Pharmacokinetic and pharmacodynamic properties of gamithromycin in turkey poult with respect to *Ornithobacterium rhinotracheale*

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**ABSTRACT** The macrolide gamithromycin (GAM) has the ability to accumulate in tissues of the respiratory tract. Consequently, GAM might be a suitable antibiotic to treat bacterial respiratory infections in poultry, such as *Ornithobacterium rhinotracheale*. As O. *rhinotracheale* infections are common in turkey flocks, the aim of this study was to determine the pharmacokinetic (PK) parameters of GAM in plasma, lung tissue, and pulmonary epithelial lining fluid (PELF) of turkeys and to correlate them with pharmacodynamic (PD) characteristics (PK/PD). The animal experiment was performed with 64 turkeys, which received either a subcutaneous (SC, n = 32) or an oral (PO, n = 32) bolus of 6 mg GAM/kg body weight (BW). GAM concentrations in plasma, lung tissue, and PELF were measured at different time points post administration (p.a.), and PK characteristics were determined using non-compartmental modeling. The maximum plasma concentration after PO administration was ten-fold lower than after SC injection (0.087 and 0.89 μg/mL, respectively), whereas there was no difference in lung concentrations between both routes of administration. However, lung concentrations at day 1 p.a. were significantly higher than plasma levels for both routes of administration (2.22 and 3.66 μg/g for PO and SC, respectively). Consequently, lung/plasma ratios were high, up to 50 and 80 after PO and SC administration, respectively. GAM could not be detected in PELF, although this might be attributed to the collection method of PELF in birds. The GAM minimum inhibitory concentration (MIC) was determined for 38 O. *rhinotracheale* strains; MIC<sub>50</sub> and MIC<sub>90</sub> were 2 and >32 μg/mL, respectively. PK/PD correlation for lung tissue demonstrated that the time above the MIC<sub>90</sub> of the susceptible population (2 μg/mL) was 1 day after PO bolus and 3.5 days after SC administration. The area under the curve (AUC<sub>last</sub>)/MIC ratios for lung tissue after SC and PO administration were 233 and 90, respectively. To conclude, GAM is highly distributed to lung tissue in turkey poult, suggesting that it has the potential to be used to treat respiratory infections such as O. *rhinotracheale*.

**Key words:** gamithromycin, turkey poult, pharmacokinetic, pharmacodynamic, *Ornithobacterium rhinotracheale*

INTRODUCTION

Gamithromycin (GAM) is a second-generation macrolide antibiotic, belonging to the azalide subgroup. Macrolides are widely used antibiotics in veterinary medicine. A unique feature of these compounds is their ability to accumulate in the respiratory tract (Giguère, 2013). GAM is indicated for the treatment of bovine respiratory disease (BRD) (Baggott et al., 2011), but is currently not registered for use in other species. Nevertheless, the manufacturer has intentions to register the product for treatment of swine respiratory disease (SRD), since maximum residue limits have been established for porcine species recently (EMA, 2015).

In poultry, bacterial infections of the respiratory tract frequently result in economic losses due to increased mortality and feed conversion rates, reduced growth, and high medical costs (Van Empel and Hafez, 1999). *Ornithobacterium rhinotracheale* is a gram-negative bacterium causing respiratory symptoms in several bird species. Infections with *O. rhinotracheale* have been treated with several classes of antimicrobials, including β-lactam antibiotics, tetracyclines, fluoroquinolones, florfenicol, and macrolides, but with variable outcomes (Marien et al., 2006, 2007; Garmyn et al., 2009, Warner et al., 2009; Agunos et al., 2013; Watteyn et al., 2013b). Several studies demonstrated that the sensitivity of *O. rhinotracheale* to antimicrobials is strain-dependent (Devries et al., 1995, 2001).

The pharmacokinetic (PK) behavior of GAM has been studied in cattle (Huang et al., 2010; Giguère et al., 2011), foals (Berghaus et al., 2011), broiler chickens (Watteyn et al., 2013a) and swine...
(Wyns et al., 2014). However, no data are available for turkey poult, neither for plasma nor for tissues.

GAM has a high volume of distribution (Vd > 20 L) in all investigated species, due to its accumulation in tissues and high affinity for the respiratory tract. Huang et al. (2010) analyzed whole-lung homogenate of cattle, and reported concentrations that were 250 to 400 times higher than the corresponding plasma concentrations. Also, in pulmonary epithelial lining fluid (PELF), the concentrations of GAM were much higher compared to plasma, with a maximum plasma concentration (Cmax) for cattle and foals of 0.43 and 0.33 μg/mL in plasma and 4.16 and 2.15 μg/mL in PELF, respectively (Berghaus et al., 2011; Giguère et al., 2011). This emphasizes the need to quantify the antibiotic in the target pulmonary tissues as well, and not only in plasma.

Since GAM has a spectrum against O. rhinotracheale, combined with the ability to accumulate in pulmonary tissues, it might be used to treat O. rhinotracheale infections. Therefore, the aim of the present study was to determine the PK behavior of GAM in plasma as well as in lung tissue and PELF of turkey poult, and to relate these results to the minimum inhibitory concentration (MIC) values against recent O. rhinotracheale isolates.

MATERIALS AND METHODS

Experimental Protocol

Sixty-four 3-week-old female turkey poult with a mean BW (±SD) of 0.556 (±0.057) kg (Hybrid Converter, local commercial turkey farm) were housed according to the requirements of the European Union (Anonymous, 2010). The animals were acclimatized for 4 days and received water and feed ad libitum. Feed was withdrawn from 12 h before until 6 h after GAM administration. The turkeys were randomly divided into 2 groups. Thirty-two animals received a subcutaneous (SC) bolus injection of 6 mg/kg BW GAM in the neck region. The other 32 birds were administered the same dose, but orally (PO) by gavage in the crop. Blood (1 mL) was collected from 5 animals per group by venipuncture of the leg vein into heparinized tubes (Vacutest Kima, Novolab, Geraardsbergen, Belgium) at different time points before (time 0 h) and post administration (p.a.; 0.08, 0.25, 0.5, 0.75, 1, 2, 4, 6, 8, 10, and 12 h, and furthermore once daily in the morning from day 2 (24 h) until day 10 p.a. and once on days 12 and 14). Blood samples were centrifuged at 1,500 × g at 4°C for 10 min. Plasma was collected and stored at ≤ −15°C until analysis.

From each group, 4 animals were sacrificed at different time points (day 1, 5, 10, 15, 20, 30, 40, and 50 p.a.) to collect plasma, lung tissue, and PELF. For that, the birds were anesthetized using a combination of xylazine (Xyl-M 2%, VMD, Arendonk, Belgium), zolazepam and tiletamine (Zoletil 100, Virbac, Wavre, Belgium), followed by exsanguination. The whole right lung was removed for GAM analysis. The complete left lung was used to collect PELF, as described by Bottje et al. (1999). In brief, after weighing the lung, it was lavaged with heparin-saline (200 units heparin per mL of 0.9% saline) at a volume of 2 mL/g lung through a cannula in the first bronchus. The PELF/saline solution was collected in a petri dish, and the amount of fluid was measured to determine the recovery, which ranged from 71.2 to 92.9%. The fluid was centrifuged (5,250 × g for 3 min) to remove red blood cells. Both the lung tissue and PELF were stored at ≤ −15°C until analysis.

The animal experiment was approved by the Ethical Committee of the Faculty of Veterinary Medicine and Bioscience Engineering, Ghent University (EC 2013/107).

Veterinary Drug, Analytical Standards, Chemicals, and Solutions

Zactran, containing 150 mg GAM/mL (Merial Ltd, North Brunswick, NJ, USA) was used for the animal experiment. Just before drug administration, it was diluted with aqua ad injectabilia up to a concentration of 15 mg/mL GAM.

The analytical standard of GAM and the internal standard (IS), deuterated-GAM (d5-GAM), were kindly donated by Merial Ltd. and stored at 2 to 8°C. Stock solutions of 1 mg/mL of GAM and d5-GAM were prepared in methanol (MeOH) and stored at ≤ −15°C. Working solutions of 0.025, 0.050, 0.10, 0.25, 0.50, 1.0, 2.5, 5.0, 10.0, 25.0, 50.0 and 100 μg/mL of GAM were prepared by appropriate dilution in HPLC water. Working solutions of 1.0 and 10.0 μg/mL of the IS were prepared in HPLC water by appropriate dilution of the stock solution. The working solutions of GAM and IS were stored at 2 to 8°C.

The solvents used for HPLC analysis (water and acetonitrile, ACN) were of LC-MS grade and obtained from Biosolve (Valkenswaard, The Netherlands). All other solvents and reagents were of HPLC grade (water, ACN, MeOH, and diethylether) or analytical grade (formic acid, ammonium acetate, sodium hydroxide [NaOH], and ammonium hydroxide) and purchased from VWR (Leuven, Belgium). Millex-GN Nylon (0.20 μm) syringe filters were obtained from Merck Millipore (Overijse, Belgium). Ostro protein precipitation and phospholipid removal 96-well plates (25 mg) were obtained from Waters (Zellik, Belgium). HybridSPE-Phospholipid cartridges (30 mg/mL) were purchased from Sigma-Aldrich (Bornem, Belgium).

Gamithromycin Analysis

Sample preparation for the analysis of GAM in turkey plasma, using the Ostro 96-well plates and a validated, high-performance liquid chromatography method with tandem mass spectrometry detection
(LC-MS/MS) was performed, as described by Watteyn et al. (2013a) for chicken plasma. Lung and PELF samples were analyzed using a validated LC-MS/MS method (De Baere et al., 2015).

The limit of quantification (LOQ) was set at 5 ng/mL, 50 ng/g, and 20 ng/mL for plasma, lung tissue, and PELF, respectively (De Baere et al., 2015).

**Minimum Inhibitory Concentration**

The MIC of GAM was determined using the agar dilution method. General procedures, weighing, and inoculation were according to the Clinical and Laboratory Standard Institute (CLSI) standards. Since no standard conditions for susceptible testing of *O. rhinotracheale* are described (CLSI, 2013), Columbia agar supplemented with 5% horse blood was used, as described by Devriese et al. (2001). The plates were incubated for 48 hours at 35°C in a 5% CO₂ atmosphere. Thirty-eight isolates (37 field isolates originating from poultry, and the *O. rhinotracheale* type strain LMG 9086T, originally isolated from a turkey) were used. The concentrations of GAM tested ranged between 0.03 and 32 μg/mL. *Escherichia coli* ATCC 25922 and *Staphylococcus aureus* ATCC 29213 were used as control strains, as indicated by the CLSI guidelines (CLSI, 2013).

**Pharmacokinetic and Statistical Analysis**

The following plasma PK parameters were determined by non-compartmental analysis (WinNonlin 6.3, Pharsight, CA, USA): area under the plasma concentration-time curve from time 0 to the last time point with a quantifiable concentration (AUCₗₚₜ); the AUC from time 0 to infinity (AUCᵢᵢᵢᵢ); elimination-rate constant (kₑ₁); elimination half-life (T₁/₂ₑ₁); volume of distribution (V₁); total body clearance (Cl); Cₘₚₜ, and time to Cₘₚₜ (Tₘₚₜ). The relative oral bioavailability (Fₑ₁) was calculated according to the following equation: \( Fₑ₁(\%) = \frac{AUCₑ₁_{last}p.o.}{AUCₑ₁_{last}s.c.} \times 100 \). For lung tissue, AUCₗₜₗₜ, AUCᵢᵢᵢᵢ, kₑ₁, T₁/₂ₑ₁, Cₘₚₜ, and Tₘₚₜ were calculated in a similar way. All results below the LOQ were not taken into account.

The plasma PK data are expressed as mean ± SD and were statistically analyzed by the nonparametric Mann-Whitney U test, using SPSS Statistics 22 (IBM, Chicago, IL, USA). A value of \( P < 0.05 \) was considered significant. No SD could be calculated for the lung samples, as a sparse sampling protocol was used. Hence, no statistical analysis was performed.

**RESULTS**

The semi-logarithmic plots of the mean plasma concentration–time curves of GAM after SC and PO administration are depicted in Figure 1, while Figure 2 shows the comparison between the concentration–time curves in plasma and lung tissue. Table 1 shows the main PK properties of GAM for plasma and lung tissue. As can be observed, the AUCₗₜₗₜ as well as the AUCᵢᵢᵢᵢ after PO administration for both plasma and lung tissue were much lower than after SC administration, with significant difference in plasma (\( P < 0.01 \) and \( P < 0.05 \) for AUCₗₜₗₜ and AUCᵢᵢᵢᵢ, respectively.). After PO administration, Cₘₚₜ in plasma was a ten-fold lower than after SC administration (0.087 and 0.89 μg/mL, respectively). Nevertheless, this discrepancy between SC and PO was not seen in the lung tissue (Cₘₚₜ of 2.22 and 3.66 μg/g after PO and SC administration, respectively). The V₁ and Cl were corrected for the relative oral bioavailability (Fₑ₁ = 25.0%), and were not significantly different between routes of administration. Consequently, the T₁/₂ₑ₁ in plasma for both routes of administration were not significantly different (Table 1 and Figure 1).

**Figure 1.** Mean (±SD) plasma concentration versus time curve of gamithromycin (GAM) in turkeys, after subcutaneous (SC, n = 5) or oral (PO, n = 5) administration of 6 mg/kg BW GAM. p.a., post administration.
As can be seen in Figure 2, the lung/plasma concentration ratios of GAM were up to 87.9. No plasma concentrations were detected from 10 and 15 days onwards after PO and SC administration, respectively.

The concentration of GAM in all PELF samples was below the LOQ of 20 ng/mL.

The MIC values of the 38 O. rhinotracheale isolates ranged from 0.25 to >32 μg/mL, namely 0.25, 0.5, 1.0, 2.0, 4.0, and >32 μg/mL in, respectively, 1 (2.6%), 4 (10.5%), 9 (23.7%), 7 (18.4%), 3 (7.9%), and 14 (36.8%) of the evaluated strains (Figure 3). For the type strain LMG 9086, the MIC was 0.5 μg/mL. The MIC90 were 2 and >32 μg/mL, respectively. The control strains E. coli ATCC 25922 and S. aureus ATCC 29213 showed a MIC of >32 and 4 μg/mL, respectively.

For macrolides in general, both the time the plasma concentration exceeds the MIC (T > MIC) and the area under the inhibitory curve (AUC/MIC) are taken into account as PD indices. Considering the clear bimodal MIC distribution (Figure 3), the isolates were divided into a susceptible population (MIC between 0.25 and 4 μg/mL) and a resistant population (MIC >32 μg/mL). In this study, the plasma concentrations never exceeded the MIC90 of the susceptible population,
which was 2 μg/mL. The T > MIC90 in lung tissue was approximately 3.5 days and 1 day after SC and PO administration, respectively. The AUC_{inf}/MIC in plasma was 3.43 and 1.09 after SC and PO administration, respectively. For lung tissue, the AUC_{last}/MIC was 233 and 90 after SC and PO administration, respectively.

DISCUSSION

As macrolides, including GAM, are commonly used in cattle to treat BRD, a possible positive effect of GAM to cure an *O. rhinotracheale* infection in turkeys can be put forward. To identify the disposition of GAM in turkeys, a PK study of GAM in plasma and lung tissue, as well as PELF, was performed. These results were correlated to the MIC of several *O. rhinotracheale* strains in order to establish a pharmacokinetic/pharmacodynamic (PK/PD) correlation.

The commercial formulation of GAM is only indicated for SC use, but as mass medication through drinking water and feed is the most important route of drug administration in poultry, GAM was also given orally as a single bolus in the crop.

Plasma

To the authors’ knowledge, no plasma PK studies of macrolides in turkeys have been performed. After SC administration, GAM was absorbed very rapidly, with a T_{max} of 0.08 h, whereas T_{max} after the oral bolus was delayed (0.85 h). This rapid SC absorption was also seen in broiler chickens (Watteyn et al., 2013a). The T_{1/2el} of GAM was not significantly different between SC and PO administration (34.9 h and 29.7 h, respectively), and is similar to foals after intramuscular administration of 6 mg/kg BW GAM (39.1 h; Berghaus et al., 2011). Cattle show a longer T_{1/2el}, around 50 h after SC administration (Huang et al., 2010; Giguère et al., 2011), while pigs eliminate the drug more rapidly after SC injection (T_{1/2 el} = 18.8 h; Wyns et al., 2014). In contrast with turkeys, chickens have a shorter T_{1/2el} after SC administration (11.6 and 34.9 h for chicken and turkey, respectively), which can be partially attributed to a higher clearance in comparison with turkeys (1.77 and 1.02 L/h.kg for chicken and turkey, respectively; Watteyn et al., 2013a). Notwithstanding the V_{d} is similar for GAM in cattle, chickens, and pigs (around 20 L/kg), in turkeys it was found to be higher (53.69 L/kg), and thus might also be responsible for the longer T_{1/2el} seen in turkeys. An explanation for this discrepancy is possible differences in protein binding across species (Rivièr et al., 1997). Cl and V_{d} are not corrected for the absolute SC bioavailability (F_{abs}), as there are no PK parameters available for intravenous (IV) administration in turkeys. Taking into account that GAM is completely absorbed after SC injection in other species, including cattle, chickens, and pigs, it can be suggested that it is also the case for turkeys (Huang et al., 2010; Watteyn et al., 2013a; Wyns et al., 2014). Comparing the AUC of GAM after PO and SC administration, this results in a relative bioavailability (F_{rel}) of 25% after PO. When the Cl and V_{d} are adjusted for this F_{rel}, these parameters have equal values after PO and SC administration.

The maximum plasma concentration after a SC administration of 6 mg/kg BW GAM in turkeys (0.89 μg/mL) is equivalent to the C_{max} reported for cattle and chickens (0.75 and 0.89 μg/mL respectively; Huang et al., 2010; Watteyn et al., 2013a). This value is higher compared to foals (IM administration) and pigs, namely 0.33 and 0.41 μg/mL after administration of the same dose, respectively (Berghaus et al., 2011; Wyns et al., 2014). After an oral bolus, the C_{max} in plasma is remarkably lower (0.087 μg/mL). A possible hypothesis for this difference could be the presence of the microbial flora in the crop, which could inactivate macrolides (Dutta and Devriese, 1981; Devriese and Dutta, 1984).

Lung

Although plasma concentrations of macrolides are often below the MIC of the pathogen, these drugs are effective in the treatment of respiratory diseases due to high levels of the active substance in target tissues, represented by their high V_{d}. Therefore, to evaluate the PK/PD correlation of macrolides, it is of great importance to measure drug concentrations in the target tissues. In the present study, high lung concentrations...
were detected, with lung/plasma concentration ratios between 54.7 to 87.9 after SC injection. This is in accordance with previous reports (Huang et al., 2010; Giguère et al., 2011) where lung/plasma ratios up to 200 were observed after SC administration of GAM in cattle. Although lower compared to SC administration, high lung/plasma ratios were also observed after oral administration (51.9–54.4). Notwithstanding the $C_{\text{max}}$ in plasma after PO was a ten-fold lower than after SC administration, this discrepancy was not observed in the lung (3.66 and 2.22 $\mu$g/g after SC and PO administration on day 1 p.a.). As macrolides can be considered to be time-dependent antibiotics, the AUC is even more important than $C_{\text{max}}$. If the AUC were a parameter to compare the amount of drug in plasma and lung tissue, these ratios ($\text{AUC}_{\text{lung}}/\text{AUC}_{\text{plasma}}$) remain constant after SC as well as PO administration (respectively, 53.6 and 51.9 on day 1 p.a.; 55.5 and 45.3 on day 5 p.a.). After SC injection, the $T_{1/2}$ of GAM in lung tissue was similar for cattle and turkeys, namely around 90 h (Huang et al., 2010; Giguère et al., 2011), while it was shorter after oral administration (59.8 h).

**PELF**

Currently, the pathogenesis of *O. rhinotracheale* and the factors determining colonization of the host tissue are still unclear. *O. rhinotracheale* adheres to avian erythrocytes and tracheal cells, behaving as an extracellular pathogen (De Haro-Cruz et al., 2013). In contrast, Zahra et al. (2013) isolated small-colony variants of *O. rhinotracheale* that persist intracellularly in murine RAW 264.7 macrophages. This new insight is of great importance for a successful treatment with antimicrobials, although it is not clear if *O. rhinotracheale* is also able to persist in avian macrophages. It is most likely that the distribution of GAM varies among the different compartments of the respiratory tract, such as intracellularly in host defense cells (e.g., macrophages), extracellularly, and in bronchial fluid (Huang et al., 2010; Giguère, 2013). As in this study, whole lung-tissue homogenates were analyzed, and the mean concentration in all these compartments was measured. Determination of GAM in PELF might give a more accurate prediction, as these concentrations are of importance for extracellular pathogens. Therefore, Giguère and Tessman (2011) concluded that measurement of the concentrations of macrolides in PELF would be a better predictor of their efficacy than either lung or plasma concentrations. As macrolides reach high intracellular concentrations, tissue homogenates could overestimate extracellular concentrations in relation to the PELF.

To date, no PK data of macrolides in PELF from poultry are available. Giguère et al. (2011) detected PELF concentrations of GAM in cattle that were much higher than in plasma, but lower than in lung tissue (ratios between 4.7 and 127 for PELF/plasma and between 16 and 650 for lung/plasma). In foals, GAM reached high levels in PELF, with PELF/plasma ratios between 4.7 to 70 (Berghaus et al., 2011). Remarkably, in this study no concentrations of GAM above the LOQ could be detected in PELF of turkeys. A possible explanation could be the typical anatomical arrangement of the respiratory system in avian species. The intrapulmonary primary bronchus ramifies in several secondary bronchi and ends in the abdominal air sac. The ventro- and laterobronchi end also in air sacs via ostia, while the dorsobronchi give rise to parabronchi. In contrast to mammals, birds have flow-through lungs with a nearly constant volume, in which the gas exchange takes place in the parabronchi. As air sacs act as bellows, they are the sites of volume expansion and move air through the parabronchi (Brown et al., 1997; Fedde, 1998; Powell, 2000). These anatomical differences have an influence on the collection method for PELF. In mammals, PELF is collected by intrabronchial administration of saline in live animals, followed by aspiration of the saline solution and a recovery correction based on an endogenous component, such as ureum. In poultry, on the other hand, the bronchi are connected with the air sacs via ostia. As a consequence, it is impossible to apply the same technique as in mammals. The used technique in this study was based on a heparin-saline solution to flush the *ex vivo* lungs, which distributed in the lung and was immediately flushed out of the lungs through these ostia as was reported by Bottje et al. (1999). In contrast, Bernhard et al. (2001) used an *in situ* method in ducks and chickens. The air sacs were ligated and lungs were flushed with saline, followed by aspiration of the fluid. *In vivo* collection in chickens has also been described. After placing the bird on its back, tubing was threaded down the exteriorized trachea to the bronchi, and air was evacuated from the lung. Warm buffer was administered, and the fluid sample was aspirated (Holt et al., 2005). The results obtained might therefore be dependent on the collection method.

Another factor related to the discrepancy seen in GAM concentrations in PELF between mammals and turkeys is the different immunology between the two classes, as GAM also distributes in macrophages. The epithelial surface of the mammalian lung is covered by a thin layer of PELF and resident immune cells, such as macrophages (Reynolds, 1987). On the contrary, birds have fewer or even no phagocytic cells in healthy lung samples. A small number of macrophages can be found on the epithelial lining of the parabronchi, whereas leukocytes are often present on the surface of the air sacs (Hartle and Kaspers, 2014). To conclude, the avian intracellular distribution of GAM in PELF is difficult to measure, as macrophages are not a constitutively present cell population.

**MIC and PK/PD Correlation**

The sensitivity of *O. rhinotracheale* to antibiotics is very inconsistent and highly strain-dependent
strains were inhibited by erythromycin, tylosin, and tilmicosin. However, many strains originating from Germany and the Netherlands, expressed for the dosage interval, the authors decided to take into account the AUC/MIC, based on a 24-h period (Lees et al., 2010). Since GAM was given as a single bolus, no steady-state situation was achieved; instead, the AUC/MIC was calculated as a single bolus, not steady-state, for oral therapy or an adjusted dose of GAM could improve the plasma and lung concentrations after PO administration. The low GAM concentrations in PELF found in this study could be a result of the different anatomy of the respiratory system in birds compared to mammals, which would require a different collection method for PELF. Also, a difference in immune cells present in the respiratory tract of birds compared to mammals might be responsible. To date, the collection of PELF in poultry is poorly investigated and requires more research. For macrolides, there is no single PK/PD index that correlates with efficacy for all members in this class of antibiotics. The authors endeavor to correlate the plasma and lung PK parameters to the MIC values, but whether these values result in a therapeutic efficacy should be further determined in experimental and field infection studies (Marien et al., 2005, 2006, 2007; Garmyn et al., 2009).

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