958). A study of a 1-aryl cyclo hexyl amine for anesthesia. *Anesthesia and Analgesia* **37**, 283–294.

Ibrahim HM, Hogg Jr. AJ, Healy DJ, Haroutunian V, Davis KL, Meador-Woodruff JH (2000). Ionotropic glutamate receptor binding and subunit mRNA expression in thalamic nuclei in schizophrenia. *American Journal Psychiatry* **157**, 1811–1823.

Ito T, Hiraoka S, Kuroda Y, Ishii S, Umino A, Kashiwa A, Yamamoto N, Kurumaji A, Nishikawa T (2007). Effects of schizophrenomimetics on the expression of the CCN1 (CYR 61) gene encoding a matricellular protein in the infant and adult neocortex of the mouse and rat. *International Journal of Neuropsychopharmacology* **10**, 717–725.

Jakary A, Vinogradov S, Feiwell R, Deicken RF (2005). N-acetylaspartate reductions in the mediodorsal and anterior thalamus in men with schizophrenia verified by tissue volume corrected proton MRSI. *Schizophrenia Research* **76**, 173–185.

Javitt DC (2004). Glutamate as a therapeutic target in psychiatric disorders. *Molecular Psychiatry* **9**, 984–997, 979.

Javitt DC, Zukin SR (1991). Recent advances in the phencyclidine model of schizophrenia. *American Journal of Psychiatry* **148**, 1301–1308.

Kaiser S, Foltz LA, George CA, Kirkwood SC, Bemis KG, Lin X, Gelbert LM, Nisenbaum LK (2004). Phencyclidine-induced changes in rat cortical gene expression identified by microarray analysis: implications for schizophrenia. *Neurobiolgy of Disease* **16**, 220–235.

Kong KY, Kedes L (2004). Cytoplasmic nuclear transfer of the actin-capping protein tropomodulin. *Journal of Biological Chemistry* **279**, 30856–30864.

Lahti AC, Weiler MA, Tamara Michaelidis BA, Parwani A, Tamminga CA (2001). Effects of ketamine in normal and schizophrenic volunteers. *Neuropsychopharmacology* **25**, 455–467.

Långsjö JW, Kaisti KK, Aalto S, Hinkka S, Aantaa R, Oikonen V, Sipilä H, Kurki T, Silvanto M, Scheinin H (2003). Effects of subanesthetic doses of ketamine on regional cerebral blood flow, oxygen consumption, and blood volume in humans. *Anesthesiology* **99**, 614–623.

Lisman JE, Coyle JT, Green RW, Javitt DC, Benes FM, Heckers S, Grace AA (2008). Circuit-based framework for understanding neurotransmitter and risk gene interactions in schizophrenia. *Trends in Neuroscience* **31**, 234–242.

MAQC Consortium (2006). The MicroArray Quality Control (MAQC) project shows inter- and intraplatformreproducibility of gene expression measurements. *Nature Biotechnology* **24**, 1151–1161.

McClung CA, Nestler EJ (2003). Regulation of gene expression and cocaine reward by CREB and Delta-FosB. *Nature Neuroscience* **6**, 1208–1215.

Miyasaka M, Domino EF (1968). Neural mechanisms of ketamine-induced anesthesia. *International Journal of Neuropharmacology* **7**, 557–573.

Morgan JI, Curran T (1991). Stimulus-transcription coupling in the nervous system: involvement of inducible proto-oncogenes fos and jun. *Annual Review of Neuroscience* **14**, 421–451.

Nakai K, Horton P (1999). PSORT: a program for detecting sorting signals in proteins and predicting their subcellular localization. *Trends in Biochemical Sciences* **24**, 34–36.

Nagata K, Kiryu-Seo S, Kiyama H (2006). Localization and ontogeny of damage-induced neuronal endopeptidase mRNA-expressing neurons in the rat nervous system. *Neuroscience* **141**, 299–310.

Nishikawa T, Kajii Y, Hiraoka S, Fujiyama K, Sato D, Toda S, Kaneda K, Umino A, Kuroda Y (1998). A molecular pharmacological approach to neural dysfunction in schizophrenia. *Neuroscience Research* (Suppl.) **22**, S8.

Nishikawa T, Umino A, Tanii Y, Hashimoto A, Hata N, Takashima M, Takahashi K, Toru M (1991). Dysfunction of excitatory amino acidergic systems and schizophrenic disorders. In: Nakazawa T (Ed.), *Biological Basis of Schizophrenic Disorders* (pp. 65–76). Tokyo: Japan Scientific Societies Press. Basel: Karger.

Ohba N, Kiryu-Seo S, Maeda M, Muraoka M, Ishii M, Kiyama H (2004). Expression of damage-induced neuronal endopeptidase (DINE) mRNA in peri-infarct cortical and thalamic neurons following middle cerebral artery occlusion. *Journal of Neurochemistry* **91**, 956–964.

Palacios JM, Wamsley JK, Kuhar MJ (1981). High affinity GABA receptors-autoradiographic localization. *Brain Research* **222**, 285–307.

Pérez-Navarro E, Alberch J, Marsal J (1993). Postnatal development of functional dopamine, opioid and tachykinin receptors that regulate acetylcholine release from rat neostriatal slices. Effect of 6-hydroxydopamine lesion. *International Journal of Developmental Neuroscience* **11**, 701–708.

Petersen RC, Stillman RC (1978). *Phencyclidine (PCP) Abuse: An Appraisal.* National Institute on Drug Abuse Research Monograph series, Superintendent of Documents, US Government Printing Office: Washington, DC.

Reich DL, Silvay G (1989). Ketamine: an update on the first twenty-five years of clinical experience. *Canadian Journal of Anaesthesia* **36**, 186–197.

Rose SE, Chalk JB, Janke AL, Strudwick MW, Windus LC, Hannah DE, McGrath JJ, Pantelis C, Wood SJ, Mowry BJ (2006). Evidence of altered prefrontal-thalamic circuitry in schizophrenia: an optimized diffusion MRI study. *Neuroimage* **32**, 16–22.

Sakurai S, Ishii S, Umino A, Shimazu D, Yamamoto N, Nishikawa T (2004). Effects of psychotomimetic and antipsychotic agents on neocortical and striatal concentrations of various amino acids in the rat. *Journal of Neurochemistry* **90**, 1378–1388.

Sanjuán J, Tolosa A, González JC, Aguilar EJ, Pérez-Tur J, Nájera C, Moltó MD, de Frutos R (2006). Association between FOXP2 polymorphisms and schizophrenia with auditory hallucinations. *Psychiatry Genetics* **16**, 67–72.

Sato D, Umino A, Kaneda K, Takigawa M, Nishikawa T (1997). Developmental changes in distribution patterns of phencyclidine-induced c-Fos in rat forebrain. *Neuroscience Letters* **239**, 21–24.

Scalzo FM, Burge LJ (1994). The role of NMDA and sigma systems in the behavioral effects of phencyclidine in preweanling rats. *Neurotoxicology* **15**, 191–200.

Scalzo FM, Holson RR (1992). The ontogeny of behavioral sensitization to phencyclidine. *Neurotoxicology and Teratology* **14**, 7–14.

Schwartz RH, Einhorn A (1986). PCP intoxication in seven young children. *Pediatric Emergency Care* **2**, 238–241.

Segura I, Essmann CL, Weinges S, Acker-Palmer A (2007). Grb4 and GIT1 transduce ephrinB reverse signals modulating spine morphogenesis and synapse formation. *Nature Neuroscience* **10**, 301–310.

Shintomi K (1975). Effects of psychotropic drugs on methamphetamine-induced behavioral excitation in grouped mice. *Europen Journal of Pharmacology* **31**, 195–206.

Shirayama Y, Mitsushio H, Takahashi K, Nishikawa T (2000). Differential effects of haloperidol on phencyclidine-induced reduction in substance P contents in rat brain regions. *Synapse* **35**, 292–299.

Sim K, Cullen T, Ongur D, Heckers S (2006). Testing models of thalamic dysfunction in schizophrenia using neuroimaging. *Journal of Neural Transmission* **113**, 907–928.

Sturgeon RD, Fessler RG, Meltzer HY (1979). Behavioral rating scales for assessing phencyclidine-induced locomotor activity, stereotyped behavior and ataxia in rats. *European Journal of Pharmacology* **59**, 169–179.

Takahashi H, Higuchi M, Suhara T (2006). The role of extrastriatal dopamine D2 receptors in schizophrenia. *Biological Psychiatry* **59**, 919–928.

Tanabe K, Kiryu-Seo S, Nakamura T, Mori N, Tsujino H, Ochi T, Kiyama H (1998). Alternative expression of Shc family members in nerve-injured motoneurons. *Brain Research Molecular Brain Research* **53**, 291–296.

Tanabe K, Nakagomi S, Kiryu-Seo S, Namikawa K, Imai Y, Ochi T, Tohyama M, Kiyama H (1999). Expressed-sequence-tag approach to identify differentially expressed genes following peripheral nerve axotomy. *Brain Research Molecular Brain Research* **64**, 34–40.

Tanii Y, Nishikawa T, Hashimoto A, Takahashi K (1994). Stereoselective antagonism by enantiomers of alanine and serine of phencyclidine-induced hyperactivity, stereotypy and ataxia in the rat. *Journal of Pharmacology and Experimental Therapeutics* **269**, 1040–1048.

Umino A, Takahashi K, Nishikawa T (1998). Characterization of the phencyclidine-induced increase in prefrontal cortical dopamine metabolism in the rat. *British Journal of Pharmacology* **124**, 377–385.

Vollenweider FX, Leenders KL, Oye I, Hell D, Angst J (1997). Differential psychopathology and patterns of cerebral glucose utilization produced by (S)- and (R)-ketamine in healthy volunteers using positron emission tomography (PET). *European Neuropsychopharmacology* **7**, 25–38.

Watis L, Chen SH, Chua HC, Chong SA, Sim K (2008). Glutamatergic abnormalities of the thalamus in schizophrenia: a systematic review. *Journal of Neural Transmission* **115**, 493–511.

Watanabe M, Inoue Y, Sakimura K, Mishina M (1992). Developmental changes in distribution of NMDA receptor channel subunit mRNAs. *Neuroreport* **3**, 1138–1140.

Welch MJ, Correa GA (1980). PCP intoxication in young children and infants. *Clinical Pediatrics (Philadelphia)* **19**, 510–514.

White PF, Way WL, Trevor AJ (1982). Ketamine – its pharmacology and therapeutic uses. *Anesthesiology* **56**, 119–136.

ELSEVIER

Available online at www.sciencedirect.com
ScienceDirect

Drug and Alcohol Dependence 88 (2007) 174–181

DRUG and ALCOHOL DEPENDENCE

www.elsevier.com/locate/drugalcdep

Development and validation of the Stimulant Relapse Risk Scale for drug abusers in Japan☆

Yasukazu Ogai[a], Ayako Haraguchi[a], Ayumi Kondo[a,b], Yoko Ishibashi[a], Mitsuru Umeno[c], Hirotsugu Kikumoto[c], Toru Hori[d], Tokutaro Komiyama[d], Riki Kato[e], Katsuro Aso[f], Nozomu Asukai[b], Eiichi Senoo[b], Kazutaka Ikeda[a,*]

[a] *Division of Psychobiology, Tokyo Institute of Psychiatry, 2-1-8 Kamikitazawa, Setagaya-ku, Tokyo, Japan*
[b] *Division of Social Psychiatry, Tokyo Institute of Psychiatry, 2-1-8 Kamikitazawa, Setagaya-ku, Tokyo, Japan*
[c] *Tokyo Metropolitan Matsuzawa Hospital, 2-1-1 Kamikitazawa, Setagaya-ku, Tokyo, Japan*
[d] *National Center Hospital for Mental, Nervous and Muscular Disorders, National Center of Neurology and Psychiatry, 4-1-1 Ogawahigashi-cho, Kodaira, Japan*
[e] *Self Support Services, 3-61-22-202 Kameido, Koutou-ku, Tokyo, Japan*
[f] *Fukko-kai Tarumi Hospital, 566 Oshibedani-cho Nishimori, Nishi-ku, Kobe, Japan*

Received 16 March 2006; received in revised form 10 October 2006; accepted 17 October 2006

Abstract

Objective: To develop and validate a multidimensional measure of relapse risk for stimulants in Japanese drug abusers.
Methods: A Stimulant Relapse Risk Scale (SRRS) was developed based on the Marijuana Craving Questionnaire and a discussion among three psychiatrists. We created 48 items after confirming the items including a variety of relapse risk, such as craving (expectancy, compulsivity, etc.) and emotionality problems. One hundred inpatients and outpatients with a history of stimulant abuse (71 males and 29 females) were recruited with informed consent, and were administered the SRRS. The Visual Analogue Scale for drug craving (VAS), Addiction Severity Index for Japanese (ASI-J), and data on relapse within 3 and 6 months after the rating were used for the validation.
Results: Exploratory factor analysis highlighted five factors: anxiety and intention to use drug (AI), emotionality problems (EP), compulsivity for drug use (CD), positive expectancies and lack of control over drug (PL), and lack of negative expectancy for drug use (NE). These accounted for 48.3% of the total variance. Thirty of the 43 items were classified into the five subscales. Cronbach's alpha coefficient for each subscale ranged from .55 to .82, and was .86 for the total SRRS, indicating their adequate internal consistency. AI, CD, PL, and total SRRS were significantly correlated with the drug-use composite score of the ASI-J, supporting their concurrent validity. AI, PL, NE, and total SRRS were significantly correlated with relapse, implying their predictive validity.
Conclusions: The SRRS has multidimensional psychometric properties useful for assessing the various aspects of stimulant relapse risk.

Keywords: Stimulants; Relapse risk; Craving; Scale; Japanese

1. Introduction

Stimulants such as methamphetamine, methylphenidate, and methylenedioxymethamphetamine (MDMA) are the main drugs involved in cases of drug abuse in Japan (Wada et al., 2004). Stimulant dependence presents a serious problem not only for the patients but also for Japanese society (Ikeda et al., 2004). For example, about 25% of convicted prisoners have committed offences under the Stimulant Control Law (The Ministry of Justice Research and Training Institute, 2004). Medical treatment of stimulant abusers has mainly targeted their immediate psychotic symptoms such as hallucination and delusion, and the symptoms of relapse such as craving, which are significantly related to dependence and relapse has not been addressed sufficiently. Insufficient treatment of relapse risk is partly due to the lack of suitable instruments for measuring the severity of relapse risk. On the other hand, recent breakthroughs in genomic science and molecular pharmacology have made it possible to

☆ English and Japanese versions of the Stimulant Relapse Risk Scale (SRRS) can be found by accessing the online version of this paper at http://dx.doi.org by entering doi:10.1016/j.drugalcdep.2006.10.005.

* Corresponding author. Tel.: +81 3 3304 5701x508; fax: +81 3 3329 8035.
E-mail address: ikedak@prit.go.jp (K. Ikeda).

0376-8716/$ – see front matter © 2006 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.drugalcdep.2006.10.005

investigate the molecular mechanisms underlying the tendency of animals to prefer drugs, and to find candidate medicines that might inhibit this tendency (Sora et al., 2001; Takamatsu et al., 2006a,b). Some of these medicines may reduce craving, and ultimately the risk of relapse, in human drug abusers (Piasecki et al., 2002; Ciraulo et al., 2005). To further advance the development of medicines and programs for the prevention of relapse, scales for the appropriate assessment of relapse risk are necessary.

Craving, one of the main factor of relapse, is generally understood to be a subjective motivational state in which an individual experiences an intense desire to use a drug. However, craving and its generation process have been conceptualized in various ways (Drummond, 2001). For example, the 'expectancy theory' by Jones et al. (2001) has maintained that craving is a function of positive and negative expectancy for drug use. Anton and his colleagues (Anton, 2000; Anton et al., 1996), in his 'obsessive compulsive theory', have suggested that drug craving is closely related to obsessive compulsive feelings about a drug that cannot be controlled. Although each theory has some valid explanatory power, there is no theory that can explain craving integrally. Therefore, multidimensional scales have been frequently used to measure various aspects of craving.

Although it is considered that craving is closely related to relapse, the lack of consistency in the findings of studies on the relationship between craving and relapse may be due to the lack of consensus regarding the definition of craving (Drummond, 2001). Tiffany (1990) considered that craving, if simply conceptualized as a 'subjective desire for a drug', is not always related to relapse. Human's craving for drug is supposed to be expressed in various ways, such as desire, intention, expectancy, anticipation, and compulsivity. In addition, other factors such as negative emotional states (Cooney et al., 1997) and lack of insight into mental condition (denial) (Wallace, 1989) may also become the trigger of relapse. Thus, it is imperative to specify and measure a variety of factors related to relapse.

Some multidimensional scales for stimulants such as amphetamine have already been developed. Topp and Mattick (1997) have developed the Severity of Amphetamine Dependence Questionnaire (SAmDQ), which is a multidimensional scale for measuring the aspects of dependence syndrome such as withdrawal. James et al. (2004) have developed the Desires for Speed Questionnaire (DSQ) based on the Desires for Alcohol Questionnaire (DAQ) (Love et al., 1998) to measure craving for amphetamine, and this revealed four key factors: 'expectancy of positive and negative reinforcement', 'strong desires and intentions to use amphetamine', 'mild desires and intentions to use amphetamine', and 'control'. However, there is no scale that focuses on the multiple aspects of relapse risk including craving, emotional problems, and denial.

In the present study, considering the clinical importance of relapse prediction, we developed a multidimensional scale to measure relapse risk for stimulants. The development of Stimulant Relapse Risk Scale (SRRS) was based on the Marijuana Craving Questionnaire (MCQ) (Heishman et al., 2001) and a discussion among three psychiatrists who are actively involved in the treatment of drug abuse. The discussion was focused on 'various cognitive and behavioral signs shown by drug abusers, which based on the clinical experience, have been found to precede relapse'. Forty-eight items were then developed that reflects a variety of relapse risk, such as craving (expectancy, compulsivity, etc.), emotionality problems, and denial. We administered the SRRS to 100 stimulant abusers in Japan and examined its inner structure, reliability and validity. The aim of the present study was to develop and validate the SRRS as a measure of relapse risk for stimulants.

2. Methods

2.1. Participants

A total of 100 inpatients (40), outpatients (52) and non-patients (8) with a history of stimulant abuse involving mainly methamphetamine (90), methylphenidate (8), and MDMA (7) participated in the study (Table 1). They were recruited for an ongoing research studies at Tokyo Metropolitan Matsuzawa Hospital, Tokyo (44), Self Support Services (a non-profit addiction recovery facility), Tokyo (20), National Center Hospital for Mental, Nervous and Muscular Disorders, National Center of Neurology and Psychiatry, Kodaira (18), GAIA (a non-profit addiction recovery facility), Naha (15), and Fukko-kai Tarumi Hospital, Kobe (3). The subjects comprised 71 males and 29 females, ranging in age from 19 to 60 years (mean = 32.6, S.D. = 8.7).

Recruitment criteria were as follows: at least 18-year-old, has a history of stimulant (methamphetamine, methylphenidate, or MDMA) abuse, diagnosed as a drug abuser (1) or as a drug dependent (99) on the basis of the Diagnostic and Statistical Manual of Mental Disorders fourth edition (DSM-IV) criteria; be an inpatient or outpatient at a Japanese mental hospital or a recovery facility, or a non-patient recovering from stimulant abuse in a recovery facility; and has the ability to understand Japanese. The study was approved by the institutional review board of each facility. Each participant provided a written informed consent, and answered the SRRS, the Addiction Severity Index-Japanese version (ASI-J) (Senoo et al., 2006), the Visual Analogue Scale for drug craving (VAS), the Center for Epidemiological Studies Depression Scale, Japanese version (CES-D) (Shima et al., 1985), the 12-item General Health Questionnaire, Japanese version (GHQ-12) (Daibo and Nakagawa, 1985), and a number of questions related to demographics and experience with stimulants.

Table 1
Characteristics of the SRRS participants

Items	Values
Number of participants	100
Age ($M \pm$ S.D.)	32.6 ± 8.7
Gender (%female)	29
Treatment state (*N*)	
Inpatients	40
Outpatients	52
Non-patients	8
Relapse/no relapse within 3 months (*N*)	13/35
Relapse/no relapse within 6 months (*N*)	15/33
Primary substances abused[a] (*N*)	
Meth amphetamine	90
Methylphenidate	8
MDMA	7
ASI-J drug composite score (0–1; $M \pm$ S.D.)	.16 ± .17
VAS (current, 0–10; $M \pm$ S.D.)	2.74 ± 3.09
VAS (past 2 weeks, 0–10; $M \pm$ S.D.)	3.66 ± 3.69
CES-D (0–60; $M \pm$ S.D.)	20.48 ± 13.24
GHQ-12 (0–12; $M \pm$ S.D.)	4.45 ± 3.72

N: Number of participants; *M*: mean; S.D.: standard deviation.
[a] Some participants have more than one primary substance.

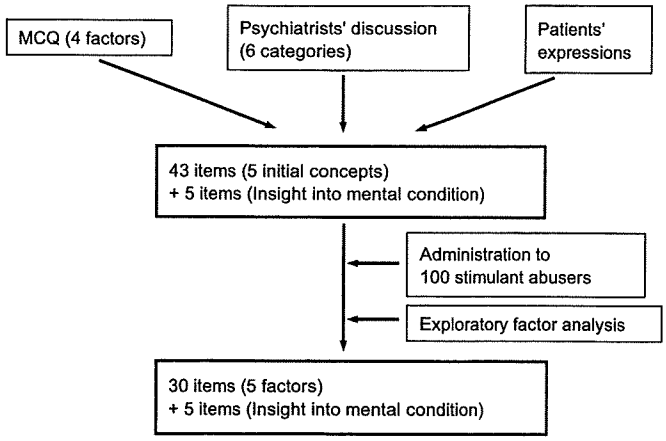

Fig. 1. A schematic flow of the development of SRRS. Four factors taken from the MCQ were compulsivity, emotionality, expectancy, and purposefulness. Six categories highlighted in the psychiatrists' discussion were patients' search for stimulants, common feelings and moods observed before relapse, recall of stimulant craving and negative moods, lack of resistance to inductive stimuli, lack of recognition of social support, and insight into mental condition. Five initial concepts of the 43 items were compulsivity (C), negative expectancy for drug (N), clear intention of drug use (I), positive expectancy for drug (P), and emotionality problems (E). These 43 items and 5 items to measure insight into mental condition were then administered to 100 subjects. The exploratory factor analysis resulted in 30 items with 5 factors that were anxiety and intention to use drug (AI), emotionality problems (EP), compulsivity for drug use (CD), positive expectancies and lack of control over drug (PL), and lack of negative expectancy for drug use (NE).

2.2. Development of the Stimulant Relapse Risk Scale[1]

The SRRS was developed based on a discussion among psychiatrists, and by referring to the MCQ (Fig. 1). Six items were adopted from the MCQ (e.g. 'smoke marijuana' was replaced with 'use the drug') and translated into Japanese. Seven items that seemed applicable to drug abusers were selected from the actual expressions used by patients during a preliminary consultation with us. The above 13 items were then classified into the four factors of the MCQ: compulsivity, emotionality, expectancy, and purposefulness. For instance, 'If I use a drug, I feel I have been saved from helpless loneliness' was classified under emotionality, and 'I am afraid of hallucinations with drug use' under expectancy (negative expectancy).

Next, 35 items were selected through a discussion among three psychiatrists who are currently involved in the treatment of drug abuse. The foci of the discussion were the following six categories of cognition and behavior that predicted relapse: (1) the action of seeking for stimulants, (2) common feelings and moods observed in patients before relapse, (3) recall of stimulant craving and negative moods, (4) lack of resistance to inductive stimuli, (5) lack of recognition of social support, (6) insight into mental condition. The fifth category included two reversal items (e.g. 'I need to make most of my friend's (and NA's) support'). The sixth category was added on the basis of the viewpoint that the lack of insight into one's mental condition (denial) may be related to relapse (e.g. I am sure that I will not use the drug in future).

After confirming the content of these items, including a variety of relapse risks such as craving (expectancy, compulsivity, etc.) and emotionality problems, the above 10 points were modified into a total of six initial concepts of the SRRS, which included a construct for insight into mental condition and five constructs as drug-reuse cues. The five constructs were: (1) compulsivity (C; inability to control stimulant-induced emotion), (2) negative expectancy for drug use (N; restraining relapse, anxiety due to negative outcome from drug use, and acknowledgment of social support), (3) clear intention of drug use (I; planning to use a drug, and intentional search for stimulants), (4) positive expectancy for drug use (P; anticipation of positive outcomes from reuse), (5) emotionality problems (E; not only feelings and moods before relapse but also a revival of memory).

Each of the 48 items was rated on a three-point Likert-type scale with a score ranging between 1 and 3 based on the subjects' strength of agreement with each statement. A three-point scale was employed to reflect patient feedbacks, which pointed out the difficulty answering a five-point scale. The written instruction, 'Please describe your state during the past week. For each statement below, please circle one answer that best describes you. For the word "drug" that appears in the statements, think about the drug you currently abuse.' was given before the 48 items.

2.3. Measurements for concurrent validity

In order to determine the severity of dependence, the Addiction Severity Index-Japanese version (ASI-J), a semi-structured interview lasting approximately 1 h, was administered to the participants. This instrument gathers information about seven areas of a patient's life: medical, employment/support, drug, alcohol, legal, family/social relationships, and psychiatric problems. Severity was rated as a composite score of between 0 and 1, calculated entirely on the basis of the patient's current status. In the present study, the composite score for the drug use was used as an index of the concurrent validity of the SRRS.

In order to evaluate the concurrent validity of the SRRS, the VAS was also administered to the participants, which measured their subjective desires for a drug. The VAS was composed of two questions: 'Please rate your current state of craving' and 'Please rate your strongest craving for the drug in the past 2 weeks'. Participants answered each question by placing a vertical mark on a 100-mm horizontal line, labeled 'not at all' at the left end and 'extremely' at the right end.

Participants also answered the CES-D and GHQ-12 that measured their emotional problems. These scales were used to examine the concurrent validity of the factor, 'emotionality problems' in the SRRS.

2.4. Measurements for predictive validity

To evaluate the risk of relapse, relapse within 3 months and 6 months after the SRRS rating were investigated. Relapse was operationally defined as "to use any stimulants-type drug including methylephedrine after the SRRS rating", and was judged from the patients' self-report and/or their psychiatrists in charge. Of 48 participants for whom the information was available, 13 and 15 participants relapsed within 3 and 6 months, respectively.

2.5. Questionnaire on drug experience and demographic factors

The participants were also asked to complete a short questionnaire in order to obtain information about their age, sex, the day the questionnaire was completed, and the main drug they were using (or had used). The question also included of the date when they had last used the drug, the period since they last used the drug, and the period for which they had used drugs.

2.6. Statistical analyses

Raw scores for the negatively worded items (item numbers 2, 6, 12, 14, 17, 18, 19, 20, 21, 23, 30, 37) were inverted to make these items positively correlate with other items. The inner structure of the 43-item SRRS without the items that assessed insight into the patient's mental condition, was examined by the exploratory factor analysis using a principal factor method with promax rotation to detect simple structure. Factors were extracted on the basis of their eigenvalues (>1) and the scree plot. Only those items loading higher than .4 were retained in the analyses, and all items cross-loading at higher than .4 were removed. The extracted factor scales were checked for their reliability by calculating the Cronbach's alpha value. Concurrent and predictive validity of the subscales, and inter-subscale correlations were analyzed by calculating the Pearson's product-moment correlation coefficient. For the analysis of relapse, 'relapse' was coded as '1', and 'no relapse' as '0'.

[1] English and Japanese versions of the Stimulant Relapse Risk Scale (SRRS) can be found by accessing the online version of this paper at http://dx.doi.org by entering doi:10.1016/j.drugalcdep.2006.10.005.

In addition, the function of the five items that assessed insight into mental condition was examined. The relationships among insight into mental condition, relapse within 6 months, and ASI-J drug composite score were analyzed by Fisher's exact test. Median split of average scores (average of the five items scores = 1.8; ASI-J composite score = .45) was used for dividing the variables into two groups. Thirty-eight participants' data on relapse within 6 months and ASI-J were used for the analysis.

All analyses were performed with the Statistical Package for the Social Sciences (SPSS) version 12.0 for Windows.

3. Results

3.1. Factor analysis

The exploratory factor analysis of the SRRS scores of 100 patients with stimulant abuse revealed 5 factors with eigenvalues of 9.38, 4.60, 2.55, 2.33 and 1.96. These factors accounted for 48.41% of the overall variance (21.82%, 10.70%, 5.93%, 5.41% and 4.56%). Cronbach's alpha values for factors 1, 2, 3, 4, 5, and all items were .82, .80, .73, .79, .55 and .86, respectively. Subsequently, the factors were rotated using the promax method. Of the original 43 items, 30 items were retained and 13 items were discarded. The factor structure after the promax rotation is shown in Table 2. Cronbach's alpha values for each subscale and the total SRRS (all 30 extracted items) are shown in Table 3.

The first factor had significant loadings for eight items, and three of these items reflecting anxiety about relapse and recall of drug use (e.g. 'I am anxious about reusing the drug'; 'The feeling I had while using the drug sometimes comes back.') loaded exclusively on this factor. The remaining item reflected intention and desire to use drug (e.g. 'I will use the drug in the near future'). Thus, the first factor was labeled 'anxiety and intention to use drug' (AI).

Eight items loaded exclusively on the second factor. All of these items reflected emotional problems related to drug use (e.g. 'I cannot control my feeling.', 'I feel tired due to impatience', 'I am irritated'). This factor was therefore labeled 'emotionality problems' (EP).

The third factor had significant loadings for four items. All of these items reflected compulsivity for drug use (e.g. 'I want to obtain the drug even by working illegally'; 'I would do anything to get money for the drug.'). Consequently, this factor was labeled 'compulsivity for drug use' (CD).

The fourth factor comprised six items. Three of these items reflected positive expectancy about drug use (e.g. 'If I used the drug, I would feel invigorated'; 'If I used the drug, I would be less nervous'), and the remaining three items reflected lack of resistance to an inductive stimulus (e.g. 'If the drug is placed in front of me, I would use it'; 'I would use the drug if I am alone'). Therefore, the fourth factor was labeled 'positive expectancies and lack of control over drug' (PL).

The fifth factor comprised four reverse-scored items. Three items had originally been classified as negative expectancy for drug use (e.g. 'I would not be able to control myself if I use the drug', 'If I use the drug, it would badly influence my job'), and the remaining one item as emotionality problems (i.e. 'I feel easier than before'). This factor was therefore labeled 'lack of negative expectancy for drug use' (NE).

In addition, we analyzed the function of the five items for assessing insight into mental condition. In the group with high ASI-J drug composite scores, the association between insight into mental condition and relapse within 6 months was nearly significant (Fisher's exact test: $p = .088$). On the other hand, the association was not significant in the group with low ASI-J drug composite scores. These results suggest that poor insight into mental condition may be related to relapse in the high-severity group, whereas insight is not related to relapse in the low-severity group.

3.2. Basic statistics of the SRRS and inter-subscale correlations

Table 4 presents mean, standard deviation, and inter-correlations of the five SRRS factor scales (subscales). There were no significant correlations between 'lack of negative expectancy for drug use (Factor 5)' and other subscales. The other factors exhibited low to moderate, positive inter-correlations. In addition, one-way ANOVA showed that the SRRS total and subscale scores were not significantly different across methamphetamine, methylphenidate, and MDMA, although there are often considerable differences in the use patterns and subjective effects of these drugs.

3.3. Concurrent validity of the SRRS

Correlation coefficients between the SRRS scores (total score for the 30 items, and subscale scores) and the variables measured to examine concurrent validity were calculated (Table 3). The ASI-J drug composite score was significantly and positively correlated with the scores of total SRRS, anxiety and intention to use drug, compulsivity for drugs, and positive expectancies and lack of control over drug score. The two VAS scores for drug craving, 'current craving' and 'craving in the past 2 weeks', were also significantly and positively correlated with the total SRRS, anxiety and intention to use drug, compulsivity for drugs, and positive expectancies and lack of control over drug scores. In addition, the scores of emotionality problems, anxiety and intention to use drug, and total SRRS were significantly and positively correlated with the CES-D and GHQ-12 scores.

3.4. Predictive validity of the SRRS

Table 3 also presents correlations between the SRRS score and relapse within 3 and 6 months after the scoring. Relapse within 3 months was significantly and positively correlated with the anxiety and intention to use drug, positive expectancies and lack of control over drug, lack of negative expectancy, and total SRRS. Similarly, relapse within 6 months was significantly and positively correlated with the positive expectancies and lack of control over drug and lack of negative expectancy. No significant relation was seen between the SRRS scores and participants' compliances with follow-up (48 participants approved, 19 participants refused, and 33 participants were not asked).

Table 2
Promax rotated factor pattern for the 43-item SRRS

	Factor				
	1	2	3	4	5
Factor 1: Anxiety and intention to use drug (AI)					
E 8) I am anxious about reusing the drug	**.806**	.251	−.046	−.014	−.284
E 3) The feeling I used to have while using the drug sometimes comes back	**.797**	.056	−.002	−.261	−.192
N 18) Thinking about my family, I can no longer use the drug (inverse)	**.648**	.123	−.126	−.237	−.009
I 46) I will use the drug in near future	**.580**	.027	.058	−.084	.232
I 4) There are times I want to use the drug	**.556**	−.048	.122	.136	.120
C 32) If my friend gives me the drug, I would use it even in the hospital	**.502**	−.029	−.036	.101	.148
C 48) Even though I know I will be arrested, I would use the drug	**.479**	−.067	.094	.086	−.256
I 38) If I have a large sum of money, I want to buy the drug	**.475**	.117	.082	.094	.081
Factor 2: Emotionality problems (EP)					
E 33) I cannot control my feeling	.158	**.685**	.005	−.058	−.124
E 36) I feel tired due to impatience	.110	**.662**	.067	−.092	−.014
E 10) I am irritated	−.167	**.601**	.050	.107	.186
E 22) I feel lonely	.095	**.574**	−.092	.206	.039
E 15) I am not motivated to do anything	.093	**.525**	.103	−.062	−.116
E 28) I am anxious about my future	.329	**.490**	−.204	.206	−.110
E 7) I am annoyed by words from others	.010	**.478**	.104	−.109	.176
E 5) I feel a constant need to put something in my mouth	.007	**.407**	.238	−.008	.068
Factor 3: Compulsivity for drug (CD)					
C 47) I want to obtain the drug even by working illegally	.062	.063	**.817**	−.220	.101
C 40) I would do anything to get money for the drug	.051	.024	**.659**	.008	−.124
C 13) I would do almost anything in order to use the drug	−.037	−.064	**.627**	.233	−.260
C 44) I want the drug even if I have to steal	.104	.152	**.586**	.057	.041
Factor 4: Positive expectancies and lack of control over drug (PL)					
P 45) If I use the drug, I would feel invigorated	−.093	.010	.046	**.820**	−.211
P 41) If I use the drug, I would be less nervous	−.079	.320	−.134	**.688**	−.122
P 43) If I use the drug, I would feel everything is going well	−.208	.294	.250	**.455**	−.080
C 35) If the drug is placed in front of me, I would use it	.253	−.139	.186	**.427**	.328
C 29) I would use the drug if I am alone	.139	.359	.168	**.421**	−.047
C 24) If someone holds the drug under my nose, I would not be able to refuse it	.212	−.237	−.038	**.418**	.291
Factor 5: Lack of negative expectancy for the drug (NE)					
N 23) I would not be able to control myself if I use the drug (inverse)	−.034	.079	−.081	−.098	**.661**
N 30) If I use the drug, it would badly influence my job (inverse)	.141	−.113	−.331	−.126	**.552**
E 14) I feel easier than before (inverse)	−.166	.272	.097	−.085	**.538**
N 20) I am afraid of hallucinations due to drug use (inverse)	−.130	−.188	.151	−.242	**.449**
Ambiguous items					
I 27) I would use the drug if my friends offer it to me on a street	**.530**	−.169	−.029	**.414**	.063
E 34) I have significant job-related problems	−.095	**.622**	.004	−.012	**.441**
E 31) I occasionally have nightmares	−.020	**.503**	**−.410**	.303	.026
P 26) The drug would save me from feeling lonely	−.154	.035	**.490**	**.424**	.038
N 12) If I use a small amount of the drug, I would not be able to stop using it (inverse)	**−.448**	.104	−.326	−.011	**.520**
Other items					
I 9) It would be difficult for me to refuse if someone offers me the drug before my eyes	.372	−.279	.068	.271	.264
I 11) I am dying to use the drug	.364	.018	.288	.066	.191
I 42) I might use the drug at a party or a gathering	.257	.195	.199	−.228	.289
E 1) I want to find a job or need to improve my work environment	−.293	.375	.156	.230	−.157
E 25) I feel bored	.277	.256	.010	−.084	.281
P 16) I recall the relief from feeling blue from the time I was using the drug	.256	.284	−.053	−.007	.315
N 39) I would feel restless if I use the drug (inverse)	−.015	−.053	−.032	.109	.383
N 2) I need to make most of my friend's (and NA's) support (inverse)	−.101	−.130	.026	−.041	.140

E: emotionality problems; C: compulsivity; I: clear intention of drug use; P: positive expectancy for drug; N: negative expectancy for drug in terms of the initial 5 concepts. Numbers followed by single parentheses indicate the order in the SRRS values higher than .4 are in bold.

4. Discussion

In the present study, we developed the SRRS to assess relapse risk for stimulant in Japanese drug abusers, and statistically examined its inner structure, reliability, and validity. As a result, five factors were found, and the internal consistency, concurrent validity, and predictive validity of these factors were revealed. It was especially meaningful that part of the SRRS was related to relapse, implying its possibility of predicting relapse. Our findings demonstrated that the SRRS has multidimensional psy-

Table 3
Cronbach's alpha of each subscale of the SRRSand correlation of the SRRS against VAS ASI, CES-D, GHQ-12, and relapse

	Cronbach's α	Correlation						
		VAS (current craving)	VAS (craving in the past 2 weeks)	ASI-drug	CES-D	GHQ-12	Relapse (3 months)	Relapse (6 months)
SRRS subscale								
Anxiety and intention to use drug (AI)	.819	.645**	.706**	.483**	.228*	.287**	.418**	.309†
Emotionality problems (EP)	.800	.138	.218*	.177	.686**	.667**	−.011	−.168
Compulsivity for drug (CD)	.730	.255*	.390**	.348**	.220*	.160	−.017	−.013
Positive expectancies and lack of control over drug (PL)	.785	.413**	.516**	.430**	.210	.265*	.414**	.353*
Lack of negative expectancy (NE)	.545	.182	.170	.170	−.014	−.026	.320*	.328*
Total SRRS	.864	.504**	.617**	.505**	.415**	.440**	.381*	.274

Note: Reliability was calculated according to Cronbach's alpha. Concurrent validity was calculated according to correlation of SRRS against VAS, ASI, CES-D, and GHQ-12. Predictive validity was calculated according to correlation of SRRS against relapse.
* $p<.05$.
** $p<.01$.
† $p<.10$.

chometric properties and thus useful for assessing the various aspects of relapse risk.

One aspect of the multidimensional structure of the SRRS was a variety of craving. In cases of 'positive expectancies and lack of control over drug' (Factor 4) and 'lack of negative expectancy' (Factor 5), the items corresponding to 'expectancy' and 'emotionality' in the MCQ were mainly extracted. These subscales were considered to reflect craving based on the 'expectancy theory' (Jones et al., 2001) and also similar to 'expectancy of positive and negative reinforcement' of the DSQ (James et al., 2004). Moreover, in 'compulsivity for drug use' (Factor 3), the items asking about a strong desire for a drug were mainly extracted from the items that were previously assumed to represent 'compulsivity' in the MCQ. This subscale was considered to reflect craving based on the 'obsessive compulsive theory' (Anton, 2000) and also similar to 'strong desires and intentions to use amphetamine' of the DSQ. The items included in 'anxiety and intention to use drug' (Factor 1) reflected anxiety about relapse, anticipation of relapse, revival of memory about drug use, and clear intention to use drugs. Therefore, we propose that not only expectancy and compulsivity, but also anxiety about relapse and intention to use drug are important components of craving.

Another aspect of the multidimensional structure of the SRRS revealed negative emotional states. In the case of 'emotionality problems' (Factor 2), the items that were considered to reflect 'common feelings and moods observed in patients before relapse' in the discussion among the psychiatrists were mainly extracted.

With regard to concurrent validity, the scores for anxiety and intention to use drug, positive expectancies and lack of control over drug, and compulsivity for drug use were moderately correlated with the ASI-J drug composite score and the VAS score. On the other hand, there was no correlation among the scores for emotionality problems, lack of negative expectancy, ASI-J, and VAS. These results indicated that anxiety and intention to use drug, positive expectancies and lack of control over drug, and compulsivity for drug use are important factors of craving related to the subjective desire for a drug and severity of drug dependence, although it should be noted that the timeframe of the SRRS (past 1 week) and the VAS (current and past 2 weeks) was not the same.

Concerning about predictive validity, the scores for 'anxiety and intention to use drug', 'positive expectancies and lack of control over drug', 'lack of negative expectancy for drug use', and 'total SRRS' were correlated with relapse within 3 months.

Table 4
Mean and S.D. of the SRRS and inter-subscale correlations

	Mean (S.D.)	AI	EP	CD	PL	NE
SRRS subscale (range: 1–3)						
Anxiety and intention to use drug (AI)	1.70 (.52)	–	.330*	.468**	.575**	.171
Emotionality problems (EP)	2.00 (.54)		–	.227*	.326**	−.098
Compulsivity for drug (CD)	1.30 (.48)			–	.505**	.160
Positive expectancies and lack of control over drug (PL)	1.82 (.60)				–	.143
Lack of negative expectancy (NE)	1.53 (.49)					–
Total SRRS (range: 1–3)	1.67 (.35)					

S.D.: standard deviation.
* $p<.05$.
** $p<.01$.

Moreover, the scores for 'positive expectancies and lack of control over drug' and 'lack of negative expectancy for drug use' were correlated with relapse within 6 months. These results indicated that the higher these scores, higher the risk of relapse. This is consistent with the idea that relapse triggered by the expectation or anxiety for the risk situation related to drug use rather than the subjective desire for the drug (Drummond, 2001; Jones et al., 2001).

The emotionality problems score was not related to the VAS or ASI-J composite score, nor to relapse. However, the moderate correlation of the emotionality problems score with the CES-D and GHQ-12 scores, and the significant correlations of this score with other subscale scores of the SRRS suggest that this factor may have an indirect effect that increases the subjective desire for a drug and thus the risk of relapse. Also, the correlation between the lack of negative expectancy score and relapse within 6 months was nearly significant, although this score had no correlation with the VAS and ASI-J drug composite scores, and internal consistence of this subscale was insufficient. Further examination with more samples may reveal the correlation between the score for lack of negative expectancy and relapse.

One possible limitation to the present study was the sampling procedure. The participants were not recruited randomly but were limited only to inpatients or outpatients who gave informed consent and whose doctors in charge recognized their ability to answer a 2 h interview. Therefore, the results of this study were not obtained from drug abusers as a whole such as dropout patients and non-patients, but from cooperative patients with a relatively low severity of drug dependence. In addition, the relatively low rate of availability of relapse data (48/100) may have influenced assessment of the SRRS's predictive validity. In order to gain a better understanding of relapse risk in stimulant abusers as a whole, it would be necessary to conduct follow-up surveys for dropout cases and to recruit participants from other facilities, including prisons. Another limitation was the relatively low sample size. A sample of one hundred participants was small to sufficiently support the factor analysis, and the further study of the SRRS to examine the stability of the factor structure by confirmatory factor analysis is required.

While the result of the items assessing insight into mental condition was not significant, it may have potential value for recognizing 'denial' patients; patients who have low scores for these items and high ASI-J drug composite scores tended to show a high risk of relapse. Since it is very important for self-rating scales to distinguish dishonest responses from honest ones, these items should be retained in the scale. It would be necessary to examine whether 'denial' patients are recognized by combination with other dependence severity ratings, such as the ASI drug composite score.

The SRRS was developed in Japanese language, thus the items shown in Table 2 were translated into English. While there was no word or phrase that could not be translated, the items were more directly expressed in English. It is possible that Japanese people use more indirect form of expression, which may explain the result that the subjective desire for drug was not significantly related to relapse. Additionally, some items of the SRRS such as the one that indicates peer pressure (e.g. If someone holds the drug under my nose, I would not be able to refuse it), may be interpreted and answered differently between a collectivistic culture (e.g. Japan) and an individualistic culture.

The present results suggest that the SRRS would be an effective tool with which psychiatrists, psychologists, social workers, and patients themselves can assess the level of craving and recognize the risk of relapse. Also, the SRRS may contribute to the assessment of craving-inhibitory effects of medicines and treatment programs. To improve the usefulness of the SRRS, further studies of at least the following will be necessary: (1) applicability of the SRRS to other substances of abuse such as alcohol, cannabis (marijuana, hashish), and solvents (e.g. toluene, benzene), (2) cross-validity using other stimulant abusers with confirmatory factor analysis, and (3) modification of the SRRS for a better prediction of relapse.

Conflict of interest

None.

Acknowledgements

We are grateful to the subjects for their participation in this study. We are also grateful to Drs. Sachiko Suetsugu, Michiko Ohara, Yoshihisa Aketa, Hideko Yamamoto, Yukio Takamatsu and Ms. Fumiyuki Chin for fruitful discussion. This work was supported by grants from the Ministry of Education, Culture, Sports, Science and Technology of Japan (17025054), Ministry of Health, Labor and Welfare of Japan (H17-Pharmaco-001, H16-Iyaku-029, H15-KOU-3-03, H14-Toxico-011), and the Japan Society for the Promotion of Science (quasi-governmental organization) (17730421, 17591238).

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.drugalcdep.2006.10.005.

References

Anton, R.F., 2000. Obsessive-compulsive aspects of craving: development of the Obsessive Compulsive Drinking Scale. Addiction 95 (Suppl. (2)), 211–217.

Anton, R.F., Moak, D.H., Latham, P.K., 1996. The obsessive-compulsive drinking scale: a new method of assessing outcome in alcoholism treatment studies. Arch. Gen. Psychiatry 53, 225–231.

Ciraulo, D.A., Sarid-Segal, O., Knapp, C.M., Ciraulo, A.M., Locastro, J., Bloch, D.A., Montgomery, M.A., Leiderman, D.B., Elkashef, A., 2005. Efficacy screening trials of paroxetine, pentoxifylline, riluzole, pramipexole and venlafaxine in cocaine dependence. Addiction 100 (Suppl. (1)), 12–22.

Cooney, N.L., Litt, M.D., Morce, P.A., Bauer, L.O., Gaupp, L., 1997. Alcohol cue reactivity, negative-mood reactivity, and relapse in treated alcoholic men. J. Abnorm. Psychol. 106 (2), 243–250.

Daibo, I., Nakagawa, Y., 1985. Japanese Version of GHQ (General Health Questionnaire) by Goldberg. Nihon Bunka Kagakusha, Tokyo.

Drummond, D.C., 2001. Theories of drug craving, ancient and modern. Addiction 96, 33–46.

Heishman, S.J., Singleton, E.G., Liguori, A., 2001. Marijuana Craving Questionnaire: development and initial validation of a self-report instrument. Addiction 96, 1023–1034.

Ikeda, K., Yamamoto, H., Takamatsu, Y., Haraguchi, A., Umeno, M., Senoo, E., 2004. New approaches toward treatment of methamphetamine dependence. Seishin Igaku 46 (8), 57–72.

James, D., Davies, G., Willner, P., 2004. The development and initial validation of a questionnaire to measure craving for amphetamine. Addiction 99, 1181–1188.

Jones, B.T., Corbin, W., Fromme, K., 2001. A review of expectancy theory and alcohol consumption. Addiction 96, 57–72.

Love, A., James, D., Willner, P., 1998. A comparison of two alcohol craving questionnaire. Addiction 93, 1091–1102.

Piasecki, M.P., Steinagel, G.M., Thienhaus, O.J., Kohlenberg, B.S., 2002. An exploratory study: the use of paroxetine for methamphetamine craving. J. Psychoactive Drugs 34 (3), 301–304.

Senoo, E., Ogai, Y., Haraguchi, A., Kondo, A., Ishibashi, Y., Umeno, M., Kikumoto, H., Hori, T., Komiyama, T., Kato, R., Aso, K., Asukai, N., Wada, K., Saitoh, S., Ikeda, K., 2006. Reliability and validity of the Japanese version of the Addiction Severity Index (ASI-J). Nihon Arukoru Yakubutsu Igakkai Zasshi 41 (4), 368–379.

Shima, S., Shikano, T., Kitamura, T., Asai, M., 1985. New self-rating scales for depression. Seishin Igaku 27, 717–723.

Sora, I., Hall, F.S., Andrews, A.M., Itokawa, M., Li, X.F., Wei, H.B., Wichems, C., Lesch, K.P., Murphy, D.L., Uhl, G.R., 2001. Molecular mechanisms of cocaine reward: combined dopamine and serotonin transporter knockouts eliminate cocaine place preference. Proc. Natl. Acad. Sci. U.S.A. 98 (9), 5300–5305.

Takamatsu, Y., Yamanishi, Y., Hagino, Y., Yamamoto, H., Ikeda, K., 2006a. Differential effects of donepezil on methamphetamine and cocaine dependence. Ann. N. Y. Acad. Sci. 1074, 418–426.

Takamatsu, Y., Yamamoto, H., Ogai, Y., Hagino, Y., Markou, A., Ikeda, K., 2006b. Fluoxetine as a potential pharmacotherapy for methamphetamine dependence: studies in mice. Ann. N. Y. Acad. Sci. 1074, 295–302.

The Ministry of Justice Research and Training Institute, 2004. White paper on crime in Japan 2003. Ministry of Finance Printing Bureau, Tokyo, pp. 305–314.

Tiffany, S.T., 1990. A cognitive model of drug urge and craving research: role of automatic and non-automatic process. Psychol. Rev. 97, 147–168.

Topp, L., Mattick, R.P., 1997. Validation of the amphetamine dependence syndrome and the SAmDQ. Addiction 92 (2), 151–162.

Wada, K., Kikuchi, A., Nakano, R., Ozaki, S., 2004. Current situation on drug abuse in Japan: using a general population survey and a junior high school student's survey. Nihon Arukoru Yakubutsu Igakkai Zasshi 39 (1), 28–34.

Wallace, B.C., 1989. Psychological and environmental determinants of relapse in crack cocaine smokers. J. Subst. Abuse Treat. 6 (2), 95–106.

Drug and Alcohol Dependence 101 (2009) 20–26

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

Application of the Relapse Risk Scale to alcohol-dependent individuals in Japan: Comparison with stimulant abusers☆

Yasukazu Ogai[a], Masahiro Yamashita[b], Keiko Endo[c], Ayako Haraguchi[a], Yoko Ishibashi[a], Tatsuya Kurokawa[d], Tatsuyuki Muratake[e], Ryoichi Suga[b], Toru Hori[f], Mitsuru Umeno[g], Nozomu Asukai[a], Eiichi Senoo[a], Kazutaka Ikeda[a,*]

[a] *Tokyo Institute of Psychiatry, 2-1-8 Kamikitazawa, Setagaya-ku, Tokyo 156-8585, Japan*
[b] *Nakajo Daini Hospital, 2941 Nakajoki, Tokamachi, Japan*
[c] *Urabe Mental Health Clinic, 5-36-8 Oshima, Koto-ku, Tokyo, Japan*
[d] *Hirakawa Hospital, 1076 Miyama-cho, Hachioji, Japan*
[e] *Niigata University Graduate School of Medical and Dental Sciences, 1-754 Asahimachi, Niigata, Japan*
[f] *National Center of Neurology and Psychiatry, Musashi Hospital, 4-1-1 Ogawahigashi-cho, Kodaira, Japan*
[g] *Tokyo Metropolitan Matsuzawa Hospital, 2-1-1 Kamikitazawa, Setagaya-ku, Tokyo, Japan*

ARTICLE INFO

Article history:
Received 26 March 2008
Received in revised form 5 September 2008
Accepted 17 October 2008
Available online 11 December 2008

Keywords:
Alcohol
Relapse risk
Craving
Scale
Japanese

ABSTRACT

Objective: To develop and validate the Alcohol Relapse Risk Scale (ARRS) for Japanese alcohol-dependent individuals and to compare the features of relapse risk for alcohol-dependent individuals with those for stimulant abusers.
Methods: The ARRS is a multidimensional self-rating scale consisting of 32 items based on the Stimulant Relapse Risk Scale (SRRS). Two hundred eighteen inpatients and outpatients with a history of alcohol dependence (181 males and 36 females) were recruited, provided informed consent, and were administered the ARRS. The Visual Analog Scale (VAS) for alcohol craving, current state of drinking, and data on relapse within 1 month after the rating were used for validation.
Results: Exploratory factor analysis highlighted five factors: stimulus-induced vulnerability (SV), emotionality problems (EP), compulsivity for alcohol (CA), lack of negative expectancy for alcohol (NE), and positive expectancy for alcohol (PE). Cronbach's α coefficient for each of the subscales ranged from .55 to .90 and was .90 for the total ARRS, indicating their adequate internal consistency. SV, EP, CA, PE, and total ARRS were significantly correlated with the VAS and current drinking state, supporting their concurrent validity. SV and total ARRS were significantly correlated with relapse, suggesting that the ARRS is useful for predicting relapse risk in alcohol-dependent individuals, similar to the SRRS for stimulant abusers. Compared with stimulant abusers, alcohol-dependent individuals tended to express their desires related to relapse more honestly on the scales.
Conclusions: The ARRS has multidimensional psychometric properties that are useful for assessing the various aspects of alcohol relapse risk.

1. Introduction

In 2003, approximately 800,000 adults out of the Japanese general population of 120 million presented with alcohol dependence, making this group one of the largest among the various mental disorders (Osaki et al., 2005). A serious problem with the treatment of alcohol-dependent individuals is the very low rate of complete abstinence (about 20%; Noda et al., 2001).

Some clinical studies have examined psychosocial factors related to relapse in individuals with alcohol dependence. Relapse-promoting factors include anxiety (Lucht et al., 2002), craving (Gordon et al., 2006), negative mood, childhood sexual abuse (Walitzer and Dearing, 2006), and psychological distress (Sander and Jux, 2006). Some researchers have placed emphasis on relapse-inhibiting factors such as self-efficacy, social support, coping (Brown et al., 1995), other-efficacy beliefs (Demmel et al., 2006), spirituality (Gordon et al., 2006), peer support group attendance, and continuing care program involvement (Miller et al., 1999).

☆ English and Japanese versions of the Alcohol Relapse Risk Scale (ARRS) can be found by accessing the online version of this paper at http://dx.doi.org by entering doi:10.1016/j.drugalcdep.2008.10.021.

* Corresponding author. Tel.: +81 3 3304 5701x508; fax: +81 3 3329 8035.
E-mail address: ikedak@prit.go.jp (K. Ikeda).

0376-8716/$ – see front matter © 2008 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.drugalcdep.2008.10.021

Zywiak et al. (2006) developed the "Relapse Questionnaire" and examined its inner multiple construction of relapse-onset factors of alcohol dependence with a follow-up study. This study revealed three factors: Negative Affect/Family Influences, Craving/Cues, and Social Pressure. These factors appear to cover most of the psychosocial factors related to alcohol relapse. This questionnaire, however, is intended for relapsed patients, not for the prediction of relapse risk. Additionally, difficulty with administering the questionnaire remains problematic because it is part of a research interview.

No multidimensional scale that measures relapse risk for alcohol dependence currently exists in Japan. To further advance the development of medicines and programs for the prevention of relapse, scales for the appropriate assessment of relapse risk are necessary. We previously developed a 48-item multidimensional scale for the measurement of relapse risk for Japanese patients with stimulant dependence (i.e., the Stimulant Relapse Risk Scale, SRRS; Ogai et al., 2007) based on the Marijuana Craving Questionnaire (Heishman et al., 2001). The reliability and validity of this scale were demonstrated by analyzing 100 inpatients and outpatients with a history of stimulant abuse in Japan. Exploratory factor analysis revealed five subscales: "anxiety and intention to use drug" (AI), "emotionality problems" (EP), "compulsivity for drug use" (CD), "positive expectancy and lack of control over drug" (PL), and "lack of negative expectancy for drug use" (NE). AI, PL, NE, and total SRRS scores were significantly and positively related to relapse within 3 and 6 months. Shaffer et al. (2004) proposed a common etiology for addiction to stimulants, alcohol, and other drugs. Relapse risk may be similar between stimulant abusers and alcohol-dependent individuals.

In the present study, we developed a multidimensional scale, the Alcohol Relapse Risk Scale (ARRS), based on the SRRS. Forty-eight items in the ARRS reflect a variety of relapse risk factors, such as intention, compulsivity, expectancy for alcohol, and emotional problems. We administered the ARRS to 218 inpatients and outpatients with a history of alcohol dependence in Japan and examined its inner structure, reliability, and validity. Moreover, certain relapse risk factors appear to be common between stimulants and alcohol; we therefore compared the relapse risk for alcohol-dependent individuals with that for stimulant abusers.

2. Methods

2.1. Participants

A total of 218 patients (29 inpatients, 182 outpatients, and 7 unknown patients) with a history of alcohol dependence participated in the study (Table 1). They were recruited for ongoing research studies at Nakajo Daini Hospital, Tokamachi (n = 68), National Center of Neurology and Psychiatry, Musashi Hospital, Kodaira (n = 63), Tokyo Metropolitan Matsuzawa Hospital, Tokyo (n = 34), Urabe Mental Health Clinic, Tokyo (n = 30), and Hirakawa Hospital, Hachioji (n = 20). All of these treatment facilities specialized in the treatment of alcohol dependence. The participants comprised 181 males and 36 females, ranging in age from 28 to 81 years (mean = 53.6, S.D. = 11.06).

Table 1
Characteristics of the ARRS participants.

Items	Values
Number of participants	218
Age ($M \pm$ S.D.)	53.6 ± 11.5
Gender (% female)	16.6
Treatment state (N)	
Inpatients	29
Outpatients	182
Unknown	7
Participants with follow-up (%)	56.9
Current drinking/not drinking (N)	55/163
Relapse/no relapse within 1 month (N)	31/93
VAS (current, 0–10; $M \pm$ S.D.)	2.07 ± 2.51
VAS (past 2 weeks, 0–10; $M \pm$ S.D.)	2.47 ± 3.20
CES-D (0–60; $M \pm$ S.D.)	16.82 ± 11.06
GHQ-12 (0–12; $M \pm$ S.D.)	2.32 ± 3.63

N: number of participants, M: mean, S.D.: standard deviation.

The five eligibility criteria were the following: at least 20 years of age, a history of alcohol dependence, diagnosed as alcohol-dependent on the basis of the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV; American Psychiatric Association, 1994), an inpatient or outpatient at a Japanese mental hospital, and the ability to understand Japanese. The study was approved by the Institutional Review Board of each facility. After an explanation of the research by a psychiatrist or a psychologist, each participant provided informed written consent and completed the ARRS, the Visual Analog Scale (VAS) for alcohol craving, the Center for Epidemiological Studies Depression Scale Japanese version (CES-D) (Shima et al., 1985), the 12-item General Health Questionnaire Japanese version (GHQ-12) (Daibo and Nakagawa, 1985), and a questionnaire on alcohol experience and demographics. One hundred twenty-four participants also answered a follow-up questionnaire about their drinking state within 1 month after the rating.

2.2. Development of the Alcohol Relapse Risk Scale

The ARRS was developed on the basis of 48 preliminary items from the Stimulants Relapse Risk Scale (SRRS). For all items, "use the drug" was replaced by "drink alcohol." Two items related to illegal activities were replaced by behaviors related to alcohol drinking (i.e., "Even though I know I will be arrested, I would use the drug" was replaced with "Even though I know I will lose my family and/or job, I would drink alcohol"; "I want to obtain the drug even by working illegally" was replaced with "I want to drink alcohol even if it deteriorates my health").

Forty-three of the preliminary items comprised the five initial factors of alcohol relapse: (i) compulsivity (C), (ii) negative expectancy for alcohol (N), (iii) clear intention of alcohol drinking (I), (iv) positive expectancy for alcohol (P), and (v) emotional problems (E). The remaining five preliminary items were provided to measure the lack of insight into one's own mental condition (i.e., denial; e.g., "I am sure that I will not drink alcohol in the future").

Each item was rated on a three-point Likert-type scale with a score ranging from 1 to 3 based on the participant's level of agreement with each statement. The anchors were "Strongly Disagree and Disagree," "Neither Agree nor Disagree," and "Strongly Agree and Agree." A three-point scale was used to reflect patient feedback, indicating the difficulty in answering a five-point scale. The following written instruction was given: "Please describe your state during the past week. For each statement below, please circle one answer that best describes you."

2.3. Measurements of concurrent validity

To evaluate the concurrent validity of the ARRS, the VAS was administered to the participants to measure their subjective desires for alcohol. The VAS was composed of two questions: "Please rate your current state of craving" and "Please rate your strongest craving for alcohol in the past 2 weeks." Participants answered each question by placing a vertical mark on a 100-mm horizontal line, labeled "not at all" on the left and "extremely" on the right end. The current state of drinking (i.e., drinking or not drinking) was also asked.

Participants also answered the CES-D and GHQ-12 that measured their emotional problems. These scales were used to examine the concurrent validity of the factor "emotionality problems" in the ARRS.

2.4. Measurements of predictive validity

To evaluate relapse risk, relapse within 1 month after the ARRS rating was investigated. Relapse was operationally defined as "consumption of any alcohol after the ARRS rating" and was determined from the patients' self-reports and/or their psychiatrists. Of 124 participants whose information was available, 16 were drinking at baseline and follow-up, 15 were abstinent at baseline but drinking at follow-up, 8 were drinking at baseline but not at follow-up, and 85 were abstinent throughout. Thirty-one participants who were drinking at follow-up were considered relapsed patients.

2.5. Questionnaire on alcohol experience and demographic factors

The participants were also asked to complete a short questionnaire to determine their age and gender, the day the questionnaire was completed, and the principal type of alcohol they were drinking (or had consumed). The questions also asked the date on which the patient had last consumed alcohol, the period of abstinence, the number of years they had consumed alcohol, other problems apart from alcohol, perceived stress, perceived social support, and the availability of social support for their problems.

Table 2
Promax rotated factor pattern for the 43-item ARRS.

	Factor				
	1	2	3	4	5
Factor 1: Stimulus-induced vulnerability (SV)					
(C 35) If alcohol is placed in front of me, I would drink it.	**.855**	−.240	.083	.078	.023
(I 9) It would be difficult for me to refuse if someone placed alcohol in front of me.	**.849**	−.063	−.155	−.007	.056
(C 24) If someone held alcohol under my nose, I would not be able to refuse it.	**.838**	.047	−.017	−.066	−.018
(I 27) I would drink alcohol if my friends offered it to me on a street.	**.823**	.059	−.043	−.096	−.037
(I 42) I might drink alcohol at a party or a gathering.	**.661**	.084	−.074	−.051	.142
(C 29) I would drink alcohol if I am alone.	**.580**	−.118	.187	.156	.083
(I 46) I will drink alcohol in near future.	**.536**	.095	−.079	−.051	.185
(C 47) I want to drink alcohol even if it deteriorates my health.	**.522**	−.038	.226	.067	.004
(C 32) If my friend gave me alcohol, I would drink it even in the hospital.	**.479**	−.056	.272	.027	−.133
Factor 2: Emotionality problems (EP)					
(E 22) I feel lonely.	−.046	**.823**	−.114	−.019	−.015
(E 15) I am not motivated to do anything.	.112	**.733**	.119	−.290	−.236
(E 28) I am anxious about my future.	.225	**.565**	−.175	.319	−.031
(E 33) I cannot control my feeling.	.149	**.554**	−.029	.020	−.054
(E 7) I am annoyed by words from others.	−.150	**.486**	.112	−.049	.052
(E 10) I am irritated.	−.297	**.476**	.354	.009	.198
(E 34) I have significant job-related problems.	.107	**.442**	.060	.293	−.165
(E 25) I feel bored.	.149	**.404**	.079	−.236	.102
Factor 3: Compulsivity for alcohol (CA)					
(C 44) I want alcohol even if I have to steal.	.098	.029	**.702**	−.036	−.137
(C 13) I would do almost anything in order to drink alcohol.	−.109	.044	**.534**	.047	.128
(C 40) I would do anything to get money for alcohol.	.132	−.013	**.502**	.001	.047
Factor 4: Lack of negative expectancy for alcohol (NE)					
(N 30) If I drink alcohol, I think it would badly influence my job (reverse-coded).	.103	.047	−.079	**.798**	−.143
(N 23) I would not be able to control myself if I drink alcohol (reverse-coded).	−.141	.118	.145	**.541**	−.146
(N 12) If I drink a small amount of alcohol, I would not be able to stop drinking (reverse-coded).	−.001	−.129	.282	**.464**	.198
(N 39) I would feel restless if I drank alcohol (reverse-coded).	−.213	.013	.103	**.441**	.156
Factor 5: Positive expectancy for alcohol (PE)					
(P 43) If I drink alcohol, I will feel everything is going well.	.169	−.197	.039	−.025	**.780**
(P 45) If I drink alcohol, I will feel invigorated.	.181	.085	.016	−.005	**.541**
(P 26) Alcohol would save me from feeling lonely.	.186	.252	−.003	.011	**.410**
Ambiguous items					
(I 38) If I had a large sum of money, I would want to buy alcohol.	**.564**	−.089	.443	**−.107**	−.001
Other items					
(I 11) I am dying to drink alcohol.	.370	.094	.320	−.201	.103
(C 48) Even though I know I will lose my family or job, I would drink alcohol.	.341	.169	.158	.168	−.044
(E 3) The feeling I used to have while drinking alcohol sometimes comes back.	.297	.124	.092	.123	.103
(E 5) I feel a constant need to put something in my mouth.	.266	.219	−.140	−.040	.068
(E 36) I feel tired due to impatience.	−.092	.395	.227	.224	.111
(E 31) I occasionally have nightmares.	−.034	.328	.107	.008	.200
(N 20) I am afraid of withdrawal due to alcohol dependence (reverse-coded).	−.058	.326	.050	.124	.015
(E 8) I am anxious about relapse.	.163	.161	.312	−.040	−.037
(E 14) I feel easier than before (reverse-coded).	.085	−.124	−.332	.391	.123
(E 1) I want to find a job or need to improve my work environment.	.256	.158	−.025	.357	
(N 2) I need to make the most of my friend's (and AA's) support (reverse-coded).	.001	.000	−.175	.296	.089
(N 18) Thinking about my family, I can no longer drink alcohol (reverse-coded).	−.216	−.075	.055	.257	−.020
(P 16) I recall the relief from feeling blue from the time I was drinking alcohol.	−.027	.282	−.076	.102	.379
(I 4) There are times I want to drink alcohol.	.305	.119	−.130	−.063	.328
(P 41) If I drink alcohol, I would be less nervous.	.229	.300	.003	.028	.311

E: emotionality problems; C: compulsivity; I: clear intention of alcohol use; P: positive expectancy for alcohol; N: negative expectancy for alcohol in terms of the initial five concepts. Numbers followed by single parentheses indicate the order in the ARRS. Values higher than 0.4 are in bold.

2.6. Statistical analysis

Raw scores for the negatively worded items (items 2, 6, 12, 14, 17, 18, 19, 20, 21, 23, 30, 37) were reversed to make these items positively correlated with other items. The inner structure of the 43-item ARRS without the items that assessed insight into the patient's mental condition was examined by exploratory factor analysis using a principal factor method with promax rotation to detect simple structure. Exploratory factor analysis was used instead of confirmatory factor analysis because the inner structure of the ARRS was expected to be different from that of the SRRS. The items that assessed insight into mental condition were excluded from factor analysis of the relapse risk structure because they were added to the questionnaire to distinguish patients who are "in denial." Factors were extracted on the basis of their eigenvalues (>1) and the scree plot. Only the items loading higher than 0.4 were retained in the analyses, and all items cross-loading at higher than 0.4 were removed. The reliability of the extracted factor scales was checked by calculating Cronbach's α value. Concurrent and predictive validity of the subscales and inter-subscale correlations were analyzed by calculating Pearson's product-moment correlation coefficient. With regard to predictive validity, logistic regression analysis was also used to examine whether the ARRS subscales as independent variables predict relapse as a dependent variable. All subscales of the ARRS were analyzed at the same time. For analysis of current state of drinking and relapse, "drinking" and "relapse" were coded as 1, and "not drinking" and "no relapse" were coded as 0.

Additionally, the function of the five items that assessed insight into mental condition was examined. Relationships among insight into mental condition, relapse, and the period of abstinence were analyzed by Fisher's exact test. Median split (i.e., median of the five items' average scores = 2.0; period of abstinence = 150) was used to divide the variables into two groups. Data on relapse and the period of abstinence for 66 participants were used for the analysis.

All analyses were performed with the Statistical Package for the Social Sciences (SPSS) version 12.0 for Windows.

Table 3
Cronbach's α for each subscale of the ARRS and correlation of the ARRS against current drinking, VAS, CES-D, GHQ-12, and relapse.

	Cronbach's α	Correlation					
		Current drinking state	VAS (current craving)	VAS (craving in the past 2 weeks)	CES-D	GHQ-12	Relapse (1 month)
ARRS subscale [number of items]							
Stimulus-induced vulnerability (SV) [9]	.897	.497**	.472**	.604**	.306**	.495**	.268**
Emotionality problems (EP) [8]	.794	.197**	.255**	.386**	.537**	.578**	.131
Compulsivity for alcohol (CA) [3]	.730	.196**	.212**	.350**	.319**	.219	.004
Lack of negative expectancy for alcohol (NE) [4]	.785	.165*	.011	−.003	−.158*	−.316**	.169
Positive expectancy for alcohol (PE) [3]	.545	.341**	.272**	.480**	.328**	.435**	.178
Total ARRS [27]	.864	.410**	.357**	.541**	.445**	.394**	.215*

Note: Reliability was calculated according to Cronbach's alpha. Concurrent validity was calculated according to correlation of ARRS against current drinking, VAS, CES-D, and GHQ-12. Predictive validity was calculated according to correlation of ARRS against relapse.
* $p < .05$.
** $p < .01$.

3. Results

3.1. Factor analysis

Exploratory factor analysis of the ARRS scores for 218 participants revealed five factors with eigenvalues of 9.38, 4.60, 2.55, 2.33, and 1.96. These factors accounted for 47.54% of the overall variance (26.60%, 8.10%, 4.84%, 4.40%, and 3.62% for factors 1–5, respectively). Cronbach's α values for factors 1, 2, 3, 4, 5, and all items were .89, .79, .73, .78, .54, and .86, respectively. The factors were subsequently rotated using the promax method. Of the original 43 items, 27 were retained and 16 were discarded. The factor structure after the promax rotation is shown in Table 2. Cronbach's α values for each subscale and the total ARRS (all 27 extracted items) are shown in Table 3.

The first factor had significant loadings for nine items, including all seven items that reflect stimulus-induced vulnerability (e.g., "If alcohol is placed in front of me, I would drink it" and "It would be difficult for me to refuse if someone placed alcohol in front of me"). The two remaining items reflected intention and desire to drink alcohol (e.g., "I will drink alcohol in the near future" and "I want to drink alcohol even if it deteriorates my health"). The first factor, therefore, was labeled "stimulus-induced vulnerability" (SV).

Eight items loaded exclusively on the second factor. All of these items reflected emotional problems related to alcohol consumption (e.g., "I feel lonely" and "I am not motivated to do anything"). This factor, therefore, was labeled "emotionality problems" (EP).

The third factor had significant loadings for three items, all of which reflecting compulsivity for alcohol (e.g., "I want alcohol even if I have to steal" and "I would do almost anything to drink alcohol"). This factor, therefore, was labeled "compulsivity for alcohol" (CA).

The fourth factor comprised four items that had originally been classified as negative expectancy for alcohol drinking (e.g., "If I drink alcohol, it would badly influence my job" and "I would not be able to control myself if I drink alcohol"). This factor, therefore, was labeled "lack of negative expectancy for alcohol drinking" (NE).

The fifth factor comprised three items that reflected positive expectancy about alcohol drinking (e.g., "If I drink alcohol, I will feel everything is going well" and "If I drink alcohol, I will feel invigorated"). The fifth factor, therefore, was labeled "positive expectancy for alcohol" (PE). Although the internal consistency of this factor was insufficient, its items were retained in the scale because positive expectancy is a significant factor of relapse risk in stimulant abusers (Ogai et al., 2007).

Additionally, we analyzed the function of the five items for assessing insight into mental condition. Cronbach's α values for these items were .68. The association between insight into mental condition and relapse was not significant regardless of the duration of abstinence.

3.2. Basic statistics of the ARRS and inter-subscale correlations

Table 4 presents means, standard deviations, and inter-correlations of the five ARRS factor scales (subscales). No significant correlations were found between "stimulus-induced vulnerability" (Factor 1) and "lack of negative expectancy for drug use" (Factor 4). The other subscales exhibited low to moderate positive inter-correlations.

3.3. Concurrent validity of the ARRS

Correlation coefficients between the ARRS scores (i.e., subscale scores and total score for the 27 items) and the variables that were measured to examine the concurrent validity were calculated (Table 3). The current state of drinking was significantly and positively correlated with the scores for stimulus-induced vulnerability, emotionality problems, compulsivity for alcohol, positive

Table 4
Mean and S.D. of the ARRS and inter-subscale correlations.

	Mean (S.D.)	SV	EP	CA	NE	PE
ARRS subscale (range: 1–3)						
Stimulus-induced vulnerability (SV)	1.53 (0.53)	–	.446**	.404**	−.076	.560**
Emotionality problems (EP)	1.80 (0.53)		–	.362**	−.318**	.507**
Compulsivity for alcohol (CA)	1.20 (0.38)			–	−.276**	.375**
Lack of negative expectancy for alcohol (NE)	1.94 (0.59)				–	−.250**
Positive expectancy for alcohol (PE)	1.54 (0.61)					–
Total ARRS (range: 1–3)	1.62 (0.34)					

S.D.: standard deviation.
** $p < .01$.

Table 5
Logistic regression analysis of each ARRS subscale as independent variable and relapse within 1 month as dependent variable.

	Coefficient *B* (SE)	Wald statistic (d.f.)	*p*-Value	Odds ratio	95% Confidence interval
ARRS subscale					
Stimulus-induced vulnerability (SV)	.994 (.565)	3.095 (1)	.079	2.703	.893–8.186
Emotionality problems (EP)	.392 (.549)	.508 (1)	.476	1.479	.504–4.342
Compulsivity for alcohol (CA)	−.351 (.691)	.258 (1)	.612	.704	.182–2.729
Lack of negative expectancy for alcohol (NE)	1.008 (.461)	4.771 (1)	.029	2.740	1.109–6.769
Positive expectancy for alcohol (PE)	.574 (.499)	1.323 (1)	.250	1.77	5.668–4.721

Note: Predictive validity was also calculated according to odds ratio of ARRS against relapse. 118 data was used for analysis.

expectancy for alcohol drinking, and total ARRS. The current state of drinking was significantly and negatively correlated with lack of negative expectancy. The two VAS scores for alcohol craving ("current craving" and "craving in the past two weeks") were also significantly and positively correlated with the scores for stimulus-induced vulnerability, emotionality problems, compulsivity for alcohol, positive expectancy, and total ARRS. Additionally, the CES-D and GHQ-12 scores were significantly and positively correlated with the scores for all subscales, with the exception of compulsivity for alcohol in the GHQ-12 and total ARRS.

3.4. Predictive validity of the ARRS

Table 3 also presents correlations between the ARRS scores and relapse within 1 month. Relapse was significantly and positively correlated with stimulus-induced vulnerability and total ARRS. Craving in the past 2 weeks (measured by VAS; $r = 0.317$) and the period of abstinence ($r = -0.252$) were significantly correlated with relapse. A significant and positive relationship was found between lack of negative expectancy in the ARRS and participants' compliance at follow-up ($r = 0.199$; 127 participants approved, 75 refused, and 20 were not asked). Logistic regression analysis (Table 5) revealed that lack of negative expectancy significantly and positively predicted relapse (odds ratio = 2.740, $p < .05$), and stimulus-induced vulnerability showed a tendency toward positively predicting relapse (odds ratio = 2.703, $p = .079$).

3.5. Gender differences and differences between inpatients and outpatients

The relationship between ARRS scores and current state of drinking and the relationship between ARRS scores and relapse were differentiated by treatment state (i.e., inpatient *vs.* outpatient) and gender (i.e., male *vs.* female) (Table 6). Among outpatients, a significant positive correlation was observed between lack of negative expectancy and current state of drinking. For inpatients, in contrast, the current state of drinking was significantly and negatively correlated with lack of negative expectancy.

For males, stimulus-induced vulnerability, positive expectancy, and total ARRS were significantly and positively correlated with relapse. For females, lack of negative expectancy was significantly and positively correlated with relapse.

4. Discussion

The present study developed the ARRS to assess relapse risk for Japanese alcohol-dependent individuals and statistically examined its inner structure, reliability, and validity. Five factors were found, and their internal consistency, concurrent validity, and predictive validity were revealed. Notably, part of the ARRS was related to relapse, implying its potential application for relapse prediction. Our findings demonstrated that the ARRS has multidimensional psychometric properties. Thus, the ARRS may be useful for assessing various aspects of relapse risk in alcohol-dependent individuals, similar to the SRRS for stimulant abusers.

Some similarities were found in the multidimensional structures of the ARRS and the SRRS; emotionality problems (Factor 2), compulsivity for alcohol (Factor 3), lack of negative expectancy (Factor 4), and positive expectancy (Factor 5) were similar to "emotionality problems," "compulsivity for drug," "lack of negative expectancy," and "positive expectancy" of the SRRS subscales, respectively. Factor 2 revealed negative emotional states (e.g., anxiety and negative mood) that have been shown previously to be related to relapse in alcohol-dependent individuals (Lucht et al., 2002; Walitzer and Dearing, 2006). Factor 3 was considered to reflect craving based on "obsessive compulsive theory" (Anton, 2000). Factor 4 and Factor 5 were considered to reflect craving based on "expectancy theory" (Jones et al., 2001). Positive expectancy for substance increases the risk of relapse, whereas negative expectancy for substance (understanding the harmful effects of the substance) decreases the risk. The above four factors are risk factors that may trigger relapse in alcohol-dependent individuals, as well as in stimulant abusers.

Differences were also found between the ARRS and the SRRS. "Stimulus-induced vulnerability" (Factor 1) in the ARRS and "anxiety and intention to drug use" in the SRRS, both of which relating to relapse, have differences in content. This may reflect the fact that alcohol-dependent individuals often encounter environmental stimuli related to alcohol because it is not illegal and is commonly

Table 6
Correlation of the ARRS against relapse by treatment state and gender.

	Correlation with current state of drinking				Correlation with relapse	
	Inpatient ($N = 29$)	Outpatient ($N = 182$)	Male ($N = 183$)	Female ($N = 35$)	Male ($N = 97$)	Female ($N = 27$)
ARRS subscale						
Stimulus-induced vulnerability (SV)	.615**	.447**	.543**	.201	.344**	.075
Emotionality problems (EP)	.656**	.082	.312**	−.378*	.185	−.005
Compulsivity for alcohol (CA)	.565**	.094	.229**	.032	.037	−.087
Lack of negative expectancy for alcohol (NE)	−.399**	.289**	.156*	.267	.076	.503**
Positive expectancy for alcohol (PE)	.664**	.262**	.435**	−.157	.280**	−.149
Total ARRS	.690**	.341**	.512**	−.031	.357**	−.046

* $p < .05$.
** $p < .01$.

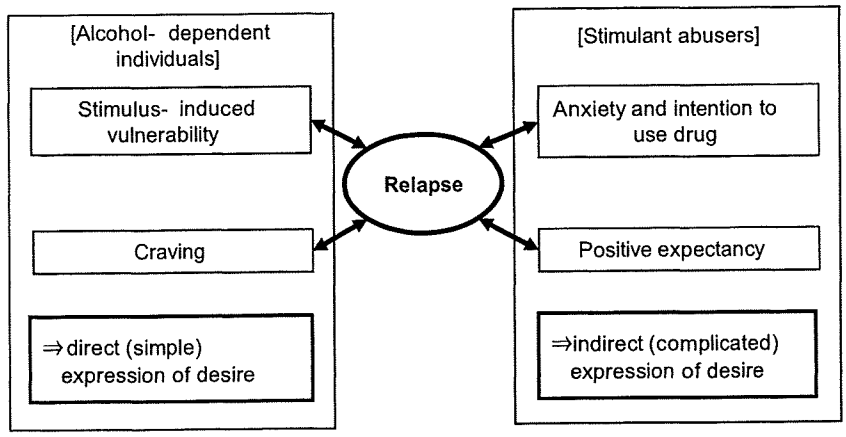

Fig. 1. Differences in the factors related to relapse between alcohol-dependent individuals and stimulant abusers. In alcohol-dependent individuals, stimulus-induced vulnerability in the ARRS and craving measured by the VAS were significantly related to relapse within 1 month. Anxiety, intention, and positive expectancy in the SRRS in stimulant abusers were significantly related to relapse within 3 months. These results indicate that alcohol-dependent individuals express signs of relapse more directly, such as craving for alcohol, and appear to be easily influenced by the environment. Stimulant abusers, in contrast, express signs of relapse indirectly, such as anxiety and expectancy, which are inner feelings.

consumed. In fact, social pressure is one of the relapse risks for alcohol-dependent individuals (Zywiak et al., 2006).

With regard to concurrent validity, the scores for total ARRS and all subscales except lack of negative expectancy were significantly correlated with the current state of drinking and the VAS scores. Specifically, the coefficients for stimulus-induced vulnerability and positive expectancy for alcohol were more than 0.4. These results suggest that stimulus-induced vulnerability and positive expectancy are important factors that govern the severity of alcohol dependence and craving related to the subjective desire for alcohol, although the difference in time frames of the ARRS (past 1 week) and the VAS (the current and past 2 weeks) must be considered.

With regard to predictive validity, the scores for stimulus-induced vulnerability and total ARRS were significantly correlated with relapse within 1 month, suggesting that these scores predict relapse risk. This was supported by the nearly significant prediction shown in the logistic regression analysis. The correlation between the scores for stimulus-induced vulnerability and relapse supports the hypothesis of a prior study of more than 900 individuals in which relapse was found to be triggered by social pressure such as temptation from alcohol-drinking friends (Zywiak et al., 2006). Particularly in Japanese collectivistic culture, refusing an offer to drink alcohol at a party is difficult. According to Hendershot et al. (2005), alcohol use is influenced by cultural background. Thus, the influence of culture on stimulus-induced vulnerability (e.g. "It would be difficult for me to refuse if someone placed alcohol in front of me") may be a more prevalent risk factor in Japan.

Interestingly, the logistic regression analysis showed that lack of negative expectancy significantly predicted relapse. This result suggested that lack of understanding of negative effects of alcohol drinking was an important factor leading to relapse. This result was also consistent with a report in which relapsed alcohol-dependent individuals and their families reported that "reduced cognitive vigilance" was the most common relapse sign (Malhotra et al., 1999). The differences between correlation analysis (Table 3) and logistic regression analysis (Table 5) relating Factor 4 with relapse indicate that some indirect effects of Factor 4 on relapse via other factors (e.g., positive expectancy) counterbalanced the direct effect of Factor 4 in the correlation score.

Although preliminary, stimulus-induced vulnerability and lack of negative expectancy in the ARRS and craving measured by the VAS among alcohol-dependent individuals were significantly related to relapse within 1 month. In stimulant abusers, in contrast, anxiety, intention, positive expectancy, and lack of negative expectancy were significantly related to relapse within 3 months. These results indicate that alcohol-dependent individuals express signs of relapse more directly, such as craving for alcohol, and appear to be easily influenced by the environment. In contrast, stimulant abusers express signs of relapse indirectly through inner feelings such as anxiety and expectancy (Fig. 1).

Other subscales (e.g., emotionality problems, compulsivity for alcohol, and positive expectancy) were not related to relapse. However, the significant correlations of these subscales with stimulus-induced vulnerability, lack of negative expectancy, and craving measured by the VAS suggest that these factors may have an indirect effect on relapse. Additionally, internal consistency of positive expectancy was low.

The relationships among the ARRS, current state of drinking, and relapse were influenced by treatment state and gender. Among inpatients, higher negative expectancy was associated with the risk of current drinking. By contrast, lower negative expectancy in outpatients was associated with the risk of current drinking. These results may reflect the fact that inpatients check into hospitals because they are more aware of the risk of drinking than outpatients. With regard to gender, higher vulnerability and positive expectancy were related to higher risk of relapse in males. By contrast, lower negative expectancy in females was related to high risk of relapse. These results were consistent with a report showing that alcohol-dependent males had a more positive affect during the week before relapse than females (McKay et al., 1996). The above results suggest the necessity of gender-specific intervention.

One possible limitation to the present study was the sampling procedure. The participants were not recruited randomly but were limited only to inpatients or outpatients who gave informed consent and whose doctors recognized their ability to answer the questionnaire. Therefore, the data of this study were not obtained from alcohol-dependent individuals as a whole, including dropout patients and non-patients, but rather only from cooperative patients with a relatively low severity of alcohol dependence. Additionally, the relatively low availability of relapse data (124/218) may have influenced the assessment of the ARRS's predictive validity. Conducting follow-up surveys for dropout cases and recruiting participants from other facilities and programs, including Alcoholics Anonymous, are necessary to gain a better understanding of relapse risk in alcohol-dependent individuals. Another limitation of the present study was the relatively low sample size. A sample of 218 participants was rather small to sufficiently support the factor analysis of 43 items. In the present